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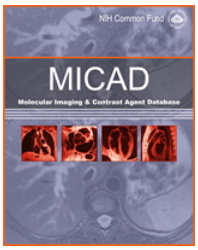

Gd-DOTA-c(Cys-Arg-Gly-Asp-Cys)

P975

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Chemical name:	Gd-DOTA-c(Cys-Arg-Gly-Asp-Cys)	
Abbreviated name:	P975	
Synonym:		
Agent category:	Peptide	
Target:	Platelet glycoprotein GPIIb/IIIa receptor (CD61/CD41)	
Target category:	Receptor	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal:	Gd	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure is not available in PubChem.

Background

[PubMed]

Magnetic resonance imaging (MRI) maps information about tissues spatially and functionally. Protons (hydrogen nuclei) are widely used to create images because of their abundance in water molecules, which comprise >80% of most soft tissues. The contrast of proton MRI images depends mainly on the density of nuclear proton spins, the relaxation times of the nuclear magnetization (T1, longitudinal; 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 use of contrast agents. Most contrast agents affect the T1 and T2 relaxation of the surrounding nuclei, mainly the protons of water. T2* is the spin–spin relaxation time composed of variations from molecular interactions and intrinsic magnetic heterogeneities of tissues in the magnetic field (1). Cross-linked iron oxide (CLIO) and other iron oxide formulations affect T2 primarily and lead to a decreased signal. On the other hand, paramagnetic T1 agents, such as gadolinium (Gd^{3+}) and manganese (Mn^{2+}), accelerate T1 relaxation and lead to increased contrast images.

Thrombosis plays a major role in many cardiovascular diseases, such as myocardial infarction, pulmonary embolism (PE), deep venous thrombosis (DVT), atherothrombosis, or cerebral venous thrombosis (2, 3). DVT is

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a significant cause of PE, which is a potentially life-threatening clinical problem. Thrombosis occurs when platelets deposit in regions of low flow in the deep venous system, followed by an activation process of thrombin, which then converts fibrinogen into fibrin. Platelets become activated and bind to fibrinogen, resulting in platelet aggregation *via* the platelet integrin GPIIb/IIIa ($\alpha_{IIb}\beta_3$, CD61/CD41). The thrombus may become organized or detached from the vessel wall.

A single-chain antibody (anti-LIBS 145) has been developed to recognize ligand-induced binding sites (LIBS) of GPIIb/IIIa that become exposed only upon binding to fibrinogen (4). Anti-LIBS 145 single-chain antibody does not bind to circulating platelets. Anti-LIBS 145 single-chain antibody was conjugated to microparticles of iron oxide (MPIOs) to form LIBS-MPIOs for T2-weighted MRI imaging of platelet-containing thrombi (5-8). The cyclic peptide P977 (cyclo(Cys-Arg-Gly-Asp-Cys)) was found to bind to platelet glycoprotein GPIIb/IIIa receptor with good affinity (9). P975 is composed of P977-conjugated gadolinium-tetraazacyclododecane-*N*,*N*',*N*",*N*""-tetraacetic acid (Gd-DOTA) (10). P975 is being developed as a non-invasive T1 MRI agent for GPIIb/IIIa expression in thrombi.

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (GPIIIa/CD61, GPIIb/CD41)
- Articles in OMIM (GPIIIa/CD61, GPIIb/CD41)
- Clinical trials (Integrin)
- Drug information in FDA

Synthesis

[PubMed]

Gd-DOTA was conjugated to P977 *via* a small linker at a 1:1 ratio (10). P975 exhibited an r_1 relaxivity value of 9 $mM^{-1}s^{-1}$ at 40°C and 60 MHz.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro competition binding to activated platelets was performed using FITC-fibrinogen with P975 and P977 (10). The 50% inhibition concentrations for P975 and P977 were 2.1 ± 0.3 μM and 1.6 ± 0.2 μM, respectively.

Animal Studies

Rodents

[PubMed]

Klink et al. (10) performed *in vivo* T1-weighted MRI (9.4 T) of arachidonic acid–treated right carotid arteries in mice (n = 5/group) to induce thrombosis. P975 or Gd-DOTA (0.1 mmol/kg) was injected intravenously after thrombus formation. MRI scans were performed every 15 min up to 120 min after injection. An initial signal enhancement was observed with both P975 and Gd-DOTA in the lumen of the thrombosed carotid artery at 30 min after injection. However, there was a rapid washout with Gd-DOTA. The enhancement with P975 persisted over time and was still present at 120 min. There were three-fold, six-fold, and seven-fold increases in change in contrast/noise ratio for the P975 group compared with the Gd-DOTA group, the sham surgery group, and the control group ($P < 0.01$), respectively, at 120 min after injection. Injection of eptifibatide (GPIIb/IIIa antagonist)

a few minutes before injection of P975 reduced the signal enhancement in the P975 group to the level of the Gd-DOTA group at 120 min after injection.

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.

NIH Support

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