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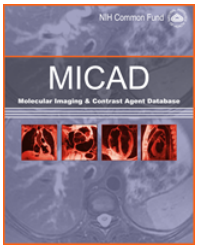

Gadolinium diethylenetriamine pentaacetic acid-Arg-Gly-Asp peptidomimetic

Gd-DTPA-g-mimRGD

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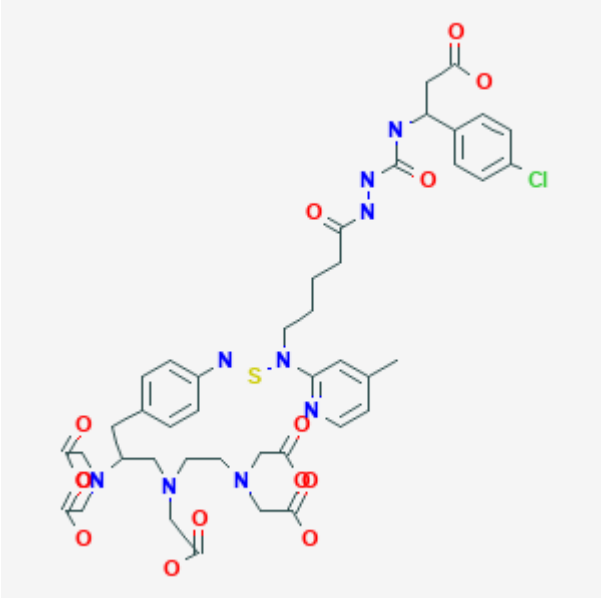
Chemical name:	Gadolinium diethylenetriamine pentaacetic acid-Arg-Gly-Asp peptidomimetic
Abbreviated name:	Gd-DTPA-g-mimRGD
Synonym:	
Agent Category:	Peptide
Target:	Integrin $\alpha_v\beta_3$
Target Category:	Receptor binding
Method of detection:	Magnetic resonance imaging (MRI)
Source of signal/ contrast:	Gd
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Magnetic resonance imaging (MRI) maps information about tissues spatially and functionally. Protons (hydrogen nuclei) are widely used in imaging because of their abundance in water molecules. Water comprises ~80% of most soft tissue. The contrast of proton MRI depends primarily on the density of the nucleus (proton spins), the relaxation times of the nuclear magnetization (T1, longitudinal, and T2, transverse), the magnetic environment of the tissues, and the blood flow to the tissues. However, insufficient contrast between normal and diseased tissues requires the development of contrast agents. Most contrast agents affect the T1 and T2 relaxation times of the surrounding nuclei, mainly the protons of water. T2* is the spin–spin relaxation time

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composed of variations from molecular interactions and intrinsic magnetic heterogeneities of tissues in the magnetic field (1).

Integrins are a family of heterodimeric glycoproteins on cell surfaces that mediate diverse biological events involving cell–cell and cell–matrix interactions (2). Integrins consist of an α and a β subunit and are important for cell adhesion and signal transduction. The $\alpha_v\beta_3$ integrin is the most prominent receptor affecting tumor growth, tumor invasiveness, metastasis, tumor-induced angiogenesis, inflammation, osteoporosis, and rheumatoid arthritis (3-8). Expression of the $\alpha_v\beta_3$ integrin is strong on tumor cells and activated endothelial cells, whereas expression is weak on resting endothelial cells and most normal tissues. The $\alpha_v\beta_3$ antagonists are being studied as antitumor and antiangiogenic agents, and the agonists are being studied as angiogenic agents for coronary angiogenesis (7, 9, 10). A tripeptide sequence consisting of Arg-Gly-Asp (RGD) has been identified as a recognition motif used by extracellular matrix proteins (vitronectin, fibrinogen, laminin, and collagen) to bind to a variety of integrins, including $\alpha_v\beta_3$. Various radiolabeled antagonists have been introduced for imaging of tumors and tumor angiogenesis (11).

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 (12, 13). Gd-Labeled diethylenetriamine pentaacetic acid (Gd-DTPA) was the first intravenous 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 cancer. Various macromolecular Gd complexes have demonstrated superior contrast enhancement for MRI of the vasculature and carcinomas (14-16); however, these Gd complexes did not proceed into further clinical development because of high tissue accumulation and slow excretion of toxic Gd ions. Furthermore, they are largely nonspecific. A low molecular weight, non-peptide, RGD mimetic (g-mimRGD, 5-{*N*'-[5-(4-Methylpyridin-2-ylamino)pentanoyl]hydrazino}-3-(4-biphenyl)-5-oxopentanoic acid trifluoroacetate) was identified to have good affinity and selectivity for the $\alpha_v\beta_3$ integrin (50% inhibition concentration, 3 nM) (17). Burtea et al. (18) conjugated mimRGD to Gd-DTPA to form Gd-DTPA-g-minRGD for non-invasive *in vivo* MRI of $\alpha_v\beta_3$ integrin expression in transgenic apolipoprotein E–deficient ($ApoE^{-/-}$) mice.

Synthesis

[PubMed]

Solid-phase synthesis was used to prepare g-mimRGD, which was coupled to DTPA with the use of 2-(4-isothiocyanatobenzyl)-DTPA (*p*-SCN-Bn-DTPA) in aqueous solution (pH 10) (18). DTPA-g-mimRGD was isolated with column chromatography and complexed with $GdCl_3.6H_2O$. The mass of Gd-DTPA-g-mimRGD was confirmed with mass spectroscopy with one DTPA per g-mimRGD. The Gd complex exhibited proton longitudinal (r_1) relaxivity values of 4.75 mM^{-1} s^{-1} at 0.47 T and 4.33 mM^{-1} s^{-1} at 1.5 T at 37°C.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Burtea et al. (18) performed *in vitro* binding studies of Gd-DTPA-g-mimRGD in cultured human Jurkat T cells with R_1 (longitudinal relaxation rate) MRI. Signal intensity was significantly higher ($P < 0.01$) with 0.4 mM Gd-DTPA-g-mimRGD than with 0.4 mM Gd-DTPA in Jurkat T cells with or without phorbol myristate acetate (PMA) stimulation. Co-incubation with 1.55 mM g-mimRGD inhibited the signal intensity by 36%. The R_1 measured at 1.5 T exhibited superior binding levels ($P < 0.05$) of Gd-DTPA-g-mimRGD to PMA-stimulated cells (0.065 s^{-1}) as compared with various controls, such as non-stimulated cells (0.023 s^{-1}), Gd-DTPA (0.012 s^{-1} for PMA samples and 0.0075 s^{-1} for non-stimulated cells), or cells submitted to g-mimRGD competition (0.038 s^{-}

^{1}). Gd-DTPA-g-mimRGD was found to be stable in blood plasma for up to 72 h of r_1 measurements, and it did not interact with human serum albumin. Gd-DTPA-g-mimRGD exhibited a higher stability against transmetallation with Zn^{2+}.

Animal Studies

Rodents

[PubMed]

Burtea et al. (18) used a 4.7-T MRI scanner to perform *in vivo* MRI in $ApoE^{-/-}$ mice (n = 10). Injection of Gd-DTPA-g-mimRGD (0.1 mmol/kg) provided strong enhancement in MRI contrast in the external structures of the aortic wall (tunica media and adventitia) within 10 min of injection; this enhancement was still visualized up to 90 min. On the other hand, Gd-DTPA provided only a diffuse contrast, and the aortic wall was not clearly outlined. Pretreatment with 0.1 mmol/kg Eu-DTPA-g-mimRGD inhibited the enhancement by 40% to 90% during the 90 min of scanning to nearly the same levels of contrast as control Gd-DTPA. Gd-DTPA-g-mimRGD exhibited a delayed clearance at 30 min and 60 min compared with Gd-DTPA. Immunohistochemical measurements of the excised aortas revealed the presence of various adhesion molecules in the aortas from the $ApoE^{-/-}$ mice but not in the aortas from wild-type control mice.

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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