# *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*-$^{11}$C]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 90 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

## *IN VIVO* DISTRIBUTION OF RADIOLABELLED CITALOPRAM IN BRAIN AS A MARKER OF 5-HT UPTAKE SITES FOR PET.

Although positron emission tomography (PET) has considerable potential for studying the biochemical bases of neurologic and pyschiatric disorders (Eriksson *et al.*, 1990; Lucignani *et al.*, 1989), its use in investigations of the serotonergic system is limited by the paucity of positron-emitting radioligands which have an *in vivo* selectivity for 5-hydroxtryptamine (5-HT) receptors or uptake sites. The antidepressant citalopram has been shown previously to be a selective inhibitor for 5-HT uptake *in vitro* in both rat (D'Amato *et al.*, 1987) and man (Plenge *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*-$^{11}$C]citalopram in rat showed only a small 'specific' signal *in vivo* (Hume *et al.*, 1990). Ratios of radioactivity in selected regions of interest (ROIs) (eg. 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*-$^{11}$C]citalopram was prepared [from (+)norcitalopram oxalate by [$^{11}$C]methylation with 'no-carrier-added' [$^{11}$C]iodomethane] 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*-$^{11}$C]citalopram showed any significant signal. The non-specific label, identified by predosing with non-radioactive (±)citalopram, was similar to that obtained with the (-)-isomer.

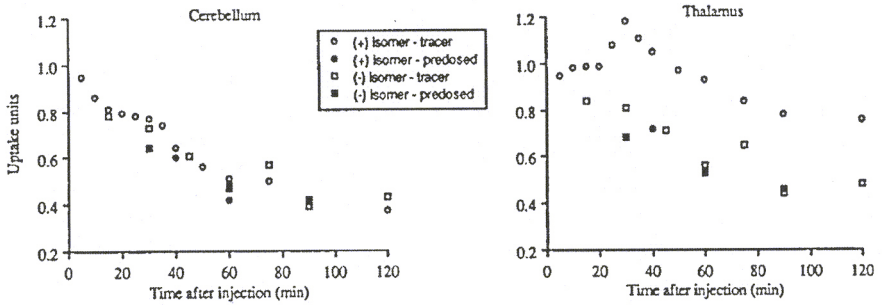


Fig. 1. Uptake in 2 regions of rat brain as a function of time after *i.v.* injection of (+)- or (-)-[*N-methyl* -$^{11}$C]citalopram. (Units are: Bq g$^{-1}$ tissue / injected Bq g$^{-1}$ body weight)

The individual cerebellum data (active isomer, tracer alone) were used as an input function in a reference tissue model, fitting for $k_3/k_4 = B_{max}/K_D$ 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* -$^{11}$C]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 vitro*, retention of a high non-specific label negates its usefulness as an *in vivo* ligand in man, using PET.

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REFERENCES

D'Amato, R.J., B.L. Largent, A.M. Snowman and S.H. Snyder (1987). Selective labelling of serotonin uptake sites in brain by [$^3$H]citalopram contrasted to the labelling of multiple sites by [$^3$H]imipramine. *J. Pharmacol. Exp. Ther.*, 242, 364-371.

Eriksson, L., M. Dahlbom and L. Widen (1990). Positron emission tomography - a new technique for studies of the central nervous system. *J. Microsc.*, 157, 305-333

Hume, S.P., C. Pascali, V.W. Pike, D.R. Turton, R.G. Ahier, R. Myers, D.M. Bateman, J.E. Cremer, L.G. Manjil and R. Dolan (1990). Citalopram: labelling with carbon-11 and evaluation in rat as a potential radioligand for in vivo PET studies of 5-HT re-uptake sites. *Nucl. Med. Biol.*, (in press)

Lucignani, G., R.M. Moresco, R.M. and F. Fazio (1989) PET-based neuropharmacology: state of the art. *Cerebrovascular and brain Metab. Rev.*, 1, 271-287

Plenge, P., E.T. Mellerup and H. Laursen (1990). Regional distribution of serotonin transport complex in human brain, identified with $^3$H-paroxetine, $^3$H-citalopram and $^3$H-imipramine. *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, 14, 61-72