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# Can autism be triggered by acetaminophen activation of the endocannabinoid system?

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Acetaminophen use in children has been associated with increased autism risk. Recent evidence suggests that acetaminophen's analgesic actions result from activation of the endocannabinoid system, and activation of this system can have neuromodulatory consequences during development. This investigation was performed to determine if there is evidence to support the hypothesis that acetaminophen use can trigger autism by activation of the endocannabinoid system.

Key words: autistic disorder, autism, acetaminophen, cannabinoid receptors, endocannabinoid system

## INTRODUCTION

Autism is a severe developmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that appear in early childhood (American Psychiatric Association 1994). Autism can be comorbid with tuberous sclerosis (1.2%), fragile X syndrome (0.3%), and congenital rubella syndrome (0.3%), although the attributable proportion of all medical disorders is less than 10%, and in most cases the cause of autism is unknown (Fombonne 2003). Two of the prominent features of autism are immune system dysregulation (Pessah et al. 2008) and abnormal brain neuron organization (Courchesne et al. 2007). In this report we present evidence of a link to autism from acetaminophen use, evidence to show that acetaminophen produces analgesia by activating cannabinoid receptors, and evidence that activation of the cannabinoid receptors may interfere with normal development to trigger autism.

## A LINK TO AUTISM FROM ACETAMINOPHEN USE

There are several theories about possible environmental triggers for autism including childhood vaccinations, mercury exposure, and viral infections. Descriptive clinical studies have suggested a link between measles, mumps, rubella (MMR) vaccination and autism/pervasive developmental disorder (Kawashima et al. 2000, Wakefield et al. 2000, Furlano et al. 2001, Singh et al. 2002, Uhlman et al. 2002, Singh and Jensen 2003). Epidemiological studies have not supported the relationship between prevalence of autism and the MMR vaccine (Peltola et al. 1998, Taylor et al. 1999, Dales et al. 2001, Madsen et al. 2002, Chen et al. 2004).

The link between the MMR vaccine and an elevated risk for autism is controversial. However, children are often given acetaminophen if they have symptoms such as fever or irritability, and the MMR vaccination can cause these symptoms (Centers for Disease Control and Prevention 2009). One study showed that administration of acetaminophen after the MMR vaccination is associated with increased risk for autism (Schultz et al. 2008).

A further report compared the features of autism with asthma and suggested a link to acetaminophen use (Becker and Schultz 2009). In this report, events in the history of acetaminophen use were compared with the number of eligible persons with autism from a 1999 report to the legislature by the California DDS (Department of Developmental Services 1999).

The three pathways for the metabolism of acetaminophen are glucuronidation, sulfation, and the

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cytochrome P-450 system. One study of children with autism indicated that these children had a sulfation deficit which causes them to process acetaminophen differently from control children (Alberti et al. 1999). Sulfation is the primary pathway for acetaminophen metabolism until age 10–12 years (Defendi and Tucker 2009). It is possible that children predisposed to developing autism have a sulfation deficit which may lead to increased blood levels of acetaminophen after therapeutic doses of acetaminophen are administered.

## EVIDENCE THAT ACETAMINOPHEN PRODUCES ANALGESIA BY ACTIVATING CANNABINOID RECEPTORS

Although acetaminophen has been used as an analgesic for more than a hundred years, its mechanism of action has remained elusive. It has recently been shown by two independent groups (Hogestatt et al. 2005, Bertolini et al. 2006) that acetaminophen produces analgesia by potentiating cannabinoid receptors in the brain. These observations have been confirmed by Mallet and colleagues (2008).

Hogestatt and colleagues have shown that acetaminophen is deacetylated to p-aminophenol which is conjugated with arachidonic acid in the brain and spinal cord by fatty acid amide hydrolase (FAAH). The resulting compound, N-arachidonoylphenolamine inhibits the cellular uptake of anandamide, a naturally occurring endogenous cannabinoid or endocannabinoid. The result is increased levels of endocannabinoids which produce an analgesic effect (Hogestatt et al. 2005).

Bertolini and colleagues (2006) noticed a similarity in the effect of acetaminophen and cannabinoids. Cannabinoids and acetaminophen both have an analgesic action and lower body temperature. They were able to show that blockage of cannabinoid receptor 1 ($CB_1$) completely prevents the analgesic activity of acetaminophen (Bertolini et al. 2006).

## EVIDENCE THAT MODULATION OF THE CANNABINOID SYSTEM MAY INTERFERE WITH NORMAL DEVELOPMENT

The endocannabinoid system plays an important role in the development of the central nervous system and its activation can induce long-lasting functional alterations (Campolongo et al. 2009). Use of cannabis (an exogenous cannabinoid) in the still-maturing brain may produce persistent alterations in brain structure and cognition (Jager and Ramsey 2008). Animal models have revealed the danger of both cannabis abuse and exposure to cannabinoid drugs during brain development (Anavi-Goffer and Mulder 2009). Developmental problems associated with the endocannabinoid system may occur through either of the two known cannabinoid receptors, $CB_1$ or $CB_2$.

$CB_1$ receptors are located in the central nervous system (CNS), peripheral nervous system, and peripheral organs. In the CNS, $CB_1$ receptors are concentrated in the cerebellum, hippocampus, and the basal ganglia (Drysdale and Platt 2003) which are areas in the brain implicated as dysfunctional in autism (Bauman and Kemper 2005, Courchesne et al. 2007). During fetal life, $CB_1$ receptors and their associated endocannabinoids are important for neuron differentiation and proper axonal migration (Fride et al. 2009). In addition, recent studies suggest that $CB_1$ cannabinoid receptors define synapse positioning (Harkany et al. 2008). Modulation of $CB_1$ cannabinoid receptors could trigger autism by interrupting normal brain development.

$CB_2$ receptors are primarily located in immune tissues and cells and may serve a regulatory function. $CB_2$ receptors have been shown to control the movement of inflammatory cells to the site of injury, and $CB_2$ receptors' reverse agonists may serve as immune system modulators (Lunn et al. 2008). The activation of $CB_2$ receptors stimulate beta-amyloid removal by macrophages which may slow the progression of Alzheimer's Disease (Tolon et al. 2009). $CB_2$ receptor agonists attenuate transendothelial migration of monocytes and monocyte-endothelial adhesion (Rajesh et al. 2007).

Monocytes are one of the primary cells of the immune system and differentiate into macrophages and dendritic cells. If the evidence is correct that acetaminophen acts as an activator of cannabinoid receptors, then activating $CB_2$ receptors could influence the growth of monocytes. Data from our lab indicates that acetaminophen in the media inhibits the cell division of monocytes in a dose dependent manner as assayed with resazurin stain for mitochondrial dehydrogenase activity. Inhibition of growth is noted even at the therapeutic concentration of 20 micrograms per milliliter. If as proposed, children with autism are poor metabolizers of acetaminophen, higher than normal therapeutic levels could be possible with recommended doses which could lead to a greater inhibition of monocytes.

It has been shown in several studies that children with autism have immune system dysregulation (Warren et al. 1996, Jyonouchi et al. 2005, Ashwood et al. 2006, Molloy et al. 2006, Li et al. 2009, Entstrom et al. 2010). This dysregulation includes differential monocyte responses, abnormal T helper cytokine levels, decreased T cell mitogen response, decreased numbers of lymphocytes, and abnormal serum immunoglobulin levels. Many studies have shown that children with autism exhibit autoimmunity, in particular antibodies against brain and central nervous system proteins (Singh et al. 1993, Connolly et al. 1999, Ashwood and Van De Water 2004, Cohly and Panja 2005, Kawashti et al. 2006, Wills et al. 2007, Martin et al. 2008). It is proposed that the immune dysregulation in children with autism is due to the influence of acetaminophen on $CB_2$ receptors during gestation or in early childhood.

## HYPOTHESIS

The hypothesis presented here is that the use of acetaminophen may trigger autism by activating the endocannabinoid system thereby interfering with normal development. Children who are poor metabolizers of acetaminophen may be at higher risk since normal therapeutic doses may lead to higher blood levels in these children.

It has been proposed that the blockage of fever with antipyretics (as acetaminophen) could lead to autism by interfering with normal immunologic development (Torres 2003). Children with autism have reported to have a decrease in autism symptoms when they have a fever (Sullivan 1980, Cotterill 1985, Torres 2003, Curran et al. 2007). It is interesting to note that activation of $CB_1$ receptors, in addition to providing an analgesic effect, causes a decrease in body temperature (Fraga et al. 2009). This type of effect may be further evidence of endocannabinoid disruption in children with autism.

## LIMITATIONS

Other environmental factors may also be involved in triggering autism. For example, low levels of breastfeeding could decrease immune protection in infants by decreasing mother to child transfer of IgA. Decreased immune protection could make a child more vulnerable to viral infection which in theory could lead to autism. Lack of breastfeeding has been shown to be associated with autism (Schultz et al. 2006). This same study found an association between use of infant formula without docosahexaenoic acid or arachidonic acid supplementation and autism. Arachidonic acid metabolism is an integral part of the endocannabinoid system and its disruption could be further evidence of a role for the endocannabinoid system in autism.

## CONCLUSION

The purpose of this report was to explore a possible correlation between acetaminophen and autism which acts through activation of the cannabinoid system. If this hypothesis is correct, it opens new avenues of investigation for possible autism treatment including agonists and antagonists of the $CB_1$ and $CB_2$ receptors.

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