Pyridine-tetra-acetate-gadolinium(III) (PTA-Gd) conjugated to 17β-estradiol (EPTA-Gd) or tamoxifen (TPTA-Gd)

EPTA-Gd; TPTA-Gd

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Chemical name:	Pyridine-tetra-acetate-gadolinium(III) (PTA-Gd) conjugated to 17β-estradiol (EPTA-Gd) or tamoxifen (TPTA-Gd)	
Abbreviated name:	EPTA-Gd; TPTA-Gd	
Synonym:		
Agent Category:	Compounds	
Target:	Estrogen receptor α (ER)	
Target Category:	Receptor	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal / contrast:	Gd	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

The luminal-A subtype of breast cancer (the other three subtypes are basal-like, epidermal growth factor receptor 2-positive, and luminal-B (1)) is characterized by overexpression of the estrogen receptor α (ERα) and has been reviewed by Geyer et al. (2). The biological activity and the mode of action of this receptor in the nucleus of a cell have been

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described by Nilsson et al. (3). In addition, ERα is known to promote cell proliferation that leads to the development of cancerous tumors in the breast (4). Therefore, the ERα is a major biomarker for the detection of ERα-positive (ER+) breast cancer, and the level of its expression in this malignancy is used to predict the response and the prognosis of anti-hormonal therapy for a patient (5). Currently, immunohistochemistry and ELISA are the most common methods used to determine the levels of ER in cancerous breast tissue, but these procedures require the use of invasive techniques to obtain biopsy samples from the primary tumor, and results generated from these tests show analytical variability due to a lack of standardized methods (6). Investigators have successfully used 16α-[^{18}F]-fluoro-17β-estradiol ([^{18}F]-FES) with positron emission tomography (PET) for the diagnostic imaging of ER+ breast cancer, but this technique may not visualize minute metastasized lesions, and the uptake of [^{18}F]-FES by the tumors has been shown to be blocked by estrogen analogs such as tamoxifen, a drug often used to treat breast cancer (6). Investigators have also used radiolabeled ER ligands with single-photon emission tomography (SPECT) to visualize this receptor in the breast tissue (7); however, no PET or SPECT agents have been approved by the United States Food and Drug Administration for the detection of ER+ tumors (8).

Recently, a magnetic resonance imaging (MRI) probe that targets the ER, pyridine-tetra-acetate-gadolinium(III) (PTA-Gd) conjugated to 17β-estradiol (EPTA-Gd), was synthesized and evaluated for the visualization of ER+ tumors in a mouse model of human breast cancer (8). In the same study, tamoxifen conjugated to PTA-Gd (TPTA-Gd) was also investigated for the imaging of these tumors.

Related Resource Links

Related chapters in MICAD

Estrogen receptor gene information; Gene ID: 2099 (NCBI)

Estrogen receptor in Online Mendelian Inheritance in Man database (OMIM)

Clinical trials related to estrogen receptor

Estrogen receptor imaging clinical trials

Estrogen replacement therapy

Synthesis

[PubMed]

The synthesis of PTA-Gd, TPTA-Gd, and EPTA-Gd has been described by Pais et al. (8). The chemical yields of TPTA-Gd and EPTA-Gd were reported to be 8-% and 86%, respectively. The T_1 relaxation rates (r_1) of TPTA-Gd, and EPTA-Gd measured at 9.4T were reported to be 4.7 ± 0.1 L/mmol/s and 6.8 ± 0.05 L/mmol/s, respectively.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In an ERα competitive binding assay with ^{3}H-labeled 17β-estradiol as the ER binding ligand, the K_i of EPTA-Gd and TPTA-Gd were determined to be 0.97 ± 0.07 μmol/L and 0.13 ± 0.006 μmol/L, respectively (8). The proton r_1 relaxivities of PTA-Gd (control), EPTA-Gd, and TPTA-Gd were measured in solution at 9.4 T and reported to be 3.0 ± 0.1(L/mmol)/s, 6.8 ± 0.7(L/mmol)/s, and 4.7 ± 0.1 (L/mmol)/s, respectively.

MDA-MB-231 cells (origin: human breast adenocarcinoma) transfected with a tetracycline-inducible ER gene (ER+ cells) were reported to have ER levels between 11,000 and 14,000 fmol/mg protein (8). Wild-type MDA-MB-231 cells (ER− cells) served as controls.

Animal Studies

Rodents

[PubMed]

Mice bearing tumors in the mammary fat pad (originating from ER+ and ER− cells, respectively) of the animals were used for the *in vivo* work described in this section (8). Both types of tumors grew at the same rate in the animals, and ER was induced in the ER + tumors by exposing the animals to doxycycline as described elsewhere (8). Induction of ER in the two tumor types was confirmed with immunostaining in the tumor tissue. Only the ER+ lesions showed strong ER staining in the nucleus, whereas very low staining was observed in the ER− tumor cell organelle.

The biodistribution of PTA-Gd, EPTA-Gd, and TPTA-Gd was studied in severe combined immune deficient mice (n = 5–6 animals/group for each compound) by injecting either 0.1 mmol/kg EPTA-Gd or 0.075 mmol/kg PTA-Gd and TPTA-Gd, respectively, through the tail vein of each rodent in a group (8). Approximately 50 min postinjection (p.i.), organs of interest were harvested from the animals to extract and measure with inductively coupled plasma-mass spectroscopy the amount of Gd(III) accumulated in the tissues. Results obtained from this study were presented as μg Gd/gram tissue (μg Gd/g). At 50 min p.i., PTA-Gd had cleared from most tissues and was present mainly in the kidneys (~40 μg Gd/g); EPTA-Gd accumulated primarily in the liver (~100 μg Gd/g), and TPTA-Gd was detected in the liver (~80 μg Gd/g), kidneys (~70 μg Gd/g), uterus (~30 μg Gd/g), and muscle (~20 μg Gd/g). This indicated that each of the contrast agents had a distinct biodistribution profile. Low amounts of the three contrast agents (less than ~5 μg Gd/g) were present in the brain. In addition, the probes showed a biphasic clearance from blood circulation, which is an initial rapid decrease in concentration followed by a gradual loss.

For *in vivo* MRI studies, mice bearing ER+ and ER– tumors were injected with 0.075 mmol/kg EPTA-Gd (n = 4–5 animals) and 0.15 mmol/kg TPTA-Gd or PTA-Gd (n = 4 animals/compound), respectively (8). The instrument settings and acquisition of MR images from the animals (under anesthesia) were described by Pais et al. (8). With EPTA-Gd, a significantly higher contrast (measured as percentage (%) enhancement over whole tumor volume) was observed in the ER+ tumors (46.1 ± 21.4%; P = 0.05) compared with the ER– lesions (28.3 ± 2.6%). Both TPTA-Gd and PTA-Gd showed a similar increase in contrast (P > 0.2) in the two types of tumors, indicating that these agents had no specific interaction or binding with the ER. At 40–45 p.i., EPTA-Gd had a contrast of 39.7 ± 17.7% in the ER+ tumors compared with 13.7 ± 3.3% in the muscles (P < 0.005). At the same time point, TPTA-Gd showed a significantly higher contrast (P < 0.01) in the muscles (28.5 ± 6.4%) compared with the ER+ tumors (12.2 ± 1.3%), indicating that this probe bound an unknown component(s) in the muscle.

For a blocking study, animals bearing ER+ and ER– tumors were given an intraperitoneal injection of tamoxifen (final dose, 0.07 mmol/kg; n = 3 mice) or 4-hydroxytamoxifen (final dose, 0.1 mmol/kg; n = 1 mouse) 1 h before the administration of EPTA-Gd through the tail vein (8). The MR images were acquired from the animals as described above. Images acquired at 20–25 min p.i. showed no significant difference in the contrast (P = 0.54) between the ER+ (38.4 ± 16.6%) and the ER– (29.1 ± 12.2%) tumors, and a similar pattern was evident at 40–45 min p.i. (contrast levels for the ER+ and the ER– tumors at this time point were 28.7 ± 7.1% and 29.4 ± 9.5%, respectively; P = 0.93). In addition, the contrast of the ER+ tumors in the anti-estrogen pretreated animals was not significantly different from that of the muscles (31.2 ± 7.0%, P = 0.36 at 20–25 min p.i., and 25.6 ± 6.5%, P =0.43 at 40–55 min p.i.). This study indicated that EPTA-Gd had a binding specificity for the ER.

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.

Supplemental Information

[Disclaimers]

No information is currently available.

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