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Neurobiology of addiction
An integrative review

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ABSTRACT

Evidence that psychoactive substance use disorders, bulimia nervosa, pathological gambling, and sexual addiction share an underlying biopsychological process is summarized. Definitions are offered for *addiction* and *addictive process*, the latter being the proposed designation for the underlying biopsychological process that addictive disorders are hypothesized to share. The addictive process is introduced as an interaction of impairments in three functional systems: motivation-reward, affect regulation, and behavioral inhibition. An integrative review of the literature that addresses the neurobiology of addiction is then presented, organized according to the three functional systems that constitute the addictive process. The review is directed toward identifying candidate neurochemical substrates for the impairments in motivation-reward, affect regulation, and behavioral inhibition that could contribute to an addictive process.

Addiction neuroscience may well be our era's most dynamic field of scientific inquiry. The quality as well as quantity of information that it generates seems almost to exceed the capacity of our theories to organize and make coherent sense of it. This article offers a framework that may be helpful in organizing and integrating the wealth of information that is the neurobiology of addiction. The cornerstone of this framework is the addictive process, an underlying biopsychological process that addictive disorders are hypothesized to share. The article begins by introducing the hypothesis that psychoactive substance use disorders, bulimia nervosa (from here on, bulimia), pathological gambling, and sexual addiction share an underlying biopsychological process. Research findings are demonstrated to accord with empirically testable predictions that were generated from the hypothesis, thereby confirming it. Definitions are then offered for the key terms, *addiction* and *addictive process*. The addictive process is brought into focus as an interaction of impairments in three functional systems: motivation-reward, affect regulation, and behavioral inhibition. The review itself then follows, in which the literature that addresses the neurobiology of addiction is selectively organized according to the three functional systems that constitute the addictive process. The review is directed toward identifying candidate neurochemical substrates for the impairments in motivation-reward, affect regulation, and behavioral inhibition that could contribute to an addictive process.

1. Addictive disorders

1.1. *A shared underlying process*

In the course of my work with individuals who suffered from psychoactive substance use disorders, bulimia, pathological gambling, or sexual addiction, I noticed that these conditions shared a number of characteristic clinical features. These included: (1) course of illness – the disorder typically begins in

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adolescence or early adulthood and follows a chronic course with remissions and exacerbations; (2) behavioral features – narrowing of behavioral repertoire, continuation of the behavior despite harmful consequences; (3) individuals' subjective experience of the condition – sense of craving, preoccupation, excitement during preparatory activity, mood-altering effects of the behavior, sense of loss of control; (4) progressive development of the condition – craving, loss of control, narrowing of behavioral repertoire, and harmfulness of consequences all tending to increase as the duration of the condition increases; (5) experience of tolerance – as the behavior is repeated, its potency to produce reinforcing effects tends to diminish; (6) experience of withdrawal phenomena – psychological or physical discomfort when the behavior is discontinued; (7) tendency to relapse – i.e., to return to harmful patterns of behavior after a period of abstinence or control has been achieved; (8) propensity for behavioral substitution – when the behavioral symptoms of the disorder have come under control, tendency for addictive engagement in other behaviors to emerge or intensify; (9) relationship between the condition and other aspects of affected individuals' lives – for example, neglect of other areas of life as the behavior assumes priority; and (10) recurrent themes in the ways individuals with these conditions relate to others and to themselves – including low self-esteem, self-centeredness, denial, rationalization, and conflicts over dependency and control. In addition, I noticed that among my patients who suffered from psychoactive substance use disorders, bulimia, pathological gambling, or sexual addiction, more were comorbid with at least one of the other three conditions and more reported relatives with at least one of the other three than chance would have predicted. On the basis of the clinical features that these four conditions shared, as well as similarities in their diagnostic criteria, I provisionally identified them as addictive disorders (definition to follow). My observations further led me to speculate that the four conditions – and, by extension, addictive disorders in general – had something important in common. In 1990, I [1] proposed the following hypothesis:

> A hypothesis may be submitted, the gist of which is that similar patterns in behavioral manifestations of the various addictive disorders. . .reflect similarities in some set of personality and/or biological variables, which may or may not be measurable by instruments currently available. In other words, addictive disorders would be most accurately described, not as a variety of addictions, but as a basic underlying addictive process, which may be expressed in one or more of various behavioral manifestations.

In brief, the hypothesis is that addictive disorders share an underlying biopsychological process. From this hypothesis, a number of empirically testable predictions can be generated:

(1) A person who has been diagnosed with an addictive disorder is at a significantly higher risk than is the general population to develop (or to have developed), at some point in his or her life, one or more of the other addictive disorders.
(2) Biological relatives of an individual who has been diagnosed with an addictive disorder are at significantly higher risk than is the general population to develop (or to have developed), at some point in their lives, one or more of the other addictive disorders.
(3) Symptoms of the various addictive disorders respond similarly to at least one major class of psychiatric medications.
(4) Results of at least one major class of empirically validated psychological tests are similar for individuals who have been diagnosed with any one of the addictive disorders.
(5) Addictive disorders have in common one or more identifiable patterns of neurobiological activity, structure, and development.
(6) Individuals who have been or who will be diagnosed with an addictive disorder tend to exhibit one or more other observable manifestations of biopsychological pathology, such as symptoms of another psychiatric disorder or dysfunctional behavior patterns, prior to the onset of the addictive disorder.

These predictions enable scientific assessment of the validity of the hypothesis that addictive disorders share an underlying biopsychological process. To the extent that the findings of research accord with the predictions, the hypothesis is confirmed (factoring in that the predictions vary in salience). To the extent that they do not accord the predictions, the hypothesis is disconfirmed. Of course, confirmation or disconfirmation is relative to the data that currently are available – particularly in a field as dynamic as neuroscience, where potentially significant data emerge with astonishing frequency.

A wealth of published research findings are relevant to assessing the accuracy of the six aforementioned predictions, and hence the validity of the hypothesis from which they were generated. Addictive disorders that have been the subjects of enough research to be considered in the validation process include psychoactive substance use disorders, bulimia, pathological gambling, and sexual addiction. Findings that are relevant to the six predictions – lifetime comorbidity, family history, response to medications, psychometric studies, neuroscience research, and temporal/predictive relationships – will now be briefly reviewed.

1.1.1. *Lifetime comorbidity*

Epidemiological and clinical research findings indicate that a person who has been diagnosed with psychoactive substance dependence with respect to one type of substance (including ethanol) is at a significantly higher risk than is the general population for dependence on (i.e., addictive use of) one or more other psychoactive substances at some point in his or her life [2–9]. More broadly, research findings indicate that a person who has been diagnosed with psychoactive substance dependence, bulimia, pathological gambling, or sexual addiction is at a significantly higher risk than is the general population to develop (or to have developed), at some point in his or her life, one of the other disorders. A person who has been diagnosed with bulimia is at a significantly higher risk than is the general population to develop (or to have developed), at some point in his or her life, a psychoactive

substance dependence [10–32], and vice versa [33–37]. A person who has been diagnosed with pathological gambling is at a significantly higher risk than is the general population to develop (or to have developed), at some point in his or her life, a psychoactive substance dependence [3,35–57], and vice versa [3,58–67]. A person who has been diagnosed with sexual addiction is at a significantly higher risk than is the general population to develop (or to have developed), at some point in his or her life, a psychoactive substance addiction [68–76], and vice versa [77,78]. A person who has been diagnosed with pathological gambling is at a significantly higher risk than is the general population to develop (or to have developed), at some point in his or her life, sexual addiction [45,79], and vice versa [71]. And a person who has been diagnosed with sexual addiction is at a significantly higher risk than is the general population to develop (or to have developed), at some point in his or her life, an eating disorder or pathological gambling or both [68,73,75,76].

Studies have found that these four conditions – psychoactive substance dependence, bulimia, pathological gambling, and sexual addiction – are associated also with affective disorders, anxiety disorders, attention deficit disorder, and personality disorders at frequencies that are higher than are their frequencies in the general population. Affective disorders, primarily major depression, have a significant degree of comorbidity with ethanol dependence [3–34,35–44,80–83], other psychoactive substance use disorders [2,4,5,84–88], bulimia [15,16,32,89–91], pathological gambling [40,41,44,45,51,92–94,51,95–97], and sexual addiction (paraphilic disorders in most of these studies) [69,71–76,98–101]. Anxiety disorders have a significant degree of comorbidity with ethanol dependence [2,79,80], other psychoactive substance dependence [3,4,85,86,88], bulimia [16,32,89,102,103], pathological gambling [42,44,47,50,96], and sexual addiction (paraphilic disorders in most of these studies) [29,71,72–78,98,100,104]. Attention deficit disorder has a significant degree of comorbidity with ethanol dependence [105–107], other psychoactive substance dependence [108,109], bulimia [32], pathological gambling [97,107,110,111], and sexual addiction (paraphilic disorders in most of these studies) [74,112–114]. And personality disorders have a significant degree of comorbidity with ethanol dependence [2,13,115–117], other psychoactive substance dependence [3,85,115–118], bulimia [32,119,120], pathological gambling [47,97,111,121–123], and sexual addiction [73,77,100,124–126].

1.1.2. *Family history*

Family history studies indicate that biological relatives of an individual who has been diagnosed with psychoactive substance dependence, bulimia, pathological gambling, or sexual addiction are at significantly higher risk than is the general population to develop (or to have developed), at some point in their lives, one of the other disorders. First-degree relatives of a person who has been diagnosed with psychoactive substance dependence are at a significantly higher risk than is the general population for pathological gambling [41,43,44,120,129]. First-degree relatives of a person who has been diagnosed with bulimia are at a significantly higher risk than is the general population for psychoactive substance dependence [12,15–17,34,127,128]. First-degree relatives of an individual who has been diagnosed with pathological gambling are at a significantly higher risk than is the general population for compulsive overeating [129] and for psychoactive substance dependence [41,44,129,130]. And first-degree relatives of a person who has been diagnosed with sexual addiction are at a significantly higher risk than is the general population for psychoactive substance dependence, for an eating disorder, and for pathological gambling [69].

1.1.3. *Response to medications*

Research indicates that symptoms of the conditions that we are considering respond similarly to a number of psychiatric medications. Antidepressants, particularly those that affect the serotonin system, have been found to reduce craving and/or symptomatic behavior in ethanol dependence [131–141].[1] other psychoactive substance dependence [141–149], bulimia [150–157], pathological gambling [154–161], and sexual addiction [69,101,104,162–170]. Opioid antagonists, most often naltrexone, have been found to be effective in treating ethanol dependence [171–177], other nicotine/tobacco dependence [178,179], pathological gambling [180–183], and sexual addiction [184,185]. Studies have supported the efficacy of stabilizers, primarily topiramate, in the treatment of ethanol dependence [186–188], cocaine dependence [189], bulimia [190–193], pathological gambling [194–197], and sexual addiction [198–200].

1.1.4. *Psychometric studies*

Similar patterns of results have been reported for alcoholics, drug abusers, bulimics, and pathological gamblers on the Minnesota Multiphasic Personality Inventory (MMPI) and on the MacAndrew Alcoholism Scale. Research with the MMPI has demonstrated similar profiles for alcoholics and heroin addicts [reviewed in 201], for women with ethanol or other drug abuse problems and women with bulimia (who have no history of substance abuse) [202], and for alcoholics and nonalcoholic pathological gamblers [203,204]. Using the MacAndrew Alcoholism Scale, researchers have found the same range of scores for problem drinkers, heroin addicts, massively obese individuals, and smokers [205–207]. In a comprehensive review, Sutker and Archer [208] concluded that alcoholics, opiate addicts, and abusers of other illicit drugs share common constellations of MMPI features; but they noted that alcoholics, as abusers of a socially sanctioned drug, differ from abusers of illicit drugs on dimensions of social nonconformity and neurotic symptomatology. Since MMPI profiles for these groups of patients are not homogeneous,

[1] While Cornelius et al. [139] found that treatment of alcoholism with antidepressants is effective only in the context of comorbid depression or anxiety, the studies that are cited here specifically excluded subjects who had any (axis I) psychiatric diagnosis other than alcohol abuse/dependence. Nonetheless, I agree with Cornelius et al. – with the caveat that the comorbid depression or anxiety do not always meet the criteria for DSM diagnosis. As I discuss in the next section, I believe that some kind of affective dysregulation is an underlying component of all addictive disorders. However, the affective and/or anxiety symptoms are often chronic, unconsciously excluded from the alcoholic's awareness, and difficult to dissect out of the alcoholic's personality, so they may tend to fly under the average clinician's radar.

some investigators have attempted to delineate homogeneous MMPI profile subgroups with the help of multivariate cluster analysis. Almost all studies of this nature have been conducted with alcoholics. A review of these studies [208] found that they consistently delineated two major subtypes or clusters, a neurotic subtype and a sociopathic subtype. Similar delineations of two major subtypes or groups of subtypes were found in one study of opiate addicts [209] and in two studies of pathological gamblers [204,210].

Assessments of field dependence have yielded similar results of greater field dependence (poorer performance on the Rod-and-Frame Test) for alcoholics [reviewed in 201], for heroin addicts [211], and for obese individuals [212,213]. A related condition, overdependence on external cues and impaired ability to recognize or correctly to interpret internal cues, has been found to be associated with both alcoholism [213,214] and obesity [213,215].

1.1.5. *Neuroscience research*

Research in the areas of clinical phenomenology, lifetime comorbidity, family history, response to medications, and psychometric studies has provided grounds for inferring that psychoactive substance dependence, bulimia, pathological gambling, and sexual addiction share an underlying biopsychological process. Neuroscience research has accepted the challenge of this inferred underlying process by investigating it directly.

To set the stage, studies with pairs of twins have yielded evidence for a shared or common vulnerability that underlies the abuse of psychoactive substances, regardless of the type of substance [216–218]. These studies found that the shared vulnerability comprised both genetically determined factors and environmentally determined factors. Other studies either did not examine the environmental component or found it to be more substance-specific, while still concluding that most of the inherited predisposition to abuse different psychoactive substances converges in a shared or substance-nonspecific liability [reviewed in 219–221].

Neuroscience research has led beyond demonstrating a shared vulnerability that underlies the abuse of psychoactive substances toward delineating the neurobiological processes that constitute this vulnerability. Among those mentioned are dysregulated mesolimbic DA circuits [222–224], reduction in DA D_2 receptors [224–229], abnormalities in the orbitofrontal cortex and the anterior cyngulate gyrus [228,230–232], abnormalities in the ventromedial prefrontal cortex [233–235], genetic variants of cannabinoid receptor 1 (CB_1/Cnr1) [236,237], up-regulation of brain-derived neurotrophic factor (BDNF) [238], and impaired leptin activity [228,239]. This research also has expanded the realm of this shared vulnerability to include pathological gambling and pathological use of the natural rewards food and sex, as well as psychoactive substance abuse [227,231,239–248].

1.1.6. *Temporal/predictive relationships*

Correlations between behavioral syndromes and patterns of psychometric or neuroscience findings raise questions about their causal relationships. Do biological and social consequences of the behavioral syndromes cause the abnormalities of psychological and neurobiological functioning that are documented in the research findings? Or do the abnormalities of psychological and neurobiological functioning that are documented in the research findings predispose to development of the behavioral syndromes? While empirical research does not provide causal information, it can illuminate temporal and predictive relationships from which causal relationships may be inferred.

Archival studies found elevations in the MMPI and MacAndrew scale scores of young individuals who later became abusers of psychoactive substances to be similar to the score elevations of psychoactive substance abusers. The results for subjects who were tested again at the time of substance abuse treatment correlated well with their premorbid test results [249–251]. In the case of field dependence, early studies determined that this tendency antedated the onset of drinking [252,253]. A number of archival, longitudinal, and prospective studies have found several premorbid personality traits to be associated with the later development of psychoactive substance abuse, including: unconventionality or nonconformity, rejection of societal values, alienation, social anxiety, pessimism, depression, sensation-seeking, impulsivity, extraversion, aggressiveness, emphasis on independence, and labile or erratic mood [105,249,254–289]. A recent prospective population-based study [55] found that subjects with a diagnosis of past-year problem gambling, ethanol dependence, cannabis dependence, or nicotine dependence at age 21 years were more characterized by anxiety, alienation, low stress tolerance, anger or aggressiveness, impulsivity, risk-taking, and nonconformity measured at age 18 years than were control subjects who did not have a past-year addictive disorder at age 21 years. Vanyukov's review of research up to 2003 [220] concluded that variation in the liability to substance use disorder is shared in common with personality phenotypic variation that predates the initiation of substance use.

Similar questions about causal relationships have arisen around findings of lifetime comorbidity between the behaviorally defined syndromes that we have been considering and other psychiatric disorders. Retrospective epidemiologic surveys have consistently found that in respondents with comorbid substance use disorders and other psychiatric disorders, the onset of the other psychiatric disorders is typically 5–10 years earlier than is the onset of the substance use disorders [290–292,87,293,86]. The WHO International Consortium in Psychiatric Epidemiology found significant predictive associations (odds ratios greater than 1.0 and 87% statistically significant at the .05 level) between temporally primary mental disorders and the subsequent first onset of psychoactive substance use, problems among users, and dependence among problem users [294,295]. The results of prospective studies up to 2004 [reviewed in 220, 296] similarly supported the temporal and predictive primacy of anxiety, mood, and attention deficit disorders when comorbid with psychoactive substance abuse. Subsequent studies [297–299] found that deficits in affect and self-regulatory functioning usually precede and increase the risk for development of substance use problems, though the data are more robust for anxiety disorders than they are for depression.

Studies of temporal and predictive relationships between bulimia, pathological gambling, or sexual addiction and other

psychiatric disorders are still scarce. A few studies found that anxiety disorders that were comorbid with bulimia usually began in childhood before the onset of the eating disorder [108,300,301], and a twin study identified a common genetic factor that influences liability to anxiety, depression, and eating disorder symptoms [302]. One epidemiologic study with pathological gambling found that among problem gamblers with comorbid depression or anxiety, onset of the depression or anxiety usually preceded onset of gambling [51].

1.1.7. *What to conclude?*

The preceding blitz-review indicates that the findings of scientific research accord with each of the predictions that were generated from the hypothesis that addictive disorders share an underlying biopsychological process. The hypothesis is thereby confirmed. In accord with this confirmation, Krueger and colleagues [303,304] proposed that co-occurrence of common psychiatric disorders at greater than chance rates suggests that the disorders are indicators of latent factors or hypothetical core psychopathological processes that underlie putatively separate conditions. The foregoing review ventured beyond comorbidity data to include a range of research that provides substantial support for the hypothesis that addictive disorders have in common an underlying biopsychological process. The discussion of temporal and predictive relationships then indicated that, for the most part, the abnormalities of psychological and neurobiological functioning that are documented in the research findings are temporally primary to and predictive of the behavioral syndromes that we have been considering. From this we can infer that the underlying biopsychological process that these conditions share precedes their onset, and is not simply a consequence of the behavior or life-style that characterizes them.

Our next step is to begin mining the neurobiology research literature for ore that can then be sifted, refined, and eventually fashioned into a neurobiological theory of the process that underlies addiction. But before we proceed any further, we need to define our key terms.

1.2. *Definitions*

1.2.1. *Addiction (or addictive disorder)*

Presenting a theory of addiction without a clear and meaningful definition of the term is a recipe for misunderstanding. The definition is a matter of controversy, and DSM-IV [305] does not employ the term at all. However, we can begin to formulate a definition by identifying the key features of drug addiction (in DSM-IV, psychoactive substance dependence), the paradigm of addictive disorders.

We now recognize that neither tolerance nor withdrawal is necessary or sufficient for a diagnosis of drug addiction [305]. These processes reflect the natural adaptive responses of our bodies' cells to a changed chemical environment, regardless of whether the chemicals had been used addictively. Extensive exploration has led me to conclude that the characteristics that are both necessary and sufficient for identifying a pattern of drug use as drug addiction are (1) recurrent failure to control the use of one or more drugs, and (2) continuation of drug use despite significant harmful consequences. (''Recurrent failure to control'' means not that addicted individuals invariably lose control when they use drugs, but that their predictions that they would remain in control of their drug use have repeatedly proved to be unreliable.)

These key features distinguish drug addiction from drug use that does not constitute addiction. However, they do not distinguish addictive behavior from compulsive behavior or from impulsive behavior. These latter distinctions depend on the behaviors' motivational functions. Compulsive behavior functions to reduce anxiety or other painful affects, but by definition it does not produce pleasure or gratification [305]. It is motivated by negative reinforcement (i.e., the alleviation of aversive stimulus conditions). Impulsive behavior functions to produce pleasure or gratification but not to reduce painful affects. It is motivated by positive reinforcement. Finally, addictive behavior functions both to produce pleasure and to reduce painful affects. It is motivated by both positive and negative reinforcement.

When we combine this distinctive dual motivational function of addictive behavior with the key features that distinguish drug addiction from ordinary drug use, we arrive at a workable, behaviorally nonspecific definition of addiction: *addiction is a condition in which a behavior that can function both to produce pleasure and to reduce painful affects is employed in a pattern that is characterized by two key features: (1) recurrent failure to control the behavior, and (2) continuation of the behavior despite significant harmful consequences*.

1.2.2. *Addictive process*

The *addictive process* is the term by which I propose that we designate the underlying biopsychological process that addictive disorders are hypothesized to share. It can be defined operationally as an enduring, inordinately strong tendency to engage in some form of pleasure-producing behavior in a pattern that is characterized by impaired control and continuation despite significant harmful consequences. The class of addictive disorders includes psychoactive substance addiction, bulimia, pathological gambling, shopping or buying addiction,[2] sexual addiction, and other enduring conditions in which a behavior that can function both to produce pleasure and to reduce painful affects is employed in a pattern that is characterized by two key features: (1) recurrent failure to control the behavior, and (2) continuation of the behavior despite significant harmful consequences. When we talk about addictive disorders as a group, what we are talking about is not a collection of distinct disorders, but an underlying process that can be expressed in one or more of various behavioral manifestations.

Thus, we can recognize that two sets of factors shape the development of an addictive disorder: those that concern the underlying addictive process, and those that relate to the selection of a particular substance or behavior as the one that is preferred for addictive use. The following discussion focuses on the former, which is the more important both theoretically and practically.

[2] Addiction or addictive disorder is a more suitable designation for this condition than is compulsion or compulsive disorder, since the symptomatic behavior usually tends to be associated with pleasure or gratification as well as alleviation of anxiety or other affective discomfort.

2. The addictive process

In the course of reviewing evidence that psychoactive substance use disorders, bulimia, pathological gambling, and sexual addiction share an underlying biopsychological process, we noted that neuroscience research has demonstrated that a shared vulnerability underlies the abuse of psychoactive substances, has begun to delineate the neurobiological processes that constitute this vulnerability, and has expanded the realm of this shared vulnerability to include pathological gambling and pathological use of food and sex, as well as psychoactive substance abuse. These developments introduce us to the possibility of formulating a neurobiological theory of the addictive process. We begin the project of actualizing this possibility with a comprehensive but selective review of the neurobiology literature, in search of raw material for such a theory. The selection process is guided by two principles, generality and specificity. To be included in this review, a research finding or idea must be relevant to addictive disorders in general, not just to a particular psychoactive substance or behavior. Findings and ideas that concern a particular psychoactive substance or behavior and do not generalize to the rest may influence which substance or behavior a person who is predisposed to developing an addictive disorder (by virtue of an addictive process) is most inclined to use addictively, but they are unlikely to participate significantly in the genesis of that predisposition. Inclusion in this review additionally requires that a research finding or idea be specific to addictive patterns of using a substance or engaging in a behavior—as distinct from being applicable to all instances of a behavior, regardless of whether they instantiate an addictive disorder. In other words, the object of our quest is not the neurobiology of what makes cocaine or sex pleasurable for people in general, but the neurobiology of what makes the drive for cocaine or sex so much more inexorable for a person who uses it addictively.

The addictive process can be understood to involve impairments in three functional systems: motivation-reward, affect regulation, and behavioral inhibition.[3] Impaired motivation-reward exposes addicts to unsatisfied states of irritable tension, emptiness, and restless anhedonia. In the context of aberrant motivation-reward function, behaviors that are associated with activation of the reward system are more strongly reinforced (via both positive and negative reinforcement) than they otherwise would have been. Impaired affect regulation renders addicts chronically vulnerable to painful affects and emotional instability. In the context of impaired affect regulation, behaviors that are associated with escape from or avoidance of painful affects are more strongly reinforced (via negative reinforcement) than they otherwise would have been. Impaired behavioral inhibition increases the likelihood that urges for some form of reinforcement (negative, positive, or both) in the short term will override consideration of longer term consequences, both negative and positive. When motivation-reward and affect regulation are impaired, impaired behavioral inhibition means that urges to engage in behaviors that are associated with both (a) activation of the reward system, and (b) escape from or avoidance of painful affects, are extraordinarily difficult to resist, despite the harmful consequences that they might entail.

We now embark on a quest to identify candidate neurochemical substrates for the impairments in motivation-reward, affect regulation, and behavioral inhibition that could contribute to an addictive process. (Candidate neuroanatomical substrates for these impairments are considered in a separate publication, as are genetic and environmental factors that shape the development of an addictive process.) Our initial assumption is that no single factor is either necessary or sufficient, and that an addictive process can result from any of a variety of multi-factor combinations. The addictive process that characterizes a person is the unique outcome of individual genetic and environmental influences. But among the array of uniquenesses, a good set of theories will enable us to recognize some patterns.

2.1. *Aberrant motivation-reward*

2.1.1. *Dopamine (DA)*

Administering any drug of abuse [306–323] or engaging in eating (especially sweets) [324–328], gambling [329,330], or sexual behavior [330–334] is associated with increased intrasynaptic levels of dopamine (DA) in the nucleus accumbens (NAc). Accumbal DA was initially thought to be the neurobiological correlate of reward or pleasure. However, recent research has clarified DA's function in signaling the incentive salience of events (including rewarding, aversive, novel, and unexpected stimuli), in driving motivated behavior, in predicting reward or non-reward, and in facilitating consolidation of memory for salient events [335–349].

Five DA receptors have been identified, all of which are G protein-coupled. They can be classified into two families: D_1 and D_5 receptors that stimulate adenylate cyclase to produce cyclic AMP; and D_2, D_3, and D_4 receptors that inhibit the production of cyclic AMP [350]. Most D_1 and D_5 receptors are located postsynaptically, while most D_2, D_3, and D_4 receptors are located presynaptically [351–353]. The functions of D_1, D_2, and D_3 receptors primarily concern motivation and reward, while D_4 and D_5 receptors are more involved with behavioral inhibition (and consequently will be discussed in the Section 2.3).

2.1.2. *DA D_1 receptors*

Activation of DA D_1 receptors has been found to be associated with ethanol reward [354], psychostimulant reward [355,356], food reward [357], cocaine-induced locomotor activity [355,358], reinstatement of cue-induced cocaine-seeking behavior [359,360], reinstatement of extinguished cocaine-conditioned place preference [356], and enhancement of food palatability [361]. Activation of D_1 receptors has been found also to be critically involved in enduring cell-surface and intracellular

[3] At this point, motivation-reward, affect regulation, and behavioral inhibition are heuristic constructs that provide an intuitively meaningful framework within which relevant research findings may be organized. As abstractions from the nonlinear system of an organism's neurobiology, they are more clearly delineated from one another than are the processes to which they refer. The organization of research findings that this framework enables can be expected to facilitate the eventual formulation of operational definitions for these terms.

changes that follow administration of psychostimulants, other drugs of abuse, and palatable food. Changes at the cell surface that are associated with activation of D_1 receptors include psychostimulant-induced externalization of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs) with promotion of long-term potentiation, which facilitates reward-related learning [362], and dendritic remodeling of medium spiny neurons in the NAc, an adaptive response to chronic cocaine exposure that is linked to addictive patterns of behavior [363,364]. Intracellular changes that are triggered by activation of D_1 receptors include induction of c-Fos, FosB, Fra-2 and JunB by acute cocaine exposure, induction of ΔFosB by repeated cocaine administration in both the NAc and caudate-putamen (CPu), and cocaine-induced expression of olfactory-specific G protein α (Gαolf), β-catenin, and BDNF in the NAc and CPu [364–366]. The processes that are involved in the dendritic remodeling of medium spiny neurons are integrated by the c-Fos that has been induced by activation of D_1 receptors [364]. Zhang et al. [366] demonstrated that cocaine-induced expression of Fos family genes, including c-Fos, FosB, and Fra-2, is mediated by activation (via phosphorylation) of extracellular signal-regulated kinase (ERK), which in turn is mediated by D_1 receptors. Valjent et al. [367] found that activation of ERK is induced not only by administration of cocaine, but also by administration of morphine, nicotine, or tetrahydrocannabinol (THC). Activation of D_1 receptors by administration of ethanol [368], cocaine [369], and palatable food [370] also results in phosphorylation at threonine-34 (T35) of the intracellular messenger DARPP-32 (dopamine and cyclic 3′, 5′ adenosine monophosphate-regulated phosphoprotein), a process that Zachariou et al. [369,371] found to be a critical mediator of cocaine's rewarding effects.

The foregoing findings provide valuable information about the relationship between DA D_1 receptors and reward, but they do not necessarily enhance our understanding of addiction. The latter depends less on knowing what makes a particular substance or behavior rewarding, than it does on knowing what makes some people more susceptible than are others to developing addictive patterns of using a rewarding substance or engaging in a rewarding behavior. So how might D_1 receptors be involved in an addictive process? One possibility is suggested by Haney et al.'s [372] findings that maintenance administration of the selective D_1 antagonist ecopipam to human subjects enhanced both self-administration and subjective effects of cocaine, compared to maintenance on placebo. These findings are consistent with the results of preclinical studies in which doses of cocaine that had been maintaining relatively low levels of self-administration maintained higher levels following chronic exposure to a D_1 antagonist [373–376]. These behavioral shifts were associated with an increased density of D_1 receptors [377–379] and enhanced D_1 receptor sensitivity within the NAc [380]. Considered together, these data suggest that maintenance administration of a D_1 antagonist results in D_1 receptor supersensitivity, which increases the reinforcing and subjective effects of cocaine. Since the influence of D_1 receptor supersensitivity on the reward effects of cocaine is almost certainly mediated by the increase in intrasynaptic DA that follows cocaine administration, D_1 receptor supersensitivity is likely to have the same influence on any substance or behavior that increases the intrasynaptic availability of DA—which includes every substance and behavior that is used addictively. Thus could D_1 receptor supersensitivity, however it may develop, contribute to an addictive process.

2.1.3. *DA D_2 receptors*

Preclinical studies in which D_2 agonists or antagonists were administered have yielded a complex array of results. Administration of the D_2/D_3 agonist quinpirole was reported to eliminate rats' preference for a highly palatable chocolate food [361], to block expression of an established cocaine-conditioned place preference (CPP), and to induce place aversions to the cocaine-paired side of the conditioning apparatus following extinction of the established cocaine preference [356]. However, it was reported also to evoke reinstatement of self-administration after extinction in both cocaine-trained and heroin-trained rats [381]. The D_2/D_3 partial agonist terguride was found to reduce self-administration of cocaine and of food [382]. Administration of D_2 receptor antagonists was reported to reduce ethanol self-administration [383], to inhibit reinstatement of cue-induced cocaine-seeking behavior [384], and, in the case of raclopride, to potentiate reinstatement of cue-induced cocaine-seeking behavior with a low dose and to attenuate it with a high dose [359]. According to a model that was presented by Welter et al. [385], D_2 receptors tonically inhibit an inhibitory signaling pathway that decreases the cocaine-induced locomotion, blocks the c-Fos induction that cocaine typically triggers, and attenuates cocaine-induced CPP. To the extent that D_2 receptor activity decreases, the inhibitory pathway is released to block these characteristic responses to cocaine.

In a more direct and readily interpretable vein, clinical studies have indicated an association between alcoholism and decreased D_2 receptors [386–388]. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies of addictive users of ethanol, cocaine, methamphetamine, and heroin have revealed reductions of D_2 receptor density in the ventral striatum that persist long after detoxification [389–392]. Studies with pathologically obese subjects found reductions in striatal D_2 receptors that were similar to those observed in studies with drug addicts, and additionally found an inverse relationship between the subjects' body mass index and their D_2 receptor levels [228,393]. An initial hypothesis that low levels of D_2 receptors predispose subjects to search for psychoactive substances as a means to compensate for the consequent decrease in reward circuit activation [224,394,395] was expanded, in response to the studies with obese subjects, by replacing ''psychoactive substances'' with the more general term, ''reinforcers'' [396].

This hypothesis has been supported both by preclinical research and by research with nonclinical populations. Rats that were high responders to novelty as measured by locomotion in an open field and thus were more likely to acquire amphetamine self-administration compared to low-responding rats [397] were found to have lower D_2 receptor levels in the NAc [398], and an inbred ethanol-preferring strain of rats was found to have lower D_2 receptor binding than did ethanol-nonpreferring rats [399–402]. Virally mediated overexpression of D_2 receptors was associated with marked reductions in ethanol preference and intake in both ethanol-preferring and

ethanol-nonpreferring rats, which reverted to status quo ante as the D_2 receptor density returned to baseline [402,403]. A study with rhesus macaques found that baseline D_2 receptor availability was negatively correlated with rates of cocaine self-administration [404]. And mice that showed an increased propensity to ethanol sensitization were found to have higher levels of D_2 receptor binding in localized brain areas than did mice that showed less propensity to sensitization [405]. Meanwhile, Yoder et al. [406] reported a study in which a low (sub-intoxicating) dose of ethanol was administered to non-addicted human subjects. They found that baseline availability of D_2 receptors in the left NAc was correlated with peak perceived "intoxication" and marginally correlated with peak perceived "high". The more D_2 receptors that were available for binding in the sober state, the more likely was the subject to feel "intoxicated" and "high" from a low dose of ethanol. The authors speculated that individuals with fewer D_2 receptors would require larger quantities of ethanol to experience the same subjective high. Similarly, Volkow et al. [407,408] reported that baseline measures of striatal D_2 receptors in non-addicted human subjects predicted their subjective responses to the reinforcing effects of intravenous methylphenidate (MP). Subjects who described MP as pleasant had significantly lower levels of D_2 receptors than did subjects who described it as unpleasant. The authors hypothesized that every person's brain has an optimal range of D_2 stimulation by MP that is experienced as pleasant, below which administration of MP is perceived as neutral or insufficient, and above which administration of the drug is experienced as aversive. The authors also noted that subjects who reported the effects of MP as pleasant, as do most cocaine abusers [409], had D_2 receptor levels similar to those that were previously reported to characterize cocaine abusers [410,411]. They interpreted these results as suggesting that low D_2 receptor levels in cocaine abusers may have antedated their use of cocaine and may have contributed to their shift from cocaine use to cocaine addiction.

While consideration of genetic factors that shape the development of an addictive process is in general being deferred to another publication, no discussion of the relationship between DA D_2 receptors and addiction would be complete without at least mentioning the findings that concern associations between the A1 allele of the D_2 receptor gene Taq1A polymorphism and alcoholism [412–417], cocaine addiction [418], psychostimulant addiction [419], cigarette smoking [420,421], pathological gambling [422–424], and exaggerated reward value of food [425,426]. Interestingly, a number of studies have found that human subjects who carry the A1 allele of the D_2 receptor gene Taq1A polymorphism have significantly reduced D_2 receptor density [427–432].

2.1.4. *DA D_3 receptors*

Research with DA D_3 receptors is a relatively recent phenomenon. While findings that D_3 receptors are located primarily in limbic regions led to speculation that D_3 receptors might be involved in addiction, their structural similarity to D_2 receptors made them elusive targets for molecular sharpshooters. Only when new compounds with high selectivity for central D_3 receptors were synthesized and characterized was research with these receptors able to proceed [433].

The era of addiction research with D_3 receptors was launched by the publication in 1999 of Pilla et al.'s [434] report that BP 897, a D_3 antagonist [435], inhibited cue-induced reinstatement of drug-seeking behavior by cocaine-trained mice that had undergone response extinction. These findings were greeted by a flurry of optimistic response [436–438], and were later extended to rats and rhesus monkeys [439–441]. Other studies found that BP 897 blocked the expression (but not the acquisition) of amphetamine-conditioned activity [442,443], reduced both cue-induced ethanol-seeking behavior and relapse-like drinking [444], and inhibited nicotine-conditioned locomotor responses [445]. Another selective D_3 antagonist, SB-277011-A, was found to block reinstatement of cocaine-seeking behavior that had been triggered by cocaine-priming [446], to attenuate cue-induced reinstatement of cocaine-seeking [384,441,447], to block stress-induced reinstatement of cocaine-seeking [448], and to lower the amount of work that rats would perform for a given dose of cocaine while raising the lower limit of the cocaine dose that would sustain a given amount of work [449]. SB-277011-A similarly was found to reduce oral self-administration of ethanol [444,450,451], cue-induced reinstatement of ethanol-seeking behavior [444,450], nicotine self-administration [452], reinstatement of nicotine-seeking behavior [453], nicotine-induced CPP [454], and the acquisition and expression of heroin-induced CPP [455]. The D_3 receptor antagonist NGB 2904 was found to inhibit cue-induced reinstatement of drug-seeking behavior by cocaine-trained rats [441]. Interestingly, SB-277011-A was found to potentiate the pharmacological MRI response to D-amphetamine [456], and NGB 2904 was found to enhance amphetamine-stimulated locomotion in wild-type mice but to have no measurable effect in mice that had been genetically modified so as not to develop D_3 receptors (D_3 receptor knockout mice) [457], effects that intuitively seem to contradict the other D_3 receptor antagonist findings. However, since NGB 2904 by itself stimulated spontaneous locomotion in wild-type mice while having no measurable effect in D_3 receptor knockout mice [457], the effects of SB-277011-A and NGB 2904 on response to amphetamine may have pertained more to amphetamine's stimulant effect on locomotion than to its reinforcing or addictive properties.

Addiction-related research with D_3 receptors that does not involve antagonists has been relatively rare. In a study that demonstrated the role of DA D_1 receptors in activating ERK and inducing c-Fos in response to acute cocaine administration, Zhang et al. [366] also showed that D_3 receptors have opposite effects on the same intracellular systems. Meanwhile, Boyce-Rustay and Risinger [458] found no difference between D_3 knockout and C57BL/6J mice in ethanol CPP, in two-bottle drinking preference, or in operant ethanol self-administration, from which they inferred that elimination of D_3 receptor function has little influence on ethanol reward or intake. The apparent discrepancy between this finding and those that were reviewed in the preceding paragraph probably reflects the difference between acute inactivation of a functioning receptor system and congenital absence of a receptor system, for which the postnatal plasticity of the mammalian brain can to some extent compensate.

The opposite effects of D_1 and D_3 receptors on ERK and c-Fos, as well as on dynorphin, neogenin, and synaptotagmin VII

[366], may suggest that D_3 receptors' potential involvement in an addictive process would similarly be opposite to that of D_1 receptors—i.e., that an addictive process could be facilitated by D_3 hyposensitivity. However, D_3 receptor antagonists inhibit processes that are associated with addiction, which suggests that an addictive process could be potentiated by D_3 receptor supersensitivity.

2.1.5. *Serotonin (5-HT)*

Serotonin (5-hydroxytryptamine, or 5-HT) activity is associated with behavioral inhibition [459,460], emotional stabilization [461], appetite modulation [462], sensory reactivity [463,464], pain sensitivity [464,465], and sleep, sexual behavior, and cognitive function [466,467]. At least 14 subtypes of 5-HT receptors have been cloned and identified. The 5-HT_1 class is inhibitory both pre- and post-synaptically, and reduces adenylate cyclase activity via Gi activation. The excitatory 5-HT_2 class is predominantly postsynaptic, and activates phospholipase C via Go. The 5-HT_3 receptor exerts its excitatory effects by acting as an ion channel. And the 5-HT_4, 5-HT_5, and 5-HT_6 classes all activate adenylate cyclase via Gs [468].

Serotonin does not directly participate in motivation-reward, but exerts influence through its effects on the DA system. Application of 5-HT onto dopaminergic neurons from the VTA increased their firing rate *in vitro*, an effect that was attributed to action of 5-HT on 5-HT_2 receptors [469]. However, increased release of DA in the NAc (presumably of VTA origin) that was elicited by electronic stimulation of the dorsal raphe nucleus (DRN) *in vivo* was counteracted by the selective 5-HT_3 antagonists ondansetron and (*S*)-zacopride [470].

In a study with pathological gamblers, Pallanti et al. [471] found that direct postsynaptic serotonergic receptor stimulation with *meta*-chlorophenylpiperazine (*m*-CPP), a mixed serotonergic agonist with highest affinity for 5-HT_{2C} receptors, elicited an enhanced prolactin response that the authors interpreted as a hypersensitive postsynaptic serotonergic function. In addition, the pathological gambling subjects reported that the ''high'' sensation that they experienced in response to *m*-CPP was similar to the one that they experienced while gambling, a result reminiscent of alcoholic subjects' reports that their *m*-CPP-induced experience was comparable to their experience with ethanol. The authors speculated that increased sensitivity to 5-HT stimulation, shared by the other addictive diseases, could be a vulnerability factor for addiction.

The most well researched and apparently most significant component of the serotonergic system that influences motivation-reward is the 5-HT_{1B} receptor, a G_i-coupled receptor that can be located on the axon terminals of many types of neuron. Axon terminals of γ-aminobutyric acid (GABA) neurons that project from the NAc shell to the VTA contain 5-HT_{1B} receptors that, when activated, inhibit GABA release. Since GABA that is released in the VTA inhibits local dopaminergic neurons, inhibition of GABA release disinhibits the mesolimbic dopaminergic neurons and thus potentiates the DA-increasing effects of cocaine [472–475] and of other rewarding (or salient) substances and behaviors. Up-regulation of 5-HT_{1B} receptors on the axon terminals of NAc shell GABAergic neurons could then contribute to a person's vulnerability to developing an addictive disorder.

A study that was designed to measure the effect of chronic cocaine injections on 5-HT_{1B} mRNA expression in the NAc shell [476] found that the latter was increased not only in rats that received cocaine but also in control rats that received injections of vehicle—and interestingly, only in those control rats that were housed with cocaine-treated rats. The authors interpreted this unexpected finding to have been mediated by social stress that the control rats experienced through interaction with their cocaine-treated cagemates.

2.1.6. *Norepinephrine (NE)*

Norepinephrine (NE) is both a neurotransmitter that is produced primarily by the locus coeruleus (LC) in the brain stem, and a hormone that is produced by the adrenal medulla. It is synthesized from DA by the action of the enzyme dopamine beta hydroxylase (DBH). NE as well as epinephrine (adrenalin) is a ligand for adrenergic receptors (adrenoceptors), G protein-coupled receptors that can be either α-adrenergic or β-adrenergic. The group of α-adrenoceptors contains two subgoups, α_1 and α_2, each of which has three subsubgroups: α_{1A}, α_{1B}, and α_{1D}; and α_{2A}, α_{2B}, and α_{2C}. The group of β-adrenoceptors contains three subgoups, β_1, β_2, and β_3. The brain noradrenergic system consists of two main ascending projections: the dorsal noradrenergic bundle (DNB), which originates in the LC and projects to the hippocampus, cerebellum, and forebrain; and the ventral noradrenergic bundle (VNB), which arises in a number of nuclei of the pons and medulla and projects to the hypothalamus, midbrain, and extended amygdala [477].

Evidence for the involvement of NE in motivation-reward has emerged from studies of self-administration, CPP, reinstatement, and locomotor activation. Ethanol self-administration was found to be attenuated by lofexidine, an agonist at the α_{2A} autoreceptor that reduces NE transmission, and to be enhanced by blockade of this receptor [478]. While wild-type mice readily self-administer cocaine or morphine orally, α_{1B} knockout mice were found not to do so [479]. NE transporter (NET) knockout mice lack the reuptake function that terminates the action of NE and consequently have elevated levels of extracellular NE. Such mice have been reported to self-administer cocaine at an average rate that is four times that of wild-type mice, suggesting that a chronic NET deficiency decreases the reinforcing properties of cocaine [480]. Chronically elevated NE levels could conceivably dysregulate the dopaminergic brain reward system, perhaps via downregulation of presynaptic DA transmission or via postsynaptic D_2/D_3 supersensitivity [481].

Establishment of CPP for opiates seems to require intact noradrenergic function. Clonidine, an α_{2A} agonist that decreases NE release by activating inhibitory autoreceptors, was reported to disrupt the establishment of heroin CPP in rats, presumably by inhibiting NE release [482]. Morphine CPP in mice was shown to be attenuated by either clonidine or prazosin (an α_{1A} antagonist) and to be increased by yohimbine (an α_{2A} antagonist) [483,484]. Furthermore, both DBH knockout mice, which are incapable of producing NE, and α_{1A} knockout mice failed to express a CPP over a wide range of morphine doses [479,485].

Noradrenergic function appears to be critical also in stress-induced reinstatement of drug-seeking for multiple classes of

abused drugs. Administration of α_{2A} agonists has been found to attenuate stress-induced reinstatement of ethanol-seeking behavior [486], cocaine-seeking behavior [487,488], and heroin-seeking behavior [489,490]. DBH inhibitors that block NE synthesis were shown to attenuate reinstatement of amphetamine self-administration and opiate self-administration [491]. Conversely, blockade of α_{2A} autoreceptors with either yohimbine or RS-79948 was reported to reinstate cocaine-seeking in the absence of any stressors [492]. In addition, the reinforcing properties of morphine, as reflected in the CPP paradigm, seem to depend on NE. Chronic treatment with venlafaxine, a dual NE/5-HT reuptake inhibitor, was reported to attenuate the reacquisition of morphine CPP by a priming injection of morphine [493]. And selective depletion of medial prefrontal cortex (PFC) noradrenergic afferents was found to abolish the reinstatement of an extinguished morphine CPP that had been produced by a priming injection of morphine [494], as well as the reinstatement of an extinguished amphetamine CPP that had been produced by a priming injection of amphetamine [495].

Finally, locomotor activation that is induced by psychostimulants or by opiates seems to involve and in some instances to depend on NE. Administration of prazosin, either systemically or directly into the PFC, has been found to attenuate the acute locomotor responses and sensitization that are produced by psychostimulants [479,496–503] or by morphine [479,496,504]. The locomotor activation that is induced by morphine was shown to be decreased also by the nonspecific α-adrenergic antagonist, phenoxybenzamine [505,506] and by pre-treatment with FLA-63, a DBH inhibitor [506]. LC lesions were found to attenuate amphetamine-induced locomotion [507], while the locomotor response to psychostimulants was reported to be amplified by blockade of α_{2A} inhibitory autoreceptors, which increases levels of extracellular NE [508], and by the non-selective β-adrenergic antagonist propranolol [509]. Additional evidence for NE mediation of drug-induced locomotion comes from studies in which NE function was modified genetically. α_{1B} knockout mice were found to be refractory to both psychostimulant-induced and morphine-induced locomotor activity and sensitization [479,496,500]. DBH knockout mice have been reported not to develop morphine-induced locomotion, a deficit that is partially reversed by pharmacological restoration of NE or by viral-mediated reexpression of DBH in the DNB or VNB [485]. Finally, genetic ablation of the NET was found to increase the locomotor response to psychostimulants [481].

Weinshenker and colleagues [510] demonstrated that DBH knockout mice were hypersensitive to the rewarding and locomotor effects of amphetamine. Further work with DBH knockout mice [511] found that they were at least as hypersensitive to the aversive effects of cocaine and amphetamine as they were to their rewarding effects. They even developed conditioned place aversion to cocaine, which control mice could not be convinced to do. Other studies have reported that DBH knockout mice are hypersensitive to the aversive effects of ethanol [512] and that mice that specifically lack NE in the PFC show a similar place aversion to amphetamine [495]. These findings can be understood in light of the relationship between the NE and DA systems. The LC noradrenergic system regulates the activity of the ascending DA pathways [496,513]. They meet in the VTA, where noradrenergic neurons modulate the DA cell firing pattern via excitatory postsynaptic α_1-adrenoceptors [514]. The LC noradrenergic system also regulates the mesencephalic dopaminergic system indirectly, via the PFC. DA release in the PFC is regulated by local noradrenergic nerve terminals [515], and electrical stimulation of the LC neurons increases both extracellular DA and NE in the PFC [516]. When NE release is blocked, DA release is similarly attenuated. If the NE block is chronic, the DA system gradually compensates by up-regulating high-affinity state postsynaptic DA receptors (i.e., increasing their density) by a factor of 3–6 [517]. This process results in hypersensitivity to psychostimulants and to any other substance (or behavior) that increases intrasynaptic DA levels.

In the course of a comprehensive review of the role of NE in drug addiction, Weinshenker and Schroeder [517], reassessed the operation of disulfiram from the perspective of its function as a potent inhibitor of DBH. While the aversiveness of ethanol after disulfiram administration had traditionally been attributed to the accumulation of acetaldehyde that results from disulfiram's inhibition of the enzyme acetaldehyde dehydrogenase, such an explanation could not account for the effectiveness of disulfiram in treating cocaine addiction when ethanol abuse is not comorbid [518–520]. Amit et al. [521] compared the efficacy of disulfiram in decreasing ethanol intake with that of calcium carbamide and of FLA-63, and also assessed the effect that each of these compounds had on acetaldehyde levels following ethanol injection. Administration of disulfiram and FLA-63, both DBH inhibitors, significantly reduced ethanol intake. Calcium carbamide, which had the greatest effect on acetaldehyde levels following ethanol injection, had the least effect on ethanol intake. FLA-63 had the least effect on acetaldehyde levels, but was the most potent suppressor of ethanol intake.

These research findings suggest that potential contributors to an addictive process could include blockade, hyposensitivity, or excessive downregulation of α_{2A} autoreceptors, and chronic deficiency or malfunction of NE transporters. The central factor in a potential relationship between the noradrenergic system and addiction seems to be an increased level of extracellular NE and its effects on the dopaminergic system. The most frequent and significant cause (or correlate) of increased levels of extracellular NE is stress. The relationship between the noradrenergic system, stress, and the addictive process will be addressed in Section 2.2.

2.1.7. *Endorphins and opioid receptors*

Administering opiate drugs directly stimulates opioid receptors in the brain [522]. Administering any other drug of abuse [519–528] or engaging in eating (especially sweets) [226,244,529–533], gambling [329], or sexual behavior [331,534,535] is associated with the release of endogenous opioids. Studies that measured μ opioid receptors in cocaine abusers showed significant increases in receptor availability that were interpreted to reflect decreased endogenous opioid release [536]. CSF β-endorphin levels in bulimic subjects were found to be lower than in controls [537]. Low baseline levels of β-endorphin and consequent μ opioid receptor hypersensitivity would constitute a vulnerability to addictive engagement in

any behavior that results in stimulation of μ opioid receptors. However, these cross-sectional studies do not address the question of whether the decreased β-endorphin levels and increased μ opioid receptor availability preceded or developed subsequent to the onset of the subjects' disorders.

2.1.8. *Dynorphin*

Dynorphin is an endogenous opioid peptide that functions as an agonist at κ opioid receptors. Dopaminergic VTA neurons that project to the NAc contain κ opioid receptors on presynaptic axon terminals in the NAc and also on cell bodies and dendrites in the VTA. Action of dynorphin on these κ opioid receptors inhibits the release of DA, thus attenuating the reward-salience effects of substances and behaviors that can be used addictively, and moreover generating dysphoria [538–540]. Dynorphin expression is induced in the NAc and related striatal regions after exposure to drugs of abuse, an effect that seems to be mediated by the gene transcription factor CREB (cAMP response element binding protein) [540]. Drugs of abuse also induce the transcription factor ΔFosB, which targets the gene that encodes dynorphin and decreases its expression [541]. Variations in CREB, ΔFosB, or the balance between them that result in decreased dynorphin expression could contribute to an addictive process.

2.1.9. *γ-Aminobutyric acid (GABA)*

γ-Aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the central nervous system. Three classes of GABA receptors have been identified: $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ and $GABA_C$ receptors are ionotropic receptors (ligand-gated ion channels). The binding of a GABA molecule to a $GABA_A$ or $GABA_C$ receptor directly triggers the opening of a chloride ion-selective pore that allows intracellular and extracellular chloride to equilibrate, thereby hyperpolarizing the neuron and inhibiting its firing [542,543]. In addition to an active binding site at which GABA binds, $GABA_A$ receptors have specific allosteric sites that bind benzodiazepines, barbiturates, ethanol, picrotoxin, neuroactive steroids, furosemide, and inhalation anesthetics [544]. $GABA_C$ receptors seem to be variants of $GABA_A$ receptors that are insensitive to the typical allosteric modulators of $GABA_A$ receptors. $GABA_B$ receptors are metabotropic (G protein-coupled) receptors that can open transmembrane potassium channels, suppress calcium channels, and reduce the activity of adenylate cyclase [545–547]. They too exert inhibitory effects when activated.

2.1.10. *$GABA_A$ receptors*

$GABA_A$ receptor antagonists that bind at or near the active site, such as picrotoxin and bicuculline, have been found to reduce self-administration of ethanol [548–552] and cocaine [553]. Nowak et al. [550] reported that microinjections of picrotoxin or of bicuculline into the VTA resulted in decreases in ethanol consumption, but that microinjections in regions outside the VTA failed to decrease ethanol intake. This neuroanatomical specificity could reflect the VTA's role in the dopaminergic reward system. VTA dopaminergic neurons that project to the NAc are under tonic inhibitory control mediated by $GABA_A$ receptors, and injections of picrotoxin into the VTA were found to increase DA release in the NAc [554]. Nowak et al. [550] hypothesized that $GABA_A$ antagonists, by producing effects on the VTA DA system similar to those of ethanol, may enable the animal to obtain the same rewarding effects while consuming less ethanol. Consistent with this hypothesis, administration of picrotoxin or of bicuculline during acquisition of ethanol-induced CPP was found to increase the magnitude of ethanol-induced CPP relative to findings for vehicle-treated controls [555], and simultaneous microinfusion of the D_2 antagonist eticlopride into the VTA and the $GABA_A$ receptor antagonist SR 95531 into either the bed nucleus of the stria terminalis (BNST) or NAc was found to completely attenuate the reduction in ethanol self-administration that was observed with eticlopride alone [383].

Partial inverse agonists that bind at the benzodiazepine site on the $GABA_A$ receptor also have been reported to reduce ethanol self-administration [551,552,556–566]. June et al. [561] found that microinfusions of β-carboline-3-carboxylate-t-butyl ester (βCCt) into the ventral pallidum (VP) produced marked reductions in ethanol-reinforced behaviors, but that no effects on ethanol-reinforced behaviors were observed following infusion into the NAc or the CPu. The VP has been found to play a role in regulating the rewarding properties of both psychostimulant and opioid drugs [567–572]. It has been reported to code the normal hedonic impact of rewards in general [573], and it is in a good position to do so, since it receives efferent projections from the NAc [574,575], serves as a centripetal final common output path for mesocorticolimbic circuits [576–578], and sends projections to other reward structures such as the amygdala [579,580], orbitofrontal and insular cortex [578,581], VTA, and parabrachial nucleus [575,582–586]. Whether the VP's role with respect to $GABA_A$ receptor partial inverse agonists is analogous to that of the VTA with respect to $GABA_A$ receptor antagonists remains to be hypothesized.

The effects of $GABA_A$ agonists on ethanol self-administration have been less consistent than have those of $GABA_A$ antagonists. The selective $GABA_A$ agonist muscimol was found to decrease operant self-administration of ethanol when injected intraperitoneally [551] or into the NAc [587]. When it was injected into the central nucleus of the amygdala, it was found to decrease self-administration in dependent but not nondependent rats [546]. Conversely, when it was injected into the dorsal, but not the median, raphe nucleus it was found to enhance ethanol self-administration [588]. Petry [563] found that the effect of the benzodiazepine agonist chlordiazepoxide depended on the dose administered: the lowest dose increased ethanol self-administration, an intermediate dose had no effect, and the highest dose decreased ethanol self-administration. That $GABA_A$ agonists produce both increases and decreases in ethanol self-administration could conceivably be explained by a combination of neuroanatomical specificity and the diversity in subunit composition of $GABA_A$ receptors [589].

These findings with $GABA_A$ receptor antagonists and agonists could lead to speculation that a deficiency or hyposensitivity of $GABA_A$ receptors in the VTA or in the VP, or perhaps an excess or supersensitivity of $GABA_A$ receptors in the dorsal raphe, could contribute to an addictive process. A couple of other studies are more directly relevant to potential relationships between $GABA_A$ receptors and the addictive process.

Tyndale and Tomkins [590] trained rats to self-administer ethanol, and 8 weeks later assessed the levels of $GABA_A$ receptor mRNA in various regions of their brains. Compared to rats that were in the lowest 15th percentile of ethanol self-administration (LES), the rats that were in the highest 15th percentile (HES) had significantly higher $GABA_A$ receptor mRNA levels in the dorsal raphe, medial raphe, cerebellum, and hippocampus. The authors noted that the $GABA_A$ receptor differences between the two groups either reflected the groups' different pre-existing propensities to consume ethanol or were caused by their differing ethanol exposure, adding that they believed that the differences were part of the cause or at least existed prior to exposure to ethanol. Their position has been supported by more recent research that demonstrated that long-term ethanol consumption leads to significant decreases in expression of $GABA_A$ receptor mRNA [591–593]. So to whatever extent the $GABA_A$ receptor mRNA levels in Tyndale and Tomkins's [590] HES rats were affected by higher levels of ethanol consumption, the effect would have been in the direction of lowering their mRNA levels relative to LES rats, whereas the study found the HES rats' mRNA levels to be higher than those of the LES rats. Thus, elevated $GABA_A$ receptor mRNA levels in the dorsal raphe, medial raphe, cerebellum, or hippocampus, most likely associated with an increased density of $GABA_A$ receptors, may predispose to the development of an addictive process.

In a fascinating study, Laviolette et al. [594] proposed that a discrete population of $GABA_A$ receptors on non-dopaminergic neurons in the VTA that tonically inhibit VTA dopaminergic neurons serves as a potential addiction switching mechanism by gating reward transmission through one of two neural motivational systems, either a dopamine-independent system or a dopaminergic system. And they demonstrated that in the latter, the functional conductance properties of the rat VTA $GABA_A$ receptor switch from an inhibitory to an excitatory signaling mode. In opiate-naïve animals, animals that have received chronic opiate exposure but not withdrawal, and animals that have completed and recovered from opiate withdrawal, opiates can produce their acute rewarding effects through a DA-independent system that is mediated through brainstem reward circuits [595–597]. On the other hand, in animals that are in a state of opiate withdrawal, the motivational effects of opiates are dependent on the mesolimbic DA system [596,598–600]. Laviolette et al. [594] referenced the suggestion by Robinson and Berridge [335,344] that DA transmission mediates a drug 'wanting' or 'craving' signal, independently of the acute rewarding properties of opiates. This suggestion makes particular sense in light of the opiate withdrawal state's mix of strongly aversive stimuli that are relieved by administration of opiates. Such negative reinforcement motivation is incentively salient and thus suitable for DA signaling, while not depending at all on reward. While Laviolette et al. [594] focused on opiate state – specifically, the difference between animals in opiate withdrawal and animals not in opiate withdrawal – as the determinant of whether VTA $GABA_A$ receptors are in an inhibitory or an excitatory mode, I believe that the scope of their findings is deeper and more far-reaching than opiate states. Neurobiologically, the state of opiate withdrawal is very similar to a state of acute stress. Both involve activation of the hypothalamic–pituitary–adrenal (HPA) axis and dysregulation of the noradrenergic system. My hypothesis is that the component of the opiate withdrawal state that determined the VTA $GABA_A$ receptor switch from inhibitory to excitatory in Laviolette et al.'s study [594] is one that they share with the state of acute stress. The significance for addiction of the VTA $GABA_A$ receptor inhibitory-excitatory switch remains to be elucidated, but I believe that it also will enhance our understanding of how recurrent acute stress can potentiate an addictive process.

2.1.11. *$GABA_B$ receptors*

In preclinical research, the $GABA_B$ receptor agonist baclofen has been found to attenuate self-administration of cocaine [601–604], heroin [605,606], ethanol [607], nicotine [608–610], and *d*-amphetamine [611]. It has been found also to reduce reinstatement of cocaine self-administration [612], to reduce reinstatement of heroin self-administration [613], and to decrease stimulus-maintained responding for either cocaine or heroin [614]. The highly selective $GABA_B$ receptor agonist CGP 44532 reduced cocaine-induced enhancement of brain stimulation reward (BSR) [615], and the positive allosteric modulator of $GABA_B$ receptors CGP 7930 reduced operant self-administration of ethanol in ethanol-preferring rats [616].

Preliminary clinical studies have demonstrated that administration of baclofen reduces craving for both cocaine and ethanol in addicted patients [617–619]. Additionally, baclofen has been reported to attenuate the limbic cortical activation induced in cocaine addicts by conditioned stimuli that previously had been paired with cocaine use [602,620].

Baclofen and other $GABA_B$ agonists are understood to attenuate the reinforcing effects of abusable psychotropics through modulation of DA transmission from the VTA to the NAc, and perhaps also to the PFC [606,621]. Their targets are inhibitory $GABA_B$ receptors that are located on the cell bodies of VTA dopaminergic neurons [622–624] and that, when stimulated, hyperpolarize the membrane potential and decrease the firing rate of these neurons [625,626]. Both $GABA_B$ agonists and $GABA_B$ antagonists can increase BSR thresholds, which suggests a complex interaction between the reward system and GABA function, possibly reflecting differential effects at pre- and post-synaptic receptors [627].

The endogenous ligand for the $GABA_B$ receptors that are located on VTA DA neurons (i.e., GABA) is tonically produced by local VTA GABAergic interneurons. Inadequate or abnormal functioning of these GABA neurons could disinhibit the dopaminergic neurons, free them to respond more enthusiastically when stimulated, and thus intensify the reinforcing effects of substances and behaviors that can be used addictively.

2.1.12. *Endocannabinoids and cannabinoid receptors*

At the current time, there are two known cannabinoid receptor subtypes: cannabinoid-type 1 (CB_1), which are widely expressed throughout the peripheral and central nervous systems, and cannabinoid-type 2 (CB_2), which show high levels of expression within the immune and enteric nervous systems as well as in glial cells of the CNS. Both are coupled to inhibitory Gi/Go proteins. The majority of neuronal CB_1 receptors appear to be expressed pre-synaptically. Endogenous cannabinoids or endocannabinoids (eCBs) appear to

function as retrograde neurotransmitters. Upon release from postsynaptic neurons via membrane depolarization, they migrate back to an adjacent presynaptic membrane and activate presynaptic CB_1 receptors, which then inhibit neurotransmitter release [223,724]. Two major classes of eCBs have been identified thus far, exemplified by anandamide and 2-arachidonoyl glycerol [628–631]. The eCB system is understood to reinforce both the motivation and the reward functions of the mesolimbic DA system in its regulation of eating behavior [632].

Dopaminergic terminals lack cannabinoid receptors [633]. Nonetheless, genetic elimination of CB_1 receptors (CB_1 knockout mice, $CB_1 1-/-$) abolished DA release in the NAc in response to morphine [634] and ethanol [635], and the cannabinoid CB_1 receptor blocker rimonabant curtailed DA responses to administration of nicotine, ethanol, and cocaine [636]. The likely anatomical locus for the CB_1 receptors that made the critical difference in these studies is the presynaptic terminals of VTA GABAergic neurons that synapse onto VTA dopaminergic neurons and modulate their activity. Under ordinary circumstances, eCBs that had been launched by VTA dopaminergic neurons would drift over to activate the presynaptic CB_1 receptors that mediate the inhibition of GABA release, thereby decreasing the GABA-mediated inhibition of DA release. Inactivation or elimination of the CB_1 receptors interrupts this process and thus attenuates the DA responses to administration of psychoactive substances and to any other behavior that is associated with DA release in the NAc. Genetic variants of cannabinoid CB_1 receptors have been identified as probable factors in a person's vulnerability to develop an addictive disorder, especially one that involves consumption of food or of psychoactive substances [236,237].

2.1.13. *Cyclic AMP response element binding protein (CREB)*

Cyclic AMP response element binding protein (CREB) is a transcription factor that mediates effects of the cAMP second messenger pathway on gene expression. Once CREB has been phosphorylated by protein kinase A (a protein kinase activated by cAMP) or another protein kinase, it forms dimers that bind to specific CRE (cAMP response element) sites on target genes and interact with the basal transcriptional complex to regulate gene transcription [637].

Administration of psychostimulant and opiate drugs induces the phosphorylation and activation of CREB in several reward-related regions [638–643]. The induction of CREB activity appears to become greater and more persistent with repeated drug exposures [644]. In the NAc, the ability of psychostimulants to induce CREB is mediated via activation of the DA D_1 receptor [638,639]. Cocaine increases cAMP-PKA signaling in the NAc, which directly decreases medium spiny neuron (MSN) excitability, while also activating CREB. CREB increases MSN excitability and thus counterbalances the magnitude of the cocaine-induced decrease [645]. Increased CREB function in the NAc decreases an animal's sensitivity to the rewarding effects of cocaine, morphine, or sucrose, while reduction in CREB activity produces opposite effects [646,647].

Chronic administration of cocaine or other stimulants induces dynorphin expression in the NAc, and this induction is dependent on CREB [639,646]. Dynorphin activates κ opioid receptors on VTA dopaminergic neurons to decrease DA release in the NAc and thus to dampen the reward-reinforcement process [648]. At least some of the CREB-related decrease in the rewarding properties of drugs is mediated by the induction of prodynorphin mRNA, which encodes dynorphin [639].

Exposure of an animal to aversive stimuli activates CREB in the NAc in much the same way as do drugs of abuse. Following the parallel, researchers found that increased CREB function in the NAc decreased an animal's responsiveness to a variety of aversive or negative emotional stimuli, including stressful, anxiogenic, and nociceptive events; and that decreased CREB function in this region increased the animal's sensitivity to these conditions [647,649]. Activation of CREB in the NAc appears to result from exposure to stimuli of high hedonic-emotional charge, whether they are rewarding or aversive. And it appears to mediate a behavioral state that is characterized by reduced sensitivity to hedonic-emotional stimuli in general, again regardless of their valence [637]. This behavioral state resembles the syndromes of anhedonia and emotional numbing that can characterize depression, post-traumatic stress disorder (PTSD), and some forms of drug withdrawal [650].

2.1.14. *ΔFosB*

ΔFosB is a member of the Fos family of transcription factors. These proteins dimerize with a Jun family member to form activator protein-1 (AP-1) transcription factor complexes, which bind to AP-1 sites within the regulatory regions of certain genes [637].

ΔFosB is induced by virtually all drugs of abuse, including psychostimulants, opiates, ethanol, and nicotine, among others [651–655]. ΔFosB also is induced by repetition of naturally rewarding behavior, such as wheel running or sucrose drinking [541,656], and by several forms of chronic stress [657,658]. Interestingly, levels of stress-related ΔFosB induction negatively correlate with the degree to which the animals develop learned helplessness, suggesting that induction of ΔFosB represents an adaptive, active coping mechanism that opposes the development of learned helplessness [657]. And ΔFosB is induced by the chronic administration of pharmaceutical antidepressants [651].

Inducible transgenic mice that overexpressed ΔFosB within the NAc and dorsal striatum showed increased sensitivity to the behavioral effects of cocaine, enhanced incentive motivation for cocaine, increased sensitivity to the behavioral effects of morphine, and greater responsiveness to naturally reinforcing behaviors, such as running and eating [539,540,637]. Nestler, the author of these studies, interpreted their findings to suggest that ΔFosB could be part of a sustained molecular switch that functions first to induce and later to maintain a state of heightened incentive motivation toward reinforced behaviors.

ΔFosB appears to be the antithesis of CREB. While CREB activation mediates a state of reduced reward and reduced emotional reactivity, ΔFosB accumulation mediates a state of heightened drug sensitivity and increased drive for rewarding behavior. Drug-induced activation of CREB in the NAc dissipates within a few days of coming off the drug, while ΔFosB increases over time and persists in the brain for up to 2 months [659].

At one time, ΔFosB may have seemed to epitomize the argument that drug addiction is caused by drug use. ΔFosB is induced by drug use, it increases sensitivity to and drive for drugs, and its extended duration of action could account for abstinent addicts' vulnerability to relapse. However, as Nestler noted [539], ΔFosB does not last long enough to underlie the near-permanent predispositions that are seen in many addicted individuals. He suggested that variations in the genes encoding ΔFosB could contribute to the genetic risk for addiction: for example, an individual with a gene that expresses ΔFosB at high levels might be more prone to addiction [660]. Another means by which levels of ΔFosB could increase and thus contribute to an addictive process is through its induction by chronic stress [658,657].

2.1.15. *Dopamine and cAMP-regulated phosphoprotein (DARPP-32)*

The dopamine and cAMP-regulated phosphoprotein (DARPP-32) is a key regulator of kinase-phosphatase signaling cascades that is found in dopaminergically innervated areas of the brain. cAMP that has been generated by activation of D_1 receptors activates protein kinase A (PKA), which phosphorylates DARPP-32 at the threonine-34 site (T34) [661,662]. When DARPP-32 is phosphorylated at this site, it acts as an inhibitor of protein phosphatase-1 (PP-1) [663], thereby maintaining the phosphorylation state of various neuronal proteins. DARPP-32 can be phosphorylated also at the threonine-75 site (T75) by cyclin-dependent kinase 5. DARPP-32 that has been phosphorylated at this site inhibits PKA activity, resulting in reduced efficacy of DA signaling [664]. In this way, DARPP-32 acts as a bidirectional signaling protein that regulates protein phosphorylation and dephosphorylation via PKA and PP-1. The phosphorylation state of DARPP-32 is influenced also by the phosphatases, calcineurin (dephosphorylates T34) and protein phosphatase 2A (dephosphorylates T75) [665].

DARPP-32 knockout mice were found to have heightened substance P-like immunoreactivity and not to show the characteristic increase in ΔFosB after repeated cocaine administration [666]. They also were reported to have reduced cocaine CPP [371], suggesting that a DARPP-32 deficit can decrease the rewarding properties of cocaine. Zachariou et al. [369] used a mutation of T34 to demonstrate that phosphorylation at T34 of DARPP-32 is a necessary mediator of cocaine-induced place conditioning, locomotor activity, and sensitization. The T34 mutation also diminished the induction of ΔFosB in the ventral striatum by chronic cocaine administration.

Donohue et al. [667] reported that transgenic mice that overexpress an ethanol-sensitive isoform of adenylate cyclase (AC7) had higher basal levels of T34 DARPP-32 in the striatum and amygdala than did wild-type mice, whereas basal levels of T75 DARPP-32 did not differ between wild-type and transgenic mice. Ethanol administration was found to increase T34 DARPP-32 in the NAc and amygdala (but not in the striatum) of wild-type and transgenic mice, with a greater effect in the amygdala of transgenic mice. It was found also to increase T75 DARPP-32 in the amygdala of the wild-type mice only, and in the NAc and striatum of both the transgenic and wild-type mice. The authors concluded that the effect of ethanol on the balance of DARPP-32 phosphorylation, especially in the amygdala, may contribute to differential motivational effects of ethanol.

2.1.16. *Neuropeptide Y (NPY)*

Neuropeptide Y (NPY) is a 36-amino acid neuromodulator that is expressed throughout the central nervous system [668]. Most of it derives from neurons in the arcuate nucleus (ARC) of the hypothalamus, which project dorsally to the paraventricular nucleus (PVN) as well as to other hypothalamic and extrahypothalamic nuclei [669]. NPY is involved with a diverse set of biological functions that include integration of emotional behavior [670,671], control of food intake [672,673], neuronal development [674,675], circadian rhythms [676–679], pain modulation [680,681], and reproduction [682,683]. NPY acts through at least five receptor subtypes – the Y1, Y2, Y4, Y5, and Y6 receptors – all of which couple to G proteins that inhibit the production of cyclic adenosine monophosphate [684]. Y5 receptors are present at significant levels in the PVN, ARC, thalamus, and amygdala, which suggests the presence of functional hypothalamic–limbic neural circuits [685].

A number of studies found that administration of NPY [686,687] reduces ethanol consumption in ethanol-preferring P rats and high ethanol-drinking HAD rats, but not in ethanol-nonpreferring NP rats, low-ethanol-drinking LAD rats, or nonselected rats. However, other studies found that administration of NPY increases [688,689] and of NPY antagonist decreases [690–693] ethanol self-administration. Schroeder et al. [694] suggested that these discrepant findings could be reconciled with the recognition that the nature of NPY's influence on ethanol intake is brain region dependent. Research indicating that NPY increases ethanol intake infused the peptide directly into the PVN, where it functions as an orexigenic agent [688,689]. Meanwhile, research indicating that NPY decreases ethanol intake administered it via intracerebroventricular infusion [686,687].

Other research speaks with a more unified voice about NPY's role in modulating ethanol consumption. Mice that overexpress NPY consume less ethanol than wild-type controls, while transgenic mice that lack NPY (NPY knockout mice) consume more ethanol than wild-type controls [695]. Ethanol consumption is suppressed by blockade of either NPY Y1 receptors [693] or NPY Y2 receptors [696,697], but elevated in Y1 receptor null mutant mice [698]. And in humans, a polymorphism in NPY (Leu7Pro) was significantly associated with addiction in European American and Finnish alcoholics, both exhibiting an increased frequency of the Pro7 allele compared with controls [699,700].

NPY is a highly potent activator of feeding behavior. When administered into the PVN, it induces feeding in satiated animals and it seems to selectively stimulate prodigious carbohydrate intake [222]. Studies indicate that NPY and 5-HT play antagonistic roles in the regulation of feeding [701,702], and that NPY's stimulation of feeding is mediated via the internal opioid system, since NPY-induced feeding is blocked by the opioid antagonists naloxone and naltrexone [703]. NPY also has been observed to bind to non-selective opiate receptors with modest activity similar to that of the endogenous opioid leu-enkephalin [704]. NPY's induction of feeding in satiated animals, its involvement with the internal opioid system, its antagonistic relationship with 5-HT, and its presence in functional hypothalamic–limbic neural circuits suggest that it could contribute to an addictive process.

2.1.17. *Galanin*

Galanin is a 29-amino acid neuropeptide that activates at least three receptor subtypes coupled to Gi, Gq, or Go [705,706]. It is synthesized in many types of neuron, including brainstem NE-producing cells of the LC and 5-HT-producing neurons of the DRN. Cells that express galanin are concentrated in several hypothalamic areas: the dorsomedial nucleus, PVN, perifornical lateral hypothalamus (PLH) and ARC. They send out dense projections throughout the hypothalamus as well as to other parts of the limbic system, including the amygdala, BNST, and hippocampus [707–711]. Galanin serves a number of disparate functions. It inhibits the firing of NE, 5-HT, and DA neurons and reduces release of these neurotransmitters in forebrain target regions [712]. It inhibits glucose-induced insulin release and reduces levels of 5-HT, NE, and acetylcholine through the inhibition of adenylate cyclase and phosphatidyl inositol hydrolysis [713]. Galanin also is a potent endogenous modulator of firing pattern in hypothalamic neuroendocrine cells [714], a hypothalamic-hypophysiotropic hormone that modulates the secretion and action of luteinizing hormone releasing hormone (LHRH) [715], and a regulator of food intake [716,717].

Injection of galanin in the PVN at a dose known to induce feeding has been found to potentiate intake of 4% ethanol, even when food and water were available as sources of calories and fluid [718]. In rats that have been trained to drink ethanol, galanin seems to stimulate the appetite for it [718,719]. We can wonder whether a similar process would occur with rats that have been trained to drink flavored solutions that have been paired with infusions of cocaine or heroin.

Galanin has interesting relationships with the endogenous opioid and dopamine systems that could contribute to its involvement in an addictive process. Galanin has been found to potentiate morphine analgesia [720]. Meanwhile, naloxone has been found to block galanin-induced feeding [721,722] and to decrease PVN galanin mRNA in ethanol-drinking rats, while having little or no effect on galanin mRNA in water-drinking rats [723]. Another study found that injection of galanin into the PVN of rats releases DA and inhibits acetylcholine release in the NAc, an effect that occurs only in rats that previously had demonstrated significant increases in their feeding behavior in response to galanin [724]. These findings were interpreted in one later study as indicating that ethanol consumption induced by PVN injections of galanin may be mediated through DA in the NAc [718], and in another as indicating that galanin-induced overeating is associated with DA release [723].

Studies have demonstrated that hypothalamic galanin increases the consumption of a fat-rich diet [725,726] and, conversely, that the consumption of fats can increase the expression of galanin in hypothalamic nuclei [727,728]. Leibowitz et al. [723] commented that these findings suggest the operation of a positive feedback loop that could contribute to overeating until the cycle is interrupted by postingestional satiety signals [717,729]. Interestingly, Thiele et al. [730] and Rada et al. [718] identified a similar positive feedback loop between galanin and ethanol intake, since ethanol increases galanin expression in the PVN and injection of galanin into the PVN potentiates consumption of ethanol. A key difference between the two positive feedback loops is that in the latter, ethanol produces no satiety signal. (Actually, some sufferers of bulimia and binge-eating disorder report that they do not experience satiety signals after eating.).

2.1.18. *Orexin*

Orexins (or hypocretins) are neuropeptides that are synthesized in neurons of the posterior and lateral hypothalamus (LH). Neurons that synthesize the excitatory peptide hypocretin also synthesize dynorphin, a peptide that usually is inhibitory [731]. Orexin neurons that are located in posterior hypothalamic areas are involved in regulating wakefulness, thermogenesis, and energy expenditure, whereas those that are located in the LH are involved in stimulation of appetitive behaviors and in reward processing. Orexin A and orexin B are produced by cleavage of a single precursor protein, and their actions are mediated by two G protein-coupled receptors, orexin receptor type 1 (OXR1) and orexin receptor type 2 (OXR2). OXR1 shows higher affinity for orexin A, while OXR2 shows equal affinity for both ligands [732]. Orexin neurons receive input from the amygdala, basal forebrain cholinergic neurons, GABAergic neurons in the preoptic area (POA), and serotonergic neurons in the median/paramedian raphe nuclei. During periods of wakefulness, emotional stimuli from the limbic system and cholinergic influences from the basal forebrain stimulate orexin neurons to maintain the activity of the monoaminergic system, while sleep-active neurons in the POA inhibit them during periods of sleep [733]. Orexin neurons of the LH-perifornical area send widespread axonal efferents to the LC, VTA, NAc, cortex, and midline thalamus, and to other regions of the lateral and medial hypothalamus. They also maintain local axonal collaterals that terminate on other cells in the LH, including orexin cells and neurons that synthesize melanin concentrating hormone (MCH), though orexin neurons show little direct response to orexin [731].

Orexin A has been demonstrated to increase the firing rate and in some cases to cause burst firing of VTA dopamine neurons in rat brain slices [734]. Orexin neurons send excitatory projections to the VTA and substantia nigra pars compacta. Intra-VTA infusions of orexin A *in vivo* have been found to increase extracellular DA levels in the PFC and in the shell region of the NAc, but not in the NAc core [735,736]. Through their enhancement of midbrain dopaminergic system activity, orexins can potentiate an increase in motor activity and thereby reduce the threshold for emitting specific (previously rewarded) behaviors [737].

Orexin neurons in the LH become activated by cues that have been associated with consummatory rewards such as food and drugs [738]. Several studies demonstrated orexin to have a critical role in activating reward-seeking or appetitive behavior in response to conditioned or discriminative stimuli. Intracerebroventricular (icv) infusion of orexin was found to evoke a dose-related reinstatement of extinguished cocaine self-administration in rats, an effect that was prevented by antagonists of receptors for NE or for corticotropin releasing factor (CRF) [739]. The inference that orexin's activation of cocaine self-administration reinstatement is mediated via NE and CRF is consistent with findings that icv administration of orexin A activates CRF-expressing neurons in the PVN and the central nucleus of the amygdala (CeA) [740]. Antagonism of

orexin OXR1 receptors by the selective orexin A antagonist SB-334867 was found to reduce operant responding for ethanol and also to abolish cue-induced reinstatement of ethanol-seeking behavior in ethanol-preferring iP rats [741]. Harris et al. [738] reported that the amount of Fos activation in LH orexin neurons of animals that had been conditioned via CCP protocol for morphine, cocaine, or food reward was correlated with the intensity of their reward-seeking. They reported also that microinjection of orexin into the VTA caused a significant reinstatement response for morphine reward; that administration of the orexin antagonist SB-334867 after morphine CPP training produced a significant reduction in preference compared to animals that were given a vehicle injection; that reinstatement of extinguished CPP by microinfusion of rPP (rat pancreatic polypeptide, an agonist at NPY Y4 receptors on orexin neurons) in the LH was similar to the reinstatement produced by systemic morphine; and that reinstatement was completely blocked by prior systemic administration of SB-334867. Harris and Aston-Jones [742] concluded that both the orexin neurons that originate in the perifornical and dorsomedial hypothalamic areas (PFA–DMH) and those that originate in the LH can participate in drug relapse, but through different processes. The PFA–DMH orexin system, which is involved in regulating wakefulness and energy expenditure, drives relapse through activation of stress systems (perhaps involving CRF or NE), whereas the LH orexin system, which is involved in reward processing, drives relapse through activation of brain circuits that are associated with reward learning and reward-seeking behavior [742].

Neuroplasticity at VTA glutamatergic synapses that is induced by drugs of abuse has been suggested to play an important role in the behavioral consequences of *in vivo* drug exposure [343,659,743]. A recent study by Borgland et al. [744] demonstrated that orexin A is a critical substrate in this process. Glutamatergic *N*-methyl-D-aspartate receptors (NMDARs) on VTA DA neurons perform two major functions: they promote burst firing [743,745], and they are necessary for the induction of long-term potentiation [746,747]. Burst firing of VTA dopamine neurons, which increases extracellular DA in the projection areas more efficiently than does a regularly spaced train of action potentials [745,748], signals the occurrence of salient stimuli and facilitates consolidation of the relevant memory traces [749]. Long-term potentiation is an enduring decrease in depolarization threshold that functionally strengthens synapses and contributes to synaptic plasticity. Borgland et al. [744] reported that *in vitro* application of orexin A potentiates NMDAR responses in VTA dopamine neurons; that the OXR1 receptor antagonist SB 334867 blocks induction of cocaine-induced potentiation of excitatory inputs onto VTA neurons; that orexin A causes late-phase increases in AMPAR-mediated synaptic transmission; and that microinjection of SB 334867 directly into the VTA blocks the development of cocaine-induced locomotor sensitization. These data provide evidence that orexin signaling pathways play an important role in the drug-induced neural plasticity that contributes to cocaine addiction—and by inference, to other addictions as well.

2.1.19. *Substance P (SP)*

Substance P (SP) is the most common of the five known mammalian neurokinins (or tachykinins), the others of which are neurokinin A (NKA), neurokinin B (NKB), neuropeptide K, and neuropeptide a. Three G protein-coupled neurokinin receptors have been identified – NK-1, NK-2, and NK-3 – for which SP, NKA, and NKB have the highest binding affinity, respectively, but all neurokinins bind to all three NK-Rs [750,751]. SP is colocalized with other neurotransmitters and has important neuromodulatory effects. Examples are colocalizations with 5-HT in the nuclei raphes, with DA in the midbrain and striatum, with GABA and acetylcholine in the cortex, and with CRH in the hypothalamus [752]. Examples for direct neuromodulatory effects of SP are the regulation of acetylcholine release in the human cortex [753] and the modulation of noradrenergic neurotransmission in the LC [754].

SP and the NK-1 receptor play a role in maintaining the activity of mesocorticolimbic DA neurons, under both basal and drug-induced conditions. Blockade of NK-1 receptors by systemic injection of the NK-1 receptor antagonist CP-96345 decreased the number of spontaneously active DA neurons in the VTA [755], and injection of a SP antibody into the NAc produced increases in concentrations of DA and metabolites, an effect consistent with intracellular accumulation and metabolism of DA following decreases in DA release [756]. SP afferents have synaptic contacts with dopaminergic neurons in the VTA [757], and SP is present in high concentration in terminals close to the VTA dopaminergic cell bodies [758,759]. Injection of SP directly into the VTA has been found to increase the levels of DA and/or its metabolites in the PFC and the NAc, suggesting that SP stimulates the release of DA from mesocortical and mesolimbic DA neurons [760–762]. SP has been shown to preferentially activate mesocortical DA neurons in a manner similar to acute stressors such as mild footshock or restraint [763]. Furthermore, evidence suggests that the increased turnover of DA in the PFC and the NAc in response to stress may be mediated by SP. Increases in DA metabolism in the PFC in response to footshock-stress can be blocked by a SP antibody in the VTA [764]. These findings suggest that not only does SP have a tonic facilitatory influence on mesocorticolimbic DA activity, it also may contribute to the DA-dependent behavioral responses to drugs. They also raise the possibility that the activation of these DA neurons in response to stress may be mediated by the endogenous SP system [765,766].

Injection of SP into the VTA has been shown to enhance responding for conditioned reward, but not selectively for the reward-paired lever [767]. Similarly, on a test of fixed interval responding, intra-VTA injection of SP was shown to increase responding on the non-reinforced lever [768]. These findings suggest that activation of VTA cell bodies by SP or its analogue produces increases in reward, but may also disrupt discrimination processes and thereby result in some degree of response generalization [765].

The experimental literature consistently affirms that SP is involved in opiate reward processes. Reward-related behavioral effects of morphine or heroin are substantially attenuated when SP's favorite receptor, NK-1, is blocked by the antagonist GR82334, ablated, or genetically deleted [766,769–771]. However, when we turn to consider the relationship between SP and psychostimulants, the research results are mixed and perplexing. Placenza et al. [766] reported a study in which icv

administration of the selective NK-1 receptor antagonist GR82334 had no effect on cocaine-induced locomotor activation or cocaine self-administration, though it had produced significant increases in heroin self-administration and attenuation of morphine-induced locomotion. Their results are consistent with studies that found that genetic deletion of the NK-1 receptor did not impair the reinforcing effects of cocaine [769,770]; that ablation of NK-1 receptors in the amygdala did not block cocaine-induced CPP [771]; and that icv injections of NK-1 receptor antagonists had no effect on the reinstatement of cocaine seeking induced by a priming injection of cocaine [772]. However, other studies found that infusion of the high-affinity nonpeptide NK-1 receptor antagonist L-733,060 prior to a systemic injection of cocaine significantly attenuated the cocaine-evoked release of DA in the striatum [773,774]; that infusion of the NK-1 receptor antagonist WIN-51,708 prevented the massive release of acetylcholine in the striatum that cocaine injection would ordinarily evoke [774]; that intrastriatal NK-1 receptor blockade by the specific NK-1 receptor antagonist LY306740 decreased amphetamine-induced behavior [775]; and that pre-treatment with the NK-1 receptor antagonist WIN-51,708 30 min before injections of methamphetamine prevented both the loss of dopamine transporters (DAT) in the striatum and methamphetamine-induced cell death [774]. An attempt to reconcile the conflicting studies by questioning whether different NK-1R antagonists are functionally equivalent would miss the larger point of perplexity: that a disruption of the mesocorticolimbic DA system that blocks incentive-reward for opiates but not for psychostimulants seems to be inconsistent with the consensus that the mesocorticolimbic DA system where SP exerts its influence is the primary conduit of incentive-reward-reinforcement for both opiates and psychostimulants. Whether SP is to be considered as a potential contributor to an addictive process hinges on how these apparent contradictions are resolved. If the SP functions that are most relevant to addiction are found to characterize opiates but not psychostimulants, then variations of the SP-NK1 system could be factors that influence whether a person who is predisposed to developing an addictive disorder is more likely to addictively use opiates or psychostimulants, but they would not be factors in an addictive process.

2.1.20. *Melanocortins (MCs) and melanocortin receptors (MCRs)*

Adrenocorticotropin (ACTH) and ⟨-, ®-, and ©-melanocyte-stimulating hormones (⟨-, ®-, and ©-MSH) are derived by enzymatic processing from proopiomelanocortin (POMC), a propeptide that is produced in the arcuate nucleus of the hypothalamus. Collectively, they are called melanocortins. The hypothalamic arcuate nucleus (ARC) contains two discrete cell groups. One group co-expresses the anorexigenic peptides α-MSH and cocaine- and amphetamine-regulated transcript peptide (CART). The second group coexpresses the orexigenic peptides agouti-related protein (AGRP) and neuropeptide Y. Melanocortins act via five receptor subtypes (MC1R–MC5R), all of which belong to the G protein-coupled receptor superfamily and are positively coupled to adenylate cyclase. In the brain, MC3R and melanocortin-4 receptor (MC4R) are mainly expressed, with little expression of MC5R. They are expressed in brain regions that modulate the reinforcing properties of drugs of abuse and natural reinforcers (e.g., food and sex), including the NAc, the VTA, and the hypothalamus [776,777]. All melanocortin receptors are activated by ACTH, whereas all melanocortin receptors except MC2R are activated by MSH. While α-MSH and AGRP bind as high-affinity agonist and antagonist, respectively, at the melanocortin MC3R and MC4R receptors, their opponent effects on feeding seem to be mediated by MC4R [778–780].

Studies indicate that melanocortins operate in relationships of mutual influence with the mesolimbic DA and endogenous opioid reward-related systems. Melanocortins have been found to enhance dopaminergic neurotransmission, and DA has been found to increase melanocortin function [781]. MCR signaling has been reported to regulate ethanol consumption by modulating endogenous opioid activity within mesolimbic DA pathways [782]. Repeated administration of cocaine has been found to increase the expression of MC4R mRNA, and administration of a low dose of morphine has been found to up-regulate the expression of MC4R mRNA in the striatum [783]. Meanwhile, chronic administration of morphine has been found to result in down-regulation of MC4R mRNA expression in the striatum and periaqueductal gray [784]. This MC4R down-regulation and the associated decrease in melanocortin function have been hypothesized to promote the development of opiate addiction [784].

At first glance, the results of research that concerns melanocortin and drugs of abuse may seem to be contradictory. The selective MC4R agonist MTII was reported to reduce ethanol self-administration, and MCR antagonists were reported to increase it [785]. Similarly, melanocortins were reported to reduce opiate self-administration [786], and mutations in MC4R were found to be associated with binge-eating disorder [787]. On the other hand, infusion of the melanocortin MC4R antagonist SHU-9119 into the NAc was reported to block the rewarding effects of cocaine: cocaine-induced CPP, cocaine-enhanced responding for conditioned reinforcement, and the reinforcing effectiveness of stimuli that were conditioned by being paired with cocaine [781]. And treatment with the MC4R agonist MTII was found to produce a robust augmentation of amphetamine reward, as measured in terms of its ability to lower the threshold for lateral hypothalamic self-stimulation (LHSS) [788]. Whether the contradiction is more apparent than real is hard to discern, since the outcome measures are not really comparable. Measures of self-administration of a substance are unquestionably related to its reward value, but not necessarily in the same way as is CPP or the lowering of the LHSS threshold. In fact, the correlation is not always in the same direction: increased reward is associated sometimes with increased self-administration and sometimes with decreased self-administration.

2.1.21. *Leptin*

Leptin is a protein hormone that is generated in adipocytes and interacts with six types of receptor (LepRa–LepRf). Its primary physiological function is the regulation of appetite. When leptin binds to LepRb receptors in the ventral medial hypothalamus (VMH), a satiety signal is generated that instructs the brain to direct the body to stop eating. The cells of the ARC, located in the VMH, receive leptin signals and then

communicate to other hypothalamic and extrahypothalamic structures via neuropeptide transmission [reviewed in 789]. Leptin receptors are expressed also by some neurons in the LH, including orexin and MCH neurons [790], which suggests that these neurons may respond directly to peripheral leptin signals. In addition, the VMH has extensive connections to the LH.

Leptin works by inhibiting the activity of neurons that contain NPY and agouti-related peptide (AgRP), and by increasing the activity of neurons that express α-MSH. It also down-regulates the expression of endocannabinoids in the hypothalamus [632].

Leptin not only suppresses food intake, but also reverses the effects of food restriction on brain stimulation reward thresholds [791] and on the reinstatement of drug-seeking [792]. Food and drugs work through common molecular substrates within the brain [793], and connections between the hypothalamus and the NAc may underlie some of the behavioral observations of cross-sensitization between natural rewards and drugs of abuse [243]. Most drugs are self-administered to higher levels after food deprivation [794], and food deprivation increases cocaine-conditioned place preference [795]. Leptin acts to reduce heroin self-administration [792], and has been shown to modulate LHSS [796]. Investigators are beginning to consider impaired leptin activity as a potential factor in a shared vulnerability to psychoactive substance addiction and bulimia [228,239].

2.1.22. *Glutamate*

Burst firing in mesencephalic DA neurons is dependent on excitatory afferents that activate ionotropic glutamatergic receptors on DA cells [498,797,798] The pause after a burst can be mediated by glutamate acting on metabotropic glutamatergic receptors (mGluRs), which induces inhibitory postsynaptic potentials (IPSPs) [799,800]. Psychostimulants selectively reduce the mGluR-induced IPSPs in DA neurons through cross-desensitization that is mediated by α-adrenoceptors [801]. As a result, acute exposure to a psychostimulant increases DA neuron bursting via α-adrenoceptors [802]. This suggests that α-adrenergic receptors play an important role in mediating drug reinforcement [803]. Indeed, Drouin et al. found that mice that lacked α-adrenoceptors exhibited neither psychostimulant-induced locomotor hyperactivity [804] nor rewarding effects [479]. Therefore, an interaction between noradrenergic and glutamatergic systems may modulate the firing pattern of DA neurons, which in turn may underlie the reinforcing value of drugs and the establishment of addictive behavior [805].

In a study by Tremblay et al. [806], a group of patients with major depressive disorder who were administered *d*-amphetamine demonstrated enhanced rewarding effects, compared with the control group. The degree of enhancement that *d*-amphetamine elicited correlated with the severity of the depressed patients' anhedonic symptoms. The hypersensitive response to *d*-amphetamine was associated with negative blood oxygen level-dependent (BOLD) signals in most of the regions of interaction. The physiological counterparts of negative BOLD signals are thought to be induced by reduced blood flow (i.e., active neuronal inhibition and decreased cortical excitability) [807–809]. The relative decrease in brain activity among depressed subjects could reflect exaggerated deactivation of glutamate–mediated transmission by amphetamine (as per the preceding paragraph).

We are considering a distinction between two groups of people that renders one of them more susceptible to develop an addictive disorder, and three possible constituents of this distinction that emerge out of the preceding discussion. First, Tremblay et al. [806] referenced a study that reported evidence of abnormal glutamate transmission in major depression [810], by way of suggesting that abnormal glutamate transmission could have generated the depressed group's enhanced sensitivity to the effects of *d*-amphetamine. Second, the converse of Drouin et al.'s findings that α-adrenoceptor *hypo*activity reduces psychostimulant-induced locomotor hyperactivity and reward is that α-adrenoceptor *hyper*activity could intensify these psychostimulant-induced effects. Such adrenergic hyperactivity is not unusual in states of chronic stress. Finally, Tremblay et al. [806] noted that the degree of enhancement that *d*-amphetamine elicited correlated with the severity of the depressed patients' anhedonic symptoms. Thus, anhedonia emerges as a risk factor or marker for the development of an addictive disorder.

2.1.23. *Glucocorticoids*

Both in rodents and in primates, positive correlations have been observed between circulating glucocorticoid levels and psychostimulant self-administration [811–813]. Most studies on self-administration have reported increases in drug responding following repeated or prolonged exposure to stress levels of glucocorticoids [812–815]. Glucocorticoids, probably via glucocorticoid receptors, facilitate DA transmission in the NAc shell [816]. During chronic stress, the repeated increase in glucocorticoid hormones and DA could result in sensitization of the reward system. This sensitized state, which can persist after the end of the stress, would render the subject more responsive to drugs of abuse and consequently more vulnerable to the development of addiction.

Glucocorticoids, the hypothalamic–pituitary–adrenal (HPA) axis, and the stress response system are discussed more extensively in the following section, where we consider the impaired affect regulation component of the addictive process.

2.2. *Impaired affect regulation*

Affect regulation comprises the neurobiological processes that maintain emotional states within ranges of intensity and stability that do not impair functioning or lead to overwhelming distress. The addictive disorders literature employs the term "impaired affect regulation" less often than it uses terms that refer to its more clearly defined and experience-near manifestations, such as chronic stress, stress hypersensitivity, depression, and anxiety. A term as important and apparently vague as "stress" also merits definition. While diverse and elaborate definitions abound, the word's etymology might be an expeditious beginning: "Middle English *stresse*, short for *destresse* (from Old French), distress." Stress/distress seems to be a synonym of pain or suffering, with a connotation of tension or strain.

2.2.1. *Corticotropin releasing factor (CRF)*

Corticotropin releasing factor (CRF) is released from two brain regions to participate in two separate (but connected) stress systems [817]. In the hypothalamic–pituitary–adrenal (HPA) stress system, CRF neurons in the parvocellular region of the paraventricular nucleus of the hypothalamus (PVNh) regulate the release of pituitary adrenocorticotropic hormone (ACTH) and adrenal glucocorticoids (GC). In the extrahypothalamic (EH) stress system, CRF neurons in the central nucleus of the amygdala (CeA) project to the locus coeruleus (LC) and increase the firing rate of LC neurons, resulting in increased NE release in the terminal fields of this ascending noradrenergic system [818–821]. One of the principal noradrenergic targets of this system is actually the CRF neurons of the PVNh. NE is the major known source of drive over CRF release from PVNh neurons during stress [822,823]. The activation of the CRF neurons of the PVNh is associated with increased activity in the nucleus tractus solitarius (NTS) and the dorsal medullary nucleus, as well as the LC.

Either stress system can contribute to both a pre-existing vulnerability to use drugs addictively and a later vulnerability to relapse. The HPA stress system seems to have the more important role in the initiation of drug-seeking and in the maintenance of drug-taking behavior, while the EH stress system seems to have the more important role in the motivational effects of both protracted abstinence and stress-induced reinstatement [824–827].

In the stress-induced reinstatement procedure, rats that previously had been trained to self-administer cocaine or heroin and then extinguished will reinstate their responding if a mild footshock is administered immediately prior to the testing session [828–832]. This reinstatement was reported to be blocked by pre-treatment with CRF antagonists administered directly into the brain, but not by removal of glucocorticoids [833–836]. Research results indicated that the key neural pathway for this process originates in CRF neurons of the CeA and ends at CRF_1 receptors on the ventral BNST [835–838].

Stress stimuli that activate CRF circuits have been found also to potentiate mesolimbic dopaminergic reward pathways in laboratory animals [839]. Similarly, human laboratory studies have shown that emotional stress and negative affect states increase drug craving in drug-addicted individuals [841,842]. Preclinical studies have demonstrated that early life stress and chronic stress can result in enduring changes in stress responses [817,839–850]. Such changes can alter the sensitivity of the DA system to stress and can increase susceptibility to self-administration of substances of abuse [840,851,852].

A suggestion by some investigators [853–855] that anxiety and affective disorders be considered to be chronic stress states makes immediate sense of the data on comorbidity between these disorders and addictive disorders. The high levels of serum cortisol that issue from a hyper-responsive HPA axis during chronic stress enhance the sensitivity of the mesolimbic DA system to the reinforcing properties of psychoactive substances and rewarding behaviors, thereby increasing the risk that affected individuals will use such substances and behaviors addictively [824,856]. Accordingly, Tremblay et al. [857] found a strong positive relationship between the severity of subjects' depressive symptoms and the degree of reward effect that they experienced from a dose of *d*-amphetamine. Compared to healthy controls, individuals with PTSD [858,859] and with depression [860–862] were found to have higher levels of CRF in their CSF.

Finally, a series of stressful episodes were reported to have led to a marked and prolonged increase in ethanol consumption in CRF_1 receptor-deficient mice but not in wild-type mice, even though CRF_1 receptor-deficient mice and the wild-type mice had not differed in ethanol consumption prior to the stressful episodes [863]. These data suggest that the CRF_1 receptor is involved in adaptive responses to stress, the lack of which leads the CRF_1 receptor-deficient mice to resort to ethanol to manage their stress [864].

Research results seem to concur that a hyper-responsive HPA axis and chronic stress conditions – including anxiety and affective disorders – are likely to be significant risk factors for the development of addictive disorders.

2.2.2. *Cortisol*

Receptors for cortisol (or glucocorticoid receptors [GRs]) are located in the hippocampus, the limbic system, and the PFC [865,866]. During periods of psychological distress, cortisol's diurnal pattern is overridden by signals to the hypothalamus that originate in the amygdala and the BNST, structures that are activated by conditioned and unconditioned stimuli and that convey information having survival value [867–869]. The BNST also provides the primary inputs to the PVN that generate an HPA response to psychological stress. These influences are augmented during periods of psychological stress by NE inputs that ascend from the LC to activate the cerebral cortex and limbic system [870,871].

Acute cortisol administration has been found to precipitate cocaine craving in human addicts [872], as has stress [873]. Stress also has been demonstrated to increase drug self-administration in animal models [874]. The stress-charged drive to self-administer drugs of abuse has been linked to increased activation of the mesolimbic DA system, which is mediated by glucocorticoid release [874–877]. Repeated exposure to stress has been shown to induce a long-lasting enhancement of the mesolimbic DA response to drugs of abuse [878].

Interestingly, a hypo-responsive HPA axis with low levels of cortisol also has been associated with enhanced drug self-administration [879,880]. These findings are consistent with human studies that demonstrated lower cortisol response to stress in individuals who had behavioral conduct problems, externalizing symptoms, and antisocial personality [881–885]. In adolescent boys, lower stress-related cortisol levels were found to be associated with subsequent increased frequency of drug use [886].

Wei et al. [887] found that transgenic mice with over-expressed GRs manifested a significant increase in anxiety-like and depression-like behaviors relative to wild type, and also to show enhanced sensitization to cocaine [887]. Meanwhile, decreasing the production of central nervous system (CNS) GRs reduced cocaine self-administration [888], which suggests that self-administration depends on feedback signals from cortisol receptors to the CNS [889].

The cortisol variant that seems to be the more likely to contribute to an addictive process is enhanced secretion or

increased receptor sensitivity, which would increase activation of the mesolimbic DA system in the short run and chronically would induce a long-lasting enhancement of the mesolimbic DA response to drugs of abuse.

2.2.3. *Norepinephrine (NE)*

When the LC is firing at normal rates, NE increases the signal to noise ratio of responses evoked by other afferents, both excitatory and inhibitory, and enhances synaptic transmission in target circuits [890–892]. In an acute stress situation, the LC firing rate increases, enhancement of signal to noise ratio decreases, and the LC becomes the brain's alarm system. Another important role of the LC-NE system during stress is inhibition of the PFC, thereby favoring rapid instinctual responses over more complex ones in the service of surviving acute life-threatening situations [890].

Early studies suggested that LC neuronal activity was driven primarily by aversive stimuli and that NE was essentially a stress neurotransmitter. These observations led to a number of hypotheses that the function of the LC-NE system was alarm- or anxiety-related. However, electrophysiological studies demonstrated that phasic responses are elicited by appetitive as well as aversive stimuli, provided that a stimulus is perceived as salient [893,894]. And microdialysis studies demonstrated elevated extracellular NE levels in response to appetitively conditioned stimuli [895–897]. Combined, these observations suggest that both phasic and tonic LC discharge activity is related to the overall salience and/or arousing nature of a given stimulus more closely than it is to the affective valence of the stimulus [898]. In this regard, our understanding of NE seems to be following the same developmental path as has our understanding of DA and CREB, from affective-hedonic valence to salience.

Noradrenergic antagonists were found to block stress-induced reinstatement [487,489,899], much as did CRF antagonists. The brain sites for these effects appear to have been the ventral noradrenergic bundle projections to the BNST. Neurotoxin-specific lesions of the ventral noradrenergic bundle were found to attenuate stress-induced reinstatement of heroin responding [489], and local injection of a β-adrenergic receptor antagonist into the BNST also blocked stress-induced reinstatement in cocaine-trained rats [488]. The conditioned release of NE in the BNST in response to stressors may elevate anxiety, which then augments the reward value of drugs through negative reinforcement processes [827,900].

2.2.4. *Norepinephrine (NE) and serotonin (5-HT)*

The College de France group [496] first demonstrated that psychostimulant- or opiate-induced locomotor activation and behavioral sensitization are entirely dependent on the stimulation of two non-dopaminergic monoaminergic receptors, α_{1b}-adrenergic and 5-HT_{2A}. They then followed up with another study [901], in which they found that repeated treatments with *d*-amphetamine increased the reactivity of both noradrenergic and serotonergic neurons, and that this hyperreactivity could be blocked by pre-treatment with an α_{1b}-adrenergic or a 5-HT_{2A} receptor antagonist. They postulated that in naïve animals both types of neuron regulate one another through these two receptors. For example, the activation of noradrenergic cells by external stimuli would be immediately attenuated by serotonergic cells, the activation of which is itself triggered by noradrenergic neurons. They hypothesized that this closely coupled control vanishes after repeated administration of *d*-amphetamine. And they proposed that this long-term uncoupling between noradrenergic and serotonergic neurons may explain the extreme sensitivity to emotions described by human addicts during withdrawal. After noting that stressful situations cross-sensitize with the effects of psychostimulants or opiates on behavioral sensitization, they concluded with the statement that chronic stress could therefore also induce an uncoupling between noradrenergic and serotonergic systems and thus be one source of mental illnesses such as bipolar disorder. They might just as easily have concluded that this noradrenergic-serotonergic uncoupling due to chronic stress could be a source of addictive disorders.

2.2.5. *Serotonin (5-HT)*

Serotonin (5-HT), 5-HT receptors, and the 5-HT transporter (5-HTT) have been the subjects of considerable interest in recent years. Genetic research has focused on the 5-HTT-linked polymorphic region (5-HTTLPR), the promoter region of the gene that encodes 5-HTT, which contains a common functional polymorphism with a variable number of tandem repeats (the short allele has 14 repeat elements, the long allele has 16) [226,680,902–910]. Research that investigates the effects of the postnatal environment on neurobiological development has focused on the 5-HT receptors, primarily the 5-HT_{1A} and to a lesser extent the 5-HT_{1B} and the 5-HT_{2A} [911–914]. And research that explores the interaction between genetic and environmental factors has thus far focused primarily on the 5-HTTLPR [915–918], and to a lesser extent on the 5-HT_{2A} receptor [919]. While discussion of developmental research has been deferred to another publication, its mention here may serve to indicate that the 5-HT system is receiving a lot more scientific attention than might be inferred from the following review.

The 5-HTT is an integral membrane glycoprotein that occurs in pre-synaptic neuronal membranes. Its job is to take up 5-HT into the pre-synaptic neurons after its release in synaptic spaces, with the function of terminating the synaptic action of 5-HT and recycling it [689].

A study reported that alcoholic subjects had a lower 5-HTT density in perigenual anterior cingulate cortex than did control subjects [920]. The difference was not explained by a nonspecific ethanol-induced down-regulation of 5-HTT, nor by a general neuronal loss in the frontal cortex [921,922]. These results also indicated that lower 5-HTT density in the perigenual anterior cingulate cortex was not correlated with age at time of death (which was presumed roughly to reflect the duration of ethanol abuse). Another study found lower midbrain and amygdala 5-HTT radioligand [11C]McN 5652 BP2 (binding potential) in subjects with major depressive disorder than in controls [850]. BP2 did not correlate with depression severity. The authors interpreted the lower [11C]McN 5652 BP2 in the subjects with major depressive disorder to reflect lower Bmax, or lower total number of available 5-HTT binding sites. Less 5-HT input to the amygdala, as suggested by the finding of lower 5-HTT BP2, may result in increased amygdala activity [923], as 5-HT enhances inhibition in the amygdala, presumably through activation of GABA interneurons [924].

2.2.6. Dopamine (DA)

The chronic mild stress model has been suggested to have the best face validity of any animal model of depression, in that repeated mild stresses over time gradually induce a state of decreased responsiveness to rewards and reduced sexual and aggressive behaviors [925]. Rodents exposed to this model demonstrate decreased D_2/D_3 receptor binding in the NAc, which is reversed by chronic antidepressant treatment (TCAs, SSRIs, or mianserin) [926].

A recent study used functional magnetic resonance imaging to assess the activity of brain reward systems after *d*-amphetamine challenge in 12 drug-free depressed patients and 12 matched controls [806]. The depressed subjects had a markedly greater behavioral response to the rewarding effects of the psychostimulant and altered brain activation of the ventrolateral PFC, orbitofrontal cortex, caudate, and putamen. These findings suggest that major depressive disorder involves dysfunction of the dopaminergic system. Two earlier sets of research results round out the picture: (1) the finding that glucocorticoids selectively facilitated DA transmission in the NAc [816]; and (2) the finding that when subjects who reported poor early life maternal care were exposed to a psychosocial stressor, their ventral striatal DA concentrations increased more than did those of subjects who did not so report, and the DA increase was correlated with an increase in salivary cortisol concentrations [927].

The high incidence of hypercortisolemia in depression, particularly in severe depression, raises speculation that elevated cortisol concentrations alter dopaminergic reward systems, thereby altering hedonic responsiveness [928]. One proposed model posits that over time, frequent bouts of stress associated with intermittent increased exposure to glucocorticoids sensitizes the mesolimbic DA system [929]. Such sensitization of the mesolimbic DA system would predispose a person to develop an addictive disorder.

2.2.7. Endocannabinoids

The endocannabinoid (eCB) system appears to be involved in modulation of depression [930], stress [931,932] and anxiety [933–935], while its absence results in a greater vulnerability to stress [936]. Chronic stress was reported to down-regulate CB_1 receptor expression and significantly reduce the content of the endocannabinoid 2-arachidonoyl glycerol within the hippocampus [937]. CB_1 knockout mice were found to show increased aggressiveness, anxiety-like responses, depressive-like responses in the chronic unpredictable mild stress procedure [938], and HPA axis changes that included reduced basal corticosterone secretion and hypersensitivity to restraint stress [939]. Evidence for an endogenous anxiolytic cannabinoid tone also comes from the anxiogenic effects of the CB_1 receptor antagonist rimonabant [940]. The eCB system might be activated in response to anxiogenic situations and might regulate emotional states by modulating amygdala outputs, as part of a negative feedback system that limits anxiety [932,941].

The primary function of the eCB system seems to be regulation or containment of chronic stress. Disruption of the eCB system would be likely to increase the level of chronic stress, which in turn would increase the likelihood of an addictive disorder developing.

2.2.8. Cyclic AMP response element binding protein (CREB)

A review article [942] proposed that cAMP response element-binding protein (CREB) has a role in anxiety and ethanol-drinking behaviors. Wistar rats with high levels of anxiety were reported to consume more ethanol than did those with low levels of anxiety [943], and strains of rats that were bred to consume large quantities of ethanol were reported to exhibit more anxiety-like behaviors than did their ethanol-nonpreferring counterparts [944–946]. The transcription factor CREB regulates the expression of the gene that encodes neuropeptide Y (NPY), which is involved in the regulation of anxiety and the modulation of ethanol consumption. Intracerebroventricular (icv) infusion of NPY was found to significantly attenuate the ethanol intake of P rats but not of NP rats [686] and to produce electrophysiological effects similar to those that ethanol produced in P rats [947]. Transgenic mice that overexpress NPY also were found to have a lower preference for ethanol [695]. Conversely, NPY-null mutant mice were observed to consume greater quantities of ethanol, and mice that lacked the RIIβ regulatory subunit of the PKA gene and thus were unable to phosphorylate CREB were reported to consume greater amounts of ethanol than did wild-type mice [948]. CREB has been proposed to regulate anxiety and ethanol abuse behaviors via NPY [949]. Noting that CREB is associated also with the molecular effects of other addictive drugs, the author suggested that changes in synaptic plasticity that are mediated by CREB might be a common factor in ethanol and drug addiction.

Another review [950] reported that CREB is stimulated in the NAc by exposure to several types of drugs of abuse or stress, and that CREB function in the NAc normally is regulated by glutamatergic and dopaminergic inputs [951]. Numerous studies have established that CREB activity in this region has a profound effect on an animal's responsiveness to emotional stimuli [952,953]. The authors understood these findings to suggest that – by determining the set point of NAc neurons [954] – CREB represents an emotional gate for behavioral responsivity. Viral vector-mediated elevations of CREB within the rat NAc were found to produce anhedonia-like signs and a generalized numbing of behavioral responses to both aversive and pleasurable emotional stimuli [646,647,649]. Similarly, overexpression of CREB in the NAc of inducible transgenic mice was found to produce a depression-like phenotype [955] and to reduce the rewarding effects of cocaine [659]. The authors observed that short-term increases in CREB activity in the NAc, induced by normal rewarding or aversive stimuli, can serve to dampen responses to subsequent stimuli and facilitate the ability to actively deal with the situation at hand. However, they noted, under more pathological conditions, larger and more sustained increases in CREB activity, induced by drugs of abuse or excessive stress, can lead to an excessive dampening of emotional reactivity and to the depression-like phenotype outlined above.

These two reviews – the first by Pandey in 2003, the second by Nestler and Carlezon in 2006 – present perspectives on CREB that are thought-provokingly divergent, yet mutually compatible. For immediate purposes, we can note that affect regulation is a non-linear dynamic balance, and that anhedonia is probably just as conducive to addictive behavior as is anxiety.

2.2.9. *Brain-derived neurotrophic factor (BDNF)*

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family. It is highly expressed in various brain regions and is involved in neuronal survival, functional differentiation, and synaptic strength [956–961]. Its action is mediated by binding to tyrosine kinase B (TrkB), a high-affinity receptor that is localized on cell bodies and dendrites as well as postsynaptically [962,963]. BDNF is involved in synaptic plasticity and cellular processes of learning, such as long-term potentiation (LTP) or memory consolidation [956]. BDNF application facilitates LTP, while reduction of BDNF levels attenuates LTP [467]. BDNF is synthesized in mesolimbic dopaminergic neurons [964]. It is responsible for the developmental appearance of the D_3 receptor, which is selective for the NAc, and for maintaining expression of the receptor during adulthood [965,966]. BDNF has been strongly connected to the effects of serotonergic agents in animal studies [967,968], and augmentation of serotonergic activity within various brain areas after infusion of BDNF into the midbrain has been reported [969].

Infusion of BDNF into the VTA promotes the behavioral actions of drugs of abuse [540]. When administered directly into the VTA or NAc, it causes a significant increase in cocaine-induced locomotor activity and in cocaine reward [970–972]. Meanwhile, a deficiency in BDNF has been reported to promote ethanol intake in mice [973,974]. Application of any of several abusable drugs – including amphetamine [975], morphine [976], cocaine [977], Δ9-tetrahydrocannabinol [978], and nicotine [979] – was found to up-regulate the expression of BDNF. Intermittent, exogenous application of BDNF either centrally or into the VTA was reported to decrease food intake and body weight and to increase behavioral activity [980–983], a set of effects that is reminiscent of the psychostimulants. Patients with eating disorders were reported to have low serum levels of BDNF, which rose to the normal range when the patients were treated with antidepressant medications [984].

Pandey et al. [985] reported finding that CREB-deficient mice that had been displaying anxiety-like behaviors and increased ethanol consumption turned out also to have deficient expression of BDNF in several brain regions, including the amygdala [986]. These results suggested that the effects of decreased CREB levels on anxiety-like behaviors and ethanol consumption may have been mediated by the reduction of BDNF levels in amygdaloid structures. Pandey et al. proposed that a deficiency of BDNF in the CeA and MeA (medial amygdala) results in decreased CREB phosphorylation in the CeA and MeA and in low levels of NPY in the CeA, both of which promote anxiety-like behaviors and ethanol consumption. A similar association between low BDNF level and the combination of anxiety-like behaviors and increased ethanol consumption was reported by Yan et al. [987] to occur in P rats, though the low BDNF levels (as compared to NP rats) were observed in the NAc, not the amygdala.

Most of the clinically relevant research about BDNF that has been published concerns the relationship between BDNF and depression. Serum levels of BDNF in patients with major depressive disorder prior to initiation of antidepressant treatment were found to be lower than were those of healthy subjects [988–992], and moreover were found to be negatively correlated with the severity of depression [988,990,992]. After several weeks of treatment with antidepressant medication (presumably effective), patients' BDNF levels increased to levels similar to those of the control subjects [991,993–995]. In studies that used animal models of depression, depressive states were shown to be associated with reduced BDNF levels in the brain, and central administration of BDNF was shown to reverse such depressive states [996–1000].

What about the relationship between BDNF and depression? One hypothesis would be that reduced BDNF might reflect a genetic vulnerability to develop depression. Another possible explanation would be that stress-induced BDNF reductions might cause neuronal damage, which would in turn lead to acquired biological vulnerability. Stress decreases levels of BDNF expression in the dentate gyrus and pyramidal cell layer of hippocampus [999,1001]. This reduction appears to be mediated partly via stress-induced glucocorticoids and partly via other processes, such as stress-induced increases in serotonergic activity [999–1003]. Stress, which can precipitate and exacerbate depression, causes neuronal atrophy and death, especially in the hippocampus [1004–1008].

From the viewpoint of stress-induced BDNF reduction, low BDNF levels in our antidepressant-naïve patients with depression may reflect the collapse of the stress-adaptation system and its failure to protect the brain from stress-induced neuronal degeneration [990]. Addictive behavior can be understood as the last resort of a stress-adaptation system that is failing to maintain allostasis.

2.2.10. *Neuropeptide Y (NPY)*

In recent years, NPY has emerged as a significant factor in affect regulation. In rodent models, central NPY is released following stress and attenuates the behavioral consequences of stress [1009–1012]. While NPY knockout mice were found to display an anxiety-like phenotype [684,1013], transgenic rats with selective NPY overexpression were shown to be resistant to stress-induced increases in anxiety-like behavior [1014,1015]. The Y1 subtype of NPY receptor has been most strongly implicated in mediating anxiolytic behaviors [1016–1021]. Meanwhile, Y2 receptors seem to be anxiogenic [1022–1026], with the possible exception of Y2 receptors in the locus coeruleus, which were reported to be involved in mediating decreases in anxiety-like behavior [1008].

The anxiolytic effects of NPY appear to be mediated by Y1 receptors in the amygdala, particularly in its central nucleus [670,1025]. The CeA receives NPYergic innervation from the nucleus of the solitary tract, arcuate nucleus, and lateral septum [1009,1027]. NPY neurons in the amygdala project to the BNST [1028], which also contains NPY Y1 receptors and NPY Y1 and Y2 receptor mRNA [1029–1031]. The BNST projects to the dorsal vagal complex and consequently may have effects on the autonomic nervous system [1028,1032].

The Y2 receptor is believed to be a presynaptic autoreceptor that limits the transmission of NPY [1033,1034]. Therefore, Y2 agonists could produce an anxiogenic-like effect by inhibiting NPY release. NPY is found within GABA interneurons in the basolateral nucleus of the amygdala (BLA) [1035], and also is colocalized with GABA in the suprachiasmatic nucleus. In the latter region, NPY can decrease the inhibitory effects of tonic GABA release via presynaptic Y2 receptors [1036–1038]. When

the inhibitory actions of GABA are reduced, both inhibition of and opposition to stimulatory glutamatergic function diminish, and neuronal activity increases significantly. Activation of Y2 receptors in the BLA could suppress the release of both NPY and GABA, thereby producing an excitatory state in the nucleus that results in the expression of anxiety-like behavior.

A number of studies have reported that ethanol-preferring P rats have lower levels of NPY in the CeA than do nonpreferring NP rats [1039–1041], and that P rats also have been found to display more anxiety-like behavior and to be more sensitive to the anxiolytic effects of ethanol [944]. Some investigators have taken the next step and hypothesized that the higher consumption of ethanol by P rats could be motivated by higher anxiety levels [1041–1043]. Pandey et al. [1041] reported that both anxiety and ethanol drinking were reduced in P rats when NPY activity in the central or medial amygdala was increased, either directly by infusion of NPY, or indirectly by increasing CREB function. They reported also that anxiety and ethanol drinking were increased in NP rats when NPY activity was reduced by decreasing CREB function in the same brain area [1041]. Primeaux et al. [1044] found that rats that had been identified as ''anxious'' on the basis of their performance in an elevated plus maze consumed more ethanol solution than did the nonanxious rats. They then found that treatment of anxious rats with a viral vector that mediated an increase in CeA NPY decreased their ethanol preference more than did treatment of other anxious rats with an antisense NPY vector. Combined with previous research findings that virally mediated increases in CeA NPY decreased anxiety-related behaviors [1045], these data can be understood to suggest that treatment that increased CeA NPY activity in anxious rats led to a reduction in their anxiety, and thus to a reduction in their preference for ethanol. The results of these studies support Valdez and Koob's [1046] ''revisionist tension reduction hypothesis'' that consumption of ethanol (especially to the point that it becomes self-damaging) subserves a motivation to alleviate negative affect and stress.

2.2.11. *Galanin*

In rodent models, expression of galanin in the brain is altered by various stressors, while administration of galanin can modulate anxiety-like responses to stress. A recent study of the central amygdala showed that, while mild stress did not alter galanin levels, a model of high stress did increase galanin release [1047]. Other studies of centrally administered galanin in rats [1048] and of galanin overexpressing transgenic mice [1049,1050] appear to support the view that galanin may modulate behavioral responses to significant stress (i.e., high levels of noradrenergic activation in the central amygdala), but may remain dormant under conditions of mild stress [1051]. Emerging evidence further supports a role for galanin in the mediation of depression-related behaviors in rodents [1052].

Stress can evoke a variety of potential modulatory interactions involving NE and galanin in the CeA and BNST, depending on the nature of the stressor and the response elicited, the subset of noradrenergic neurons activated, and the degree to which these systems are activated. Dysregulation of the normal interaction between NE and galanin may contribute to the development of stress-related behavioral disorders, including, for example, stress-induced reinstatement of drug-seeking behavior, a process that has been associated with noradrenergic mechanisms in the CeA and BNST [488] More generally, dysregulation of the interaction between NE and galanin may be involved in stress-related neuropsychiatric illnesses such as depression, PTSD, or other anxiety disorders.

Ethanol intake increases galanin mRNA expression in the rat hypothalamus [1053], whereas galanin injected into the third ventricle or the hypothalamus increases ethanol consumption in rats that have learned to consume ethanol at moderate levels [1054,781]. This suggests the possibility of a positive feedback loop between galanin and ethanol intake [1055].

A significant association between galanin haplotypes and alcoholism has been demonstrated in both Finnish Caucasian and Plains American Indian men [1056]. In both populations, the two haplotypes A and B, differing by only one allele and therefore originating from a common ancestral haplotype, were risk factors for alcoholism. The other two haplotypes, C and D, also differing by only one allele and also derived from a shared ancestral haplotype, were protective against alcoholism. These findings from two independent populations suggest that galanin may contribute to vulnerability to alcoholism, perhaps mediated by dimensional anxiety.

2.2.12. *Substance P (SP)*

Anatomical and functional studies suggest that SP is a central stress neurotransmitter. SP and its preferred tachykinin NK-1 receptor are expressed throughout the fear-processing pathways of the brain, including the amygdala, hippocampus, hypothalamus and periaqueductal grey [1057–1059]. Central injection of SP agonists produces a range of defensive behavioral and cardiovascular reactions in animals, including conditioned place aversion [1060].

Observations from basic research had suggested that SP might be involved in the etiology of affective and anxiety disorders [1061–1064]. In animal models of depression (chronic mild stress) and anxiety (social interaction test), the NK-1 receptor antagonist NKP608 was shown to exert antidepressant and anxiolytic activity [1061,1064]. A randomized double-blind placebo-controlled study was conducted to evaluate the safety and efficacy of the NK-1 receptor antagonist MK-869, and the results were encouraging [1065]. Rupniak and Kramer [1061] suggested that SP might be the neurobiological correlate of the subjective experience that has been called 'emotional pain' – a state in which the type of affect caused by trauma is expressed, but devoid of the sensation of pain. They speculated that autonomous hyperactivity in SP neurotransmission might contribute to the anxiety, fear, and emotional pain that accompany affective and anxiety disorders.

2.2.13. *Dynorphin*

Shirayama et al. [1066] reported that levels of dynorphin A and dynorphin B immunoreactivity in rats' hippocampus and NAc increased when the rats were exposed to learned helplessness (LH) and immobilization stress, and that exposure to forced swim stress increased dynorphin A levels in the hippocampus. Additionally, they found that infusions of the κ-opioid antagonist nor-binaltorphimine dihydrochloride into the dentate gyrus or CA3 regions of the hippocampus and into the shell or core regions of the NAc produced antidepressant-like effects

in the LH paradigm. Earlier studies had reported that infusion of an antagonist of the κ-opioid receptor, the primary receptor for dynorphin, produced an antidepressant effect in two behavioral models of depression, the forced swim test [649,1067] and the learned helplessness paradigm [955].

Dynorphin is co-localized with glutamate, the primary neurotransmitter in granule cells, and synaptic release of dynorphin has been reported to cause pre-synaptic inhibition of glutamate release from the mossy fiber and perforant pathway terminals [1068].

Shirayama et al. [997] found that microinfusions of BDNF into the hippocampus produced an effect similar to blockade of κ-opioid receptors. Previous studies had provided evidence of a link between BDNF and dynorphin. Infusions of BDNF were reported to decrease levels of dynorphin [1069], raising the possibility that the actions of BDNF could be accounted for by down-regulation of dynorphin. This also is consistent with reports that stress decreases BDNF, which could result in increased dynorphin, and that antidepressant treatment up-regulates the expression of this neurotrophic factor in the hippocampus [996,999; reviewed in 1070].

GABAergic projection neurons in the NAc receive inputs from VTA DA neurons that express dynorphin. Dynorphin serves a negative feedback process by acting on presynaptic κ-opioid receptors to inhibit DA neuronal function.

2.2.14. *ΔFosB*

The expression of ΔFosB can be induced by either chronic drug exposure or chronic stress. Chronic drug exposure has been reported to induce ΔFosB expression primarily in the NAc and dorsal striatum, with lower levels of induction observed in the frontal cortex and amygdala [654,1071–1075]. Chronic stress has been reported to induce ΔFosB expression predominantly in the frontal cortex, NAc, and amygdala. Perrotti et al. [1075] suggested that stress induction of ΔFosB within dynorphin + -NAc and dorsal striatal neurons would increase the drive for drugs, and could thereby mediate in part the tendency of stress to increase vulnerability for drug addiction and relapse.

2.2.15. *GABA*

Ethanol has been found to produce anti-conflict (anti-anxiety) actions in the social interaction test, elevated plus maze, and in operant procedures [1076]. These anti-anxiety effects were shown to be blocked by administration of the $GABA_A$ receptor antagonist picrotoxin [1077] and by isopropylcyclophosphate, a compound that binds near or at the $GABA_A$ chloride ionophore [1078]. Low doses of benzodiazepine inverse agonists also were found to block the anti-anxiety effects of ethanol, but to have anxiogenic-like effects on their own at these doses [1079,1080]. Administration of picrotoxin was reported to decrease ethanol intake [1081], as was pre-treatment with the picrotoxin ligand isopropylbicyclophosphate or with the benzodiazepine inverse agonist RO 15-4513 [552]. $GABA_A$ receptors seem to mediate a critical component of ethanol's anti-anxiety effect, and to affect ethanol intake in ways that suggest the significant contribution that negative reinforcement (alleviation of anxiety) makes to the motivation to consume ethanol.

A study that was reported by Castelli et al. [1082] demonstrated that $GABA_B$ receptors in limbic areas and to a lesser extent in the cortex functioned about half as well in ethanol-naïve ethanol-preferring sP rats as they did in ethanol-naïve ethanol-nonpreferring sNP rats. The sP rats required more than twice the concentration of the $GABA_B$ agonist baclofen as did the sNP rats to achieve the same result. The diminished responsivity of the $GABA_B$ receptors was attributed to genetically determined differences in G-protein activation. Previous studies were reported to have found that ethanol-naïve sP rats displayed a higher degree of anxiety-related behaviors than did ethanol-naïve sNP rats [945,1083,1084], and that $GABA_B$ receptors are involved in the neural substrate mediating anxiety-related behaviors [1085]. The authors proposed that the lower $GABA_B$ receptor function in sP than in sNP rats that they observed could have contributed to the development of the higher degree of anxiety-related behaviors that sP rats had been found to display. They suggested that baclofen-induced suppression of ethanol-drinking behavior in sP rats might have been secondary to the substitution of its anxiolytic effect for that of voluntarily consumed ethanol. Their hypothesis seems to be that genetically determined alterations of their $GABA_B$ receptors left sP rats susceptible to higher degrees of anxiety (chronic stress), the alleviation of which provided them with substantial negative reinforcement for consuming ethanol. The rats' predilection for imbibing thus resulted not from their preference for ethanol, as their sP designation implies, but from their preference for freedom from anxiety. This hypothetical vignette exemplifies the impaired affect regulation aspect of the addictive process.

2.3. *Impaired behavioral inhibition*

Impulsivity has increasingly come to be understood as a heterogeneous phenomenon that includes impaired inhibitory control of behavior, intolerance to delay of reward, and premature decision-making [1086,1087]. However, these three forms of impulsivity are not on the same level, neither theoretically nor practically. Theoretically, impaired inhibitory control of behavior is the final common pathway of all forms of impulsivity. If an organism can refrain from acting in response to an instance of delay intolerance or a premature decision, impulsive behavior does not occur. Practically, unless we are dealing with organisms that can communicate their subjective experiences of delay-intolerance, decision-making, and intent to inhibit behavior, we must infer these processes from behavior that we observe. Compared to intolerance to delay of reward and premature decision-making, impaired inhibitory control of behavior remains closer to the observational data and depends on a simpler, more direct form of inference. These considerations informed the identification of this component of the addictive process as *impaired behavioral inhibition*.

2.3.1. *Serotonin (5-HT)*

Serotonin (5-HT) has come to be recognized as being the main player in behavioral inhibition [1088]. Studies have determined that low levels of cerebrospinal fluid (CSF) 5-hydroxylindolacetic acid (5-HIAA), a major metabolite of 5-HT and an indicator of 5-HT activity, are associated primarily with impulsivity and to a lesser but still significant extent with aggression, depression, and early-onset alcoholism

[1089,1090; reviewed in 1091, 1092]. An association between low 5-HT activity and impulsive behavior has been demonstrated also by prolactin release after fenfluramine challenge [1093]. Low levels of 5-HIAA were found in the CSF of bulimic subjects [1094], and a preclinical study found decreased levels of 5-HT and 5-HIAA in the brains of rats that tended to acquire self-administration of amphetamine [1095].

The 5-HT receptors that have been most often associated with addictive disorders are 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A}. The 5-HT_{2C} receptor is the only receptor that when stimulated inhibits many addiction-related behaviors [468]. Interestingly, most of the recent research on 5-HT receptors and impaired behavioral inhibition has focused on bulimia (other than genetic and developmental studies, which are reviewed in a separate publication).

PET studies have demonstrated increased 5-HT_{1A} receptor binding in several cortical areas of patients with active bulimia [1096], and in subjects who had recovered from bulimia or from bulimic-type anorexia [1097,1098]. A wide cortical distribution of increased 5-HT_{1A} receptor binding might reflect a diffuse dysregulation of 5-HT activity that could be associated with impaired impulse control [1096,1099]. Increased receptor binding (i.e., binding of labeled ligand to receptor) can indicate either increased receptor density or decreased intrasynaptic neurotransmitter/neuromodulator concentration. In the absence of evidence that a functional 5-HT_{1A} receptor gene polymorphism is associated with bulimia [1096], increased 5-HT_{1A} receptor binding most likely reflects low levels of intrasynaptic 5-HT.

A study with mice revealed a specific association between the 5-HT_{1B} receptor and impulsivity [1100]. 5-HT_{1B} receptors are expressed on the terminals of GABAergic striatal neurons that project to the substantia nigra and VTA [1101,1102]. Activation of these receptors may inhibit the release of GABA onto dopaminergic neurons, thereby disinhibiting the dopaminergic neurons [1103].

5-HT_{2A} receptor binding was found to be reduced in the orbitofrontal cortex of subjects who had recovered from bulimia [1104], and in the cingulate, parietal, and mesial temporal cortices of subjects who had recovered from bulimic-type anorexia [1105]. Decreased 5-HT activity at orbitofrontal, cingulate, parietal, or mesial temporal 5-HT_{2A} receptors could reflect impulsiveness and altered emotional processing [1106].

5-HT transporter (5-HTT) binding was found to be decreased in the midbrain of obese binge-eating women [1107]. A follow-up of treated patients whose binge-eating disorder was in remission showed significantly increased 5-HTT binding, as compared to unchanged results in controls [1108].

While decreased 5-HTT binding in association with active binge-eating disorder that increases when the disorder remits indicates a transitory 'state' condition, reduced 5-HT activity (or increased 5-HT receptor binding) in bulimic syndromes that persists long after the disorder has gone into remission implies a chronic 'trait' condition. The latter is likely to represent a primary vulnerability that arose independently of the eating disorder and contributed to its pathogenesis [1104,1105,1109]. Collateral information about the 5-HT system suggests that this vulnerability relates not to food ingestion or gustatory-gastric sensations, but to impaired behavioral inhibition or impulsivity. Thus it is not specific to bulimia, but could contribute to the development of any addictive disorder.

2.3.2. *Dopamine (DA)*

Jentsch and Taylor [1110] hypothesized that the inhibitory modulation of reward-seeking behavior may depend critically upon the corticostriatal projections from the medial frontal cortex to the caudate nucleus and NAc. Studies had demonstrated that lesions to the frontal cortex [1111] or DA depletion within the PFC [1112,1113] can augment the locomotive and reinforcing effects of psychostimulants. A hypothesis emerged, according to which the cortical DA system tonically inhibits subcortical DA systems [1114]. Under such circumstances, dopaminergic hypofunction in the frontal cortex can result in the disinhibition of mesolimbic DA systems [1115,1116; review 1117]. Thus, a loss of DA function in the PFC can result in an increased vulnerability to self-administer psychostimulant drugs [1118,1119] or to engage addictively in another behavior that activates the mesolimbic DA system. This hypothesis is supported by the preclinical finding that animals that were more vulnerable to acquiring intravenous drug self-administration showed reduced dopaminergic activity in the PFC [1117].

Amphetamine has been shown to increase premature responding in the 5-choice serial reaction time task (5-CSRTT), which is generally considered to represent behavioral disinhibition [1120–1122]. This premature responding was shown to be attenuated by DA depletion of the NAc [1121] and by systemic administration of the non-selective DA receptor antagonist α-flupentixol [1120]. Van Gaalen et al. [1087] investigated the effects of a number of substances on rats that had been well-trained in the 5-CSRTT. Premature responding was found to be increased by amphetamine, cocaine, nicotine, and the DA reuptake inhibitor GBR 12909. It was found to be decreased by the NE reuptake inhibitor desipramine and by the DA D_1 receptor antagonist SCH 23390, but not by the DA D_2 receptor antagonist eticlopride. Meanwhile, the increments in premature responding that had been evoked by amphetamine, cocaine, and nicotine were found to be attenuated by eticlopride, whereas SCH 23390 reduced the drug-induced behavioral disinhibition only at a dose that by itself decreased premature responding. The authors concluded that premature responding in general is regulated by DA D_1, while behavioral disinhibition that is induced by drugs of abuse depends on activation of DA D_2 receptors. Supersensitivity of either D_1 or D_2 receptors could conceivably result, directly or indirectly (respectively), in impaired behavioral inhibition and thus could contribute to the development of an addictive process.

An elegant study by Dalley et al. [1123] demonstrated relationships between trait impulsivity, reduced D_2/D_3 receptor availability, and tendency to escalate self-administration of cocaine. Rats' performance on the 5-CSRTT was used to identify a group of high-impulsive rats and a group of non-impulsive rats. Positron emission tomography then demonstrated that D_2/D_3[4] receptor availability was significantly

[4] Dalley et al (2007) used the high-affinity DA D_2/D_3 receptor radiotracer [^{18}F] fallypride, which does not distinguish between D_2 and D_3 receptors.

reduced in the ventral striatum but not in the dorsolateral striatum of high-impulsive rats as compared to non-impulsive rats, and that D_2/D_3 receptor availability in the ventral striatum was inversely correlated with impulsivity. When the heretofore cocaine-naïve rats were trained to self-administer cocaine, rats that exhibited trait impulsivity on the 5-CSRTT showed a greater tendency for escalation of intravenous cocaine self-administration than did their non-impulsive counterparts. The authors concluded that their findings demonstrated that trait impulsivity predicts cocaine reinforcement and that decreased D_2 receptor availability in the striatum may be a predisposing neurobiological trait and not only a consequence of chronic cocaine exposure. This study echoes and affirms the findings related to D_2 receptors that we reviewed in the Motivation-Reward section. Further investigation of the relationships between D_2 receptors, motivation-reward, behavioral inhibition, and addictive behavior patterns is likely to be both fascinating and productive.

Research on the relationship between addiction and DA D_4 and D_5 receptors has been concerned primarily with genetic factors. A variable number tandem repeat (VNTR) polymorphism located in the third exon of the DA D_4 receptor gene has been found to be associated with impulsive personality traits [1124] and to be a risk factor for adolescent ethanol abuse [1125], adolescent hard drug use [1126], heroin abuse [1127], cue-elicited heroin craving [1128], severity of ethanol and opiate addiction [1129], pathological gambling [1124], binge-eating [1130], and cue-elicited craving for food [1131]. On the other hand, a few studies found no or negligible association between D_4 receptor gene exon III polymorphism and alcoholism [1132,1133] or heroin addiction [1134]. The common 148 bp allele of a microsatellite polymorphism at the D_5 receptor gene was found to be correlated with substance abuse and novelty seeking in females [220]. It also was found to be associated with attention-deficit/hyperactivity disorder [1135,1136], which is only weakly suggestive of a relationship to addiction but indicates a potentially fruitful direction for further research.

3. Conclusion

The present article represents the flowering of an idea that was planted in 1990:

> A hypothesis may be submitted, the gist of which is that similar patterns in behavioral manifestations of the various addictive disorders. . .reflect similarities in some set of personality and/or biological variables, which may or may not be measurable by instruments currently available. In other words, addictive disorders would be most accurately described, not as a variety of addictions, but as a basic underlying addictive process, which may be expressed in one or more of various behavioral manifestations. [1]

At the time that the preceding sentences were published, addiction neuroscience was young, and much of the research that could evaluate the hypothesis of an underlying addictive process had not yet been conducted. In the intervening years, addiction neuroscience has advanced so considerably that the hypothesis is no longer radical. Perhaps the continuing trajectory of scientific progress soon will render it no longer necessary.

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