Gadolinium-*bis*-5-hydroxytriptamide-diethylenetriamine pentaacetic acid

Gd-*bis*-5-HT-DTPA

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Chemical name:	Gadolinium-*bis*-5-hydroxytriptamide-diethylenetriamine pentaacetic acid	
Abbreviated name:	Gd-*bis*-5-HT-DTPA	
Synonym:	MPO-Gd	
Agent Category:	Compound	
Target:	Myeloperoxidase (MPO)	
Target Category:	Enzyme	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal / contrast:	Gd	
Activation:	Yes	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

Inflammation is believed to be a precursor to a variety disorders such as diabetes, cardiovascular diseases, chronic obstructive pulmonary disease, depression, dementia, cancers, etc., and low-grade systemic inflammation is recognized as a predictor of the development of most of these diseases (1). The process of inflammation is triggered when there is an anticipated or real threat (infection, injury, etc.) to tissue homeostasis, and the main aim of this response is to diminish the threat and begin repairs at the site of distress (2). Once the process of inflammation is initiated, there is a recruitment of myeloid cells

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(neutrophils, microglia, and macrophages) at the site of the trauma, and these cells secrete a variety of pro-inflammation mediators, including myeloperoxidase (MPO), a heme-containing enzyme that helps maintain the inflammatory state of the tissue. MPO is produced and secreted mainly by the myeloid cells, metabolizes hydrogen peroxide (H_2O_2) to produce elevated levels of cytotoxic reactive oxygen species (e.g., hypochlorous acid, HOCl), and promotes further tissue injury and inflammation at the site of recruitment (3, 4). Therefore, the quantification of MPO activity in normal and inflamed tissue could be an excellent biomarker to predict the potential development and progression of the various inflammatory disorders (5). For this, investigators developed gadolinium-*bis*-5-hydroxytriptamide-diethylenetriamine pentaacetic acid (Gd-*bis*-5-HT-DTPA; also known as MPO-Gd), a magnetic resonance imaging (MRI) agent, that acts as a substrate for the MPO and used it for the noninvasive visualization of MPO activity in normal and diseased tissues (3).

Oxidative activation of the paramagnetic substrate (Gd-bis-5-HT-DTPA) by MPO leads to oligomerization and entrapment of the activated Gd-bis-5-HT-DTPA within the tissue by cross-linking the monomer or the oligomer with tyrosine-containing proteins, thereby increasing the localized concentration Gd at the site of MPO activity as explained in detail by Rodriguez et al. (5). In addition, the oligomeric and entrapped Gd-bis-5-HT-DTPA has a slow clearance rate from the tissue compared to the non-activated compound, and delayed clearance of the activated Gd-bis-5-HT-DTPA allows for the imaging of MPO in the inflamed tissue.

Related Resource Links

Human myeloperoxidase nucleotide and protein sequences

Clinical trials related to myeloperoxidase

Myeloperoxidase related pathways in Pathways Interaction Database

Myeloperoxidase in Online Mendelian Inheritance in Man Database (OMIM)

Synthesis

[PubMed]

The synthesis of Gd-bis-5-HT-DTPA has been described by Rodriguez et al. (5). The final product (yield not reported) was purified with high-performance liquid chromatography and had a purity of >96%. The molecular weight of purified Gd-bis-5-HT-DTPA was determined to be 707.33 (expected 707.22) with mass spectroscopy analysis.

The biodistribution of Gd-bis-5-HT-DTPA was investigated in mice bearing matrix gel implants containing immobilized human MPO and glucose oxidase using ^{111}In-labeled *bis*-5-HT-DTPA (^{111}In-*bis*-5-HT-DTPA) as a surrogate tracer for the MRI agent (6). The synthesis of ^{111}In-*bis*-5-HT-DTPA has been described by Chen et al. (6). The

radiochemical yield, purity, and specific activity of the labeled compound were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The r_1 relaxivity value of Gd-bis-5-HT-DTPA was determined to be 5.6 $mM^{-1}s^{-1}$ (5). The reduction potential of *bis*-5-HT-DTPA alone was reported to be 0.63 (5).

The stability of Gd-bis-5-HT-DTPA was studied in a transmetallation reaction as described by Rodriguez et al. (5). Briefly, 2.5 mM Gd-bis-5-HT-DTPA in 1 mL phosphate buffer (pH 7.0) was exposed 10 µL $ZnCl_2$ (250 mM) in water, and the T_1 values of the solution were measured for 3 days at 40°C. Two different parameters were measured: the kinetic index, which is the time required to reach 80% of the initial R_1 value, and the thermodynamic index, which is the ratio of the R_1 value after 3 days (4,320 min) and the R_1 at $t = 0$ (% of R_1 after 3 days). The kinetic index and the thermodynamic index of Gd-bis-5-HT-DTPA were determined to be 2,866 min and 0.76, respectively.

In another study, up to 5 mM Gd-bis-5-HT-DTPA was shown to be non-toxic to NIH 3T3 cells for at least 12 h as determined with a cell metabolic activity assay using 3-(4,5-dimethylthiazol-2-yl)2,5-diphenyl-tetrazolium bromide (MTT) (5).

Animal Studies

Rodents

[PubMed]

The biodistribution of Gd-bis-5-HT-DTPA was investigated in mice bearing basement membrane matrix gel implants containing 15 U immobilized human MPO and 4 U glucose oxidase (generates H_2O_2 and is necessary to detect the activity of MPO) on the right thigh as described by Chen et al. (6). This model system was used to mimic the accumulation of MPO in the inflamed tissue. For use as a control, the left thigh of each animal was implanted with a matrix gel containing no enzymes. The animals ($n = 3$ animals/group) were injected intravenously with a saline solution of 2.96–3.70 MBq (80–100 µCi) ^{111}In-*bis*-5-HT-DTPA and subjected to fused single-photon emission computed tomographic and computed tomographic (SPECT/CT) imaging 3 h postinjection (p.i.). At 6 h p.i., the animals were euthanized to determine the percent dose of radioactivity present per gram tissue (% ID/g) of the major organs. From the SPECT/CT images, it was clear that high amounts of radioactivity were present in the gel matrix containing the MPO on the right leg of the animal, but almost no tracer was detected in the control gel matrix on the left leg. A 2.3 ± 0.3-fold increase in radioactivity was observed in the right leg compared to the control leg. The biodistribution data showed that 90% ID was excreted by the animals by 6 h p.i. Little radioactivity was detected in most organs except

the spleen, bowel, kidney, and liver, which contained ~2% ID/g, ~1.5% ID/g, ~0.75% ID/g, and ~0.5% ID/g of the label, respectively.

To visualize the accumulation of Gd-containing contrast agents in gel matrices containing MPO, other animals (n = 3 mice/group) were subjected to magnetic resonance imaging (MRI) at 3 h after an injection of Gd-DTPA, Gd-*bis*-tyramide-DTPA, Gd-5-HT-DOTA, or Gd-*bis*-5-HT-DTPA (6). Contrast enhancement obtained from the MRI images was reported as relative contrast/noise ratios (CNR) as described by Chen et al. (6). An increased CNR was observed only in the right leg of animals injected with Gd-5-HT-DOTA (CNR = 1.7, $P < 0.001$) or Gd-*bis*-5-HT-DTPA (CNR = 1.9, $P < 0.001$).

Rodriguez et al. showed that MRI with Gd-bis-5-HT-DTPA could detect as little as 0.005 U MPO/mg matrix gel implants in mice, indicating that the agent was suitable for detection of the early stages of inflammation in a murine model (5).

To investigate the induction and secretion of mouse endogenous MPO, matrix gel containing MPO and embedded with *Escherichia coli* lipopolysaccharide (LPS) was implanted in the right thigh of mice (n = 3 animals) (6). Matrix gel implants in the left thigh of the animals contained no LPS as a control. Four days later, an examination of the implant in the right legs showed the presence of a large number of cells that were positive for MPO by immunostaining; however, the implants in the left legs showed the presence of few cells and were negative for MPO by immunostaining. When Gd-bis-5-HT-DTPA was administered to the animals, there was a 1.3-fold increase in contrast material on the right side for at least 50 min after the Gd-bis-5-HT-DTPA injection ($P < 0.001$). No such increase was observed in the left thigh of the mice or when the animals were injected with Gd-DTPA (6).

In another study, MRI with Gd-bis-5-HT-DTPA was shown to distinguish inflammation from tumor and peritumoral edema in rats (3).

From these studies, the investigators concluded that MPO activity in matrix implants and rodent inflamed tissue can be detected with MPO-sensitive MRI probes (6).

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

No publications are currently available.

Supplemental Information

[Disclaimers]

No supplemental information is currently available.

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