In vivo Distribution of Radiolabelled Citalopram in Brain as a Marker of 5-HT Uptake Sites for PET

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ABSTRACT

In rat brain, the biologically active isomer (+)-N-methyl-11C)citalopram can be used to label 5-HT uptake sites in vivo, giving ratios of uptake in selected regions of interest relative to cerebellum of approximately 2:1. In human brain, however, the non-specific carbon-11 label is retained over a 50 min scanning period. Both (+)- and (-)-isomers gave similar summed images and similarly shaped time-activity curves for all regions analysed (including cerebellum). The reasons for the species difference in retention of non-specific label are not clear.

KEYWORDS

5-HT uptake site; citalopram; in vivo binding; PET

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Although positron emission tomography (PET) has considerable potential for studying the biochemical basis of neurologic and psychiatric disorders (Eriksson et al., 1990; Lucignani et al., 1989), its use in investigations of the serotonergic system is limited by the paucity of position-emitting radionuclides which have an in vivo selectivity for 5-hydroxytryptamine (5-HT) receptors or uptake sites. The antidepressant citalopram has been shown previously to be a selective inhibitor for 5-HT uptake in vivo in both rat (D’Amato et al., 1987) and man (Pfoege et al., 1990). Its high affinity and moderate lipophilicity make it a prospective candidate for PET, when labelled with carbon-11.

However, initial studies using the racemate (+)-N-methyl-11C)citalopram in rat showed only a small ‘specific’ signal in vivo (Hume et al., 1990). Ratios of radioactivity in selected regions of interest (ROIs) (e.g. cingulate cortex, thalamus) relative to cerebellum (a region identified by in vitro autoradiography as having no significant specific-binding) were approximately 1.5.

With the aim of augmenting the signal, the biologically active (+)-enantiomer of [N-methyl-11C]citalopram was prepared from (+)-prochiral oxazoline exsate by [11C]methylthion with non-carrier-added [11C]iodoacetic acid and its biodistribution following intravenous (i.v.) injection investigated. The distribution of the inactive (-)-enantiomer was also defined, with a view to its use in identifying the non-specific label in subsequent PET studies.

Time-activity curves for rat thalamus and cerebellum are shown in Fig. 1. Only the (+)-isomer of [N-methyl-11C]citalopram showed any significant signal. The non-specific label, identified by probing with non-radioactive (+)-citalopram, was similar to that obtained with the (-)-isomer.

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Fig. 1. Uptake in 2 regions of rat brain as a function of time after i.v. injection of (+)- or (-)-N-methyl-¹¹C)citalopram.

(Dots are Bq g⁻¹ tissue / injected Bq g⁻¹ body weight)

The individual cerebellum data (active isomer, tracer alone) were used as an input function in a reference tissue model, fitting for kₐ₀ₙ = B_mib/τ₀₀ and allowing the calculation of the specifically bound fraction. Thalamus, frontal cortex, caudate putamen, hippocampus and medulla all gave similar specific uptake curves, with a 20 % greater signal in thalamus. From 60 - 120 min, the specifically bound fraction was approximately 0.5.

In man, the shape of the time-activity curves following injection of (±)-N-methyl-¹¹C)citalopram were similar for all ROIs selected, including thalamus, caudate, frontoparietal cortex and also cerebellum. In addition, PET images of the in vivo distribution of the radiolabelled (+)- and (-)-enantiomers were similar, showing a constant cerebral concentration of carbon-11 label from 10 - 90 min post-injection. At the present time, the small specific signals identified in thalamus and caudate cannot be quantified.

In conclusion, although radiolabelled citalopram has been shown to be a very useful ligand for investigations of 5-HT uptake sites in vivo, retention of a high non-specific label negates its usefulness as an in vivo ligand in man, using PET.

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REFERENCES


