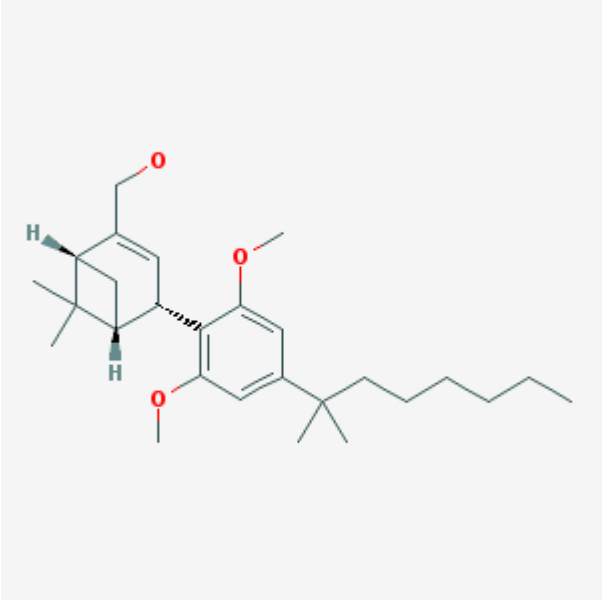
Gadolinium-HU-308-incorporated micelles

CB2R-Targeted micelles

Kam Leung, PhD[1]

Created: March 15, 2011; Updated: April 21, 2011.

Chemical name:	Gadolinium-HU-308-incorporated micelles	
Abbreviated name:	CB2R-Targeted micelles	
Synonym:		
Agent category:	Compound	
Target:	Cannabinoid receptor 2 (CNR2 or CB2)	
Target category:	Receptor	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal/ contrast:	Gadolinium, Gd	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on the above structure (HU-308) for additional information in PubChem.

[1] National for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

NLM Citation: Leung K. Gadolinium-HU-308-incorporated micelles. 2011 Mar 15 [Updated 2011 Apr 21]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

There are two subtypes of cannabinoid receptors in mammalian tissues: CB1 and CB2 (1, 2). CB1 is expressed abundantly in neuronal terminals in the central nervous system (CNS) and in some peripheral tissues to inhibit neurotransmitter release. CB1 is found predominately in the striatum, hippocampus, substantia nigra, globus pallidus, and cerebellum. CB2 is present mainly on immune cells in the blood and peripheral tissues (the spleen) to modulate cytokine release (3). However, CB2 has been found in the CNS tissues (neurons and glial cells) at very low levels (4). Both receptor subtypes are coupled through $G_{i/o}$ proteins to inhibit adenylate cyclase and to modulate potassium and calcium channels. CB1 has been shown to be involved in analgesia, regulation of food intake, and control of movement in normal subjects (3). Alteration of CB1 function has been implicated in a number of human diseases such as depression, schizophrenia, and obesity (5-7). Upregulation of CB2 in the brain is associated with neuroinflammation in disorders such as Alzheimer's disease, multiple sclerosis, encephalitis, and Down's syndrome (8). CB2 is also involved in inflammation associated with pain, osteoporosis, cancer, and liver diseases (9).

Gadolinium (Gd), a lanthanide metal ion with seven unpaired electrons, has been shown to be very effective in enhancing proton relaxation because of its high magnetic moment and water coordination (10, 11). Gd-Diethylenetriamine pentaacetic acid (Gd-DTPA) was the first intravenous magnetic resonance imaging (MRI) contrast agent used clinically, and a number of similar Gd chelates have been developed in an effort to further improve clinical use. However, these low molecular weight Gd chelates have short blood and tissue retention times, which limit their use as imaging agents in the vasculature and cancerous tissues. Various macromolecular Gd complexes have demonstrated superior contrast enhancement for MRI of the vasculature and carcinomas (12-14); however, these Gd complexes cannot proceed into further clinical development because of high tissue accumulation and slow excretion of toxic Gd ions. Furthermore, they are largely nonspecific.

HU-308 is a potent selective CB2 agonist *in vitro* and in mice (15, 16). HU-308 and Gd-DTPA were incorporated into di-stearoyl-polyethylene glycol-phosphatidylethanolamine 2000 (DSPE-PEG2000) micelles (CB2R-targeted micelles) for MRI of vulnerable atherosclerotic plaques (17, 18).

Related Resource Links:

- Chapters in MICAD (CB2)
- Gene information in NCBI (CB2)
- Articles Online Mendelian Inheritance in Man (OMIM) (CB2)
- Clinical trials (CB2)
- Drug information in FDA (CB2)

Synthesis

[PubMed]

A mixture of DSPE-PEG2000, Gd-DTPA-bisstearylamide, lissamine-rhodamine-phosphatidylethanolamine, and HU-308 in a molar ratio of 35:50:5:10 in chloroform was dried by rotary evaporation for 3 min at 40°C (18). The lipid film was subsequently hydrated for 5 min with 1 ml phosphate-buffered saline to a final lipid concentration of 10 mM and a final Gd-DTPA-bisstearylamide concentration of 5 mM. Control micelles were prepared similarly in a molar ratio of 45:5:50 without HU-308. CB2-Targeted and control micelles had diameters of 16.5 ± 1.2 nm and 19 ± 1 nm, respectively, as determined with dynamic light scattering. CB2R-Targeted micelles exhibited an r1 relaxivity value of 2.7 $mM^{-1}s^{-1}$ in phosphate-buffered saline at 9.4 T and 37°C, whereas Gd-DTPA exhibited an r1 relaxivity value of 1.8 $mM^{-1}s^{-1}$ under the same conditions.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

CB2R-Targeted micelles showed upregulation of mitogen-activated protein kinase in Chinese hamster ovary (CHO) cells transfected with CB2 but not in CHO cells without CB2 after 15 min of incubation (18). Binding studies showed that MRI contrast enhancement was only observed in CHO cells positive for CB2 with CB2R-targeted micelles and not with control micelles.

Animal Studies

Rodents

[PubMed]

te Boekhorst et al. (18) used a 9.4-T MRI scanner to perform *in vivo* MRI in apolipoprotein E–deficient/endothelial nitric oxide synthase deficient ($ApoE^{-/-}/eNOS^{-/-}$) mice, which exhibit severe atherosclerosis in the abdominal area. CB2R-Targeted micelles (n = 9, 67 μmol/kg Gd), control micelles (n = 9, 67 μmol/kg Gd), and Gd-DTPA (n = 3, 300 μmol/mouse) were injected in the mice. Both CB2R-targeted and control micelles accumulated in aortic plaque within 15 min after injection as observed with MRI. After a few hours, lymph node and liver enhancement were also observed, whereas kidney, spleen and pre-vertebral muscle did not show enhancement. The normalized enhancement ratio (NER_{CB2R} versus control) for aortic plaque remained stable at 42 h and 48 h (1.95 ± 0.29, 1.90 ± 0.33, respectively) after injection with CB2R-targeted micelles, whereas $NER_{Control}$ (1.13 ± 0.18, 1.22 ± 0.15, respectively) decreased to preinjection levels at 42 h and 48 h after injection of control micelles ($P < 0.05$–0.01). $NER_{Gd\text{-}DTPA}$ peaked at 1.57 ± 0.12 at 1.5 h after injection of Gd-DTPA, returning to baseline levels at 2.5 h. $NER_{lymph\ node}$ was 1.3 at 12 h after injection of CB2R-targeted micelles, and NER_{liver} was 1.5 at 24 h after injection of CB2R-targeted micelles. The Gd levels in the excised atherosclerotic aorta at

24 h after injection of targeted and control micelles were 4.38 ± 8.34 and 3.63 ± 2.50 μg/g, respectively. At 48 h, the Gd levels were 3.31 ± 1.57 and 1.61 ± 0.45 μg/g for targeted and control micelles ($P < 0.05$), respectively. Immunohistochemical staining showed that CB2R-targeted micelles were colocalized with macrophages in the aortic plaque. No blocking studies were performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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