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Modelling of ADAM and MADAM

Introduction

This document reviews the publications on ADAM and MADAM PET studies.

Specificity

These radioligands are developed for imaging of serotonin transporter (SERT) in living human brain. Biggest problem with SERT PET radioligands has been very low selectivity. In this sense ADAM and MADAM seem to be really good tracers. All animal and human studies show that these tracers have high affinity and selectivity to SERT. Chalon et al. state that MADAM has around 1000-fold better selectivity for the serotonin transporter than for other transporters.

At least three radiolabels have been used with ADAM: ^{11}C, ^{18}F, ^{123}I. [^{11}C]ADAM seems to be a good tracer, but the half-life is considered to be too short [Chalon et al. 2003] since equilibrium of specific binding to serotonin transporters is obtained approximately two hours after injection. Over ^{11}C, ^{18}F label has the advantage of longer half-life and also lower positron energy and convenience for radiosynthesis.

In vitro rat studies with [^{3}H]MADAM [Chalon et al. 2003] determined total binding in the absence of any drug and nonspecific binding in the presence of 10^{-6} paroxetine. Nonspesific binding was found to be around 15%. Cerebral binding values fit well with known serotonin transporter localization. Radioactivity was highest in dorsal raphe, superior colliculi, frontal cortex and latero-dorsal thalamic nuclei. Compared to other SERT ligands, binding was quite high in the frontal cortex and relatively low in the caudate putamen. Binding values of a post mortem human brain study roughly paralleled those of the rat study.

Eleven whole body scans with [^{123}I]ADAM were performed in Helsinki University Central Hospital [Kauppinen et al. 2003]. Amount of activity as a percentage of injected dose (decay corrected) was found to be 25% in the lungs, 5.9% in the liver, 4.8% in the kidneys, 3.7% in the brain and 3.4% in the heart. Effective dose of [^{123}I]ADAM was determined to be approximately a 1-year dose of additional background radiation exposure.

Hospital of the University of Pennsylvania did seven whole body scans [Newberg et al. 2004]. It was confirmed that [^{123}I]ADAM had no effect on heart rate, blood pressure or laboratory results. It was also stated that [^{123}I]ADAM compares well with other radiopharmaceuticals.

In a mice study [Ye et al. 2004] highest specific binding levels were found in olfactory tubercle, lateral septal nucleus, hypothalamic nuclei, and thalamic nuclei, globus pallidus, central grey, substantia nigra, interpeduncular nucleus, dorsal raphe and median raphe. Also in frontal cortex, caudate putamen and hippocampus were found accumulation of [^{123}I]ADAM.

A 4-^{18}F-ADAM study was done with three rats and one female baboon [Shiue et al. 2003]. It was found that 4-^{18}F-ADAM was not metabolized in rat brain but was rapidly metabolized in the blood. Uptake in blood, muscle, lung, kidney and liver was initially high but cleared rapidly. In the brain initial uptake was also high but clearance was slow. Radioactivity was quite similar between brain regions two minutes after injection but the washout rate differed between regions cerebellum being the fastest. Ratio of specific binding to nonspecific binding increased with time and reached its peak at two hours after injection.

Modelling methods

Cerebellum was considered devoid of SERT and thus suitable to be used as reference region [Shuie et al. 2003, Lin et al. 2003, Ye et al. 2004, Newberg et al. 2003].
A one-site model (single binding site) was suggested for [^{3}H]MADAM [Chalon et al. 2003].
Lin et al used the transient equilibrium (TE) model, with cerebellum as reference region, to estimate binding potential. TE was reached approximately two hours after injection but was varying with different brain regions: higher specific binding ratio seemed to cause increasing peak equilibrium time.
Newberg et al fit multiexponential functions iteratively to regional time activity curves with nonlinear least squares regression algorithm.

References

1. Shiue, G et al.: N,N-Dimethyl-2-(2-Amino-4-^{18}F-Fluorophenylthio)-Benzylamine (4-^{18}F-ADAM): An improved PET Radioligand for Serotonin Transporters, *J Nuc Med* 2003; 44:1890-1897.

2. Lin, K-J et al.: Characterization of the Binding Sites for [^{123}I]ADAM and the Relationship to the Serotonin Transporter in Rat and Mouse Brains Using Quantitative Autoradiography, *J Nucl Med* 2004; 45:673-681.

3. Ye, X-X et al.: Microautoradiography of [^{123}I]ADAM in mice treated with fluoxetine and serotonin reuptake inhibitors, *J Nuc Med Bio* 2004; 31:557-562.

4. Newberg, A et al.: Biodistribution and Imaging with ^{123}I-ADAM: A Serotonin Transporter Imaging Agent, *J Nucl Med* 2004; 45:834-841

5. Kauppinen T et al.: Biodistribution and radiation dosimetry of [^{123}I]ADAM in healthy human subjects: preliminary results, *Eur J Nuc Med* 2003; 30:132-136.

6. Chalon et al.: Pharmacological Characterization of N,N-Dimethyl-2(2-amino-4-methylphenyl thio)benzylamine as a Ligand of the Serotonin Transporter with High Affinity and Selectivity, *J of Pharmacology and Experimental Therapeutics* 2003; 304:81-87.