Mairinger et al. BMC Pharmacology 2010, 10(Suppl 1):A46
http://www.biomedcentral.com/1471-2210/10/S1/A46

BMC Pharmacology

MEETING ABSTRACT Open Access

Small-animal PET evaluation of [^{11}C]MC113 as a PET tracer for P-glycoprotein

Severin Mairinger[1,2,3], Nicola A Colabufo[4], Thomas Wanek[1], Claudia Kuntner[1], Johann Stanek[2], Thomas Erker[3], Mariangela Cantore[4], Francesco Berardi[4], Roberto Perrone[4], Markus Müller[2], Oliver Langer[1,2*]

From 16th Scientific Symposium of the Austrian Pharmacological Society (APHAR)
Vienna, Austria. 25-27 November 2010

Background

The radiolabelled inhibitor of the multidrug efflux transporter P-glycoprotein (P-gp) [^{11}C]elacridar was developed as a positron emission tomography (PET) tracer to assess expression levels of P-gp at the blood-brain barrier (BBB) [1]. [^{11}C]Elacridar was shown to interact specifically with P-gp at the rodent BBB, but its brain PET signal was very low, which was possibly caused by transport of [^{11}C]elacridar by P-gp [1]. In an attempt to gain a better understanding of the required properties of an effective P-gp PET tracer we evaluated ^{11}C-labelled MC113, a structural analogue of elacridar, which was characterised as an unambiguous non-transported P-gp inhibitor and which possesses lower molecular weight, lower lipophilicity and higher potency for P-gp inhibition than elacridar (EC_{50} for inhibition of [^{3}H]vinblastine transport in Caco-2 cell monolayers: 0.6 μM vs. 2.0 μM for elacridar) [2].

Methods

Female wild-type (n = 3) and Mdr1a/b$^{-/-}$ (n = 2) mice (Taconic Inc., USA) underwent paired PET scans with [^{11}C]MC113 using a microPET Focus220 scanner (Siemens, Medical Solutions, USA). A baseline scan (150 min), during which the P-gp inhibitor tariquidar (15 mg/kg) was administered i.v. at 60 min after radiotracer injection, was followed by a second 60-min scan at 2 h after administration of tariquidar. Whole-brain time-activity curves were calculated using the image analysis software Amide.

Results

[^{11}C]MC113 was evaluated using an identical set-up which we had previously used for [^{11}C]elacridar and which employed a combination of chemical and genetic knockout of P-gp [1]. [^{11}C]MC113 had a 3 times higher peak brain activity uptake than [^{11}C]elacridar, but otherwise behaved identically to [^{11}C]elacridar, in that brain activity uptake was higher in Mdr1a/b$^{-/-}$ than in wild-type mice and that inhibitor administration increased brain activity uptake in wild-type mice. However, the observed effects were smaller for [^{11}C]MC113 than for [^{11}C]elacridar.

Conclusions

Our data suggest that [^{11}C]MC113 interacts with P-gp at the murine blood-brain barrier, but as for [^{11}C]elacridar its *in vivo* behaviour points to transport by P-gp. The higher brain activity uptake of [^{11}C]MC113 might be an advantage over [^{11}C]elacridar for PET imaging of P-gp.

Acknowledgements
The research leading to these results has received funding from the European Community's 7th Framework Program under grant agreement no. 201380 (Euripides) and from the Austrian Science Fund (FWF) project "Transmembrane Transporters in Health and Disease" (SFB F35).

Author details
[1]Health and Environment Department, Molecular Medicine, AIT Austrian Institute of Technology GmbH, 2444 Seibersdorf, Austria and Department of Clinical Pharmacology, Medical University of Vienna, 1090 Vienna, Austria. [2]Department of Clinical Pharmacology, Medical University of Vienna, 1090 Vienna, Austria. [3]Department of Medicinal Chemistry, University of Vienna, 1090 Vienna, Austria. [4]Dipartimento Farmacochimico, Facoltà di Farmacia, Università degli Studi di Bari "A. Moro", 70125 Bari, Italy.

Published: 16 November 2010

References
1. Dörner B, Kuntner C, Bankstahl JP, Bankstahl M, Stanek J, Wanek T, Stundner G, Mairinger S, Löscher W, Müller M, Langer O, Erker T: **Synthesis**

* Correspondence: oliver.langer@meduniwien.ac.at
[1]Health and Environment Department, Molecular Medicine, AIT Austrian Institute of Technology GmbH, 2444 Seibersdorf, Austria and Department of Clinical Pharmacology, Medical University of Vienna, 1090 Vienna, Austria
Full list of author information is available at the end of the article

and small-animal positron emission tomography evaluation of [^{11}C]-elacridar as a radiotracer to assess the distribution of P-glycoprotein at the blood-brain barrier. *J Med Chem* 2009, **52**:6073-6082.

2. Colabufo NA, Berardi F, Cantore M, Perrone MG, Contino M, Inglese C, Niso M, Perrone R, Azzariti A, Simone GM, Paradiso A: **4-Biphenyl and 2-naphthyl substituted 6,7-dimethoxytetrahydroisoquinoline derivatives as potent P-gp modulators.** *Bioorg Med Chem* 2008, **16**:3732-3743.

doi:10.1186/1471-2210-10-S1-A46
Cite this article as: Mairinger *et al.*: Small-animal PET evaluation of [^{11}C] MC113 as a PET tracer for P-glycoprotein. *BMC Pharmacology* 2010 **10**(Suppl 1):A46.