Competitive PET Study of the Central Nicotinic Receptors α4β2 in Baboons

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Introduction

➢**nAChRs & Cognitive brain functions**

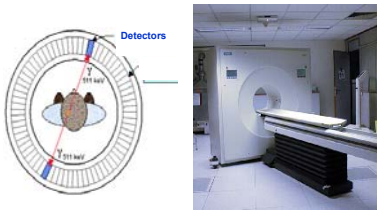
The central nicotinic acetylcholine receptors (nAChRs) mediate neurotransmission and a variety of cognitive brain functions like memory, learning, attention, drug addiction; they are involved in Alzheimer's & Parkinson's diseases, epilepsy, schizophrenia and nicotine dependence.

➢ ***In vivo* imagining techniques**, like Positron Emission Tomography (PET), offer the possibility to monitor human nAChRs in central nervous system disorders, using a suitable nicotinic radioligand: [18F]Fluoro-A-85380 (2-[18F]fluoro-3-[2(S)-2-azetidinylmethoxy] pyridine) a selective agonist of the major subtype of nicotinic receptors in the brain, α4β2.

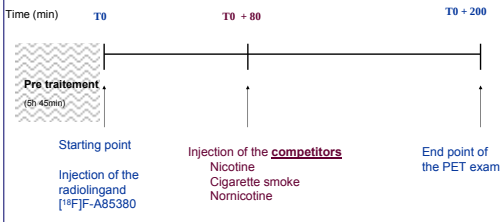
➢ **Aim of the study:** investigate the cerebral distribution of the nAChRs α4β2 using a new radioligand, in Papio papio Baboons.

Methods

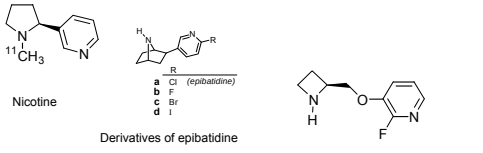
PET Scanner Ecat Exact HR+ (CTI-Siemens)



The experimental design of a *in vivo* study



[18F] Fluoro A-85380: a new radioligand for the nAChR α4 β2



[18F] Fluoro A-85380

2-[18F] fluoro-3-[2(S)-2 azetidinylmethoxy] pyridine

affinity: big for the nAChR α4 β2 in the brain

KD 40-50pmol /L

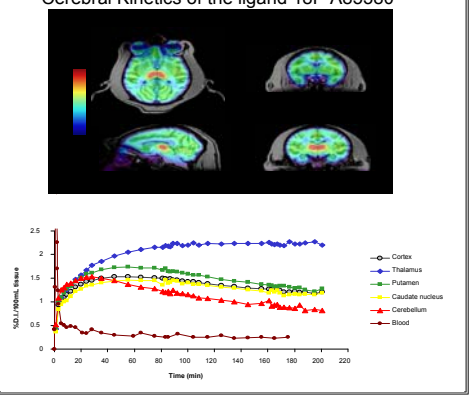
selectivity: no affinity for the R α7, $5HT_3$

toxicity: low, 50µg/Kg-with no effect in rodents

Can be used in Humans

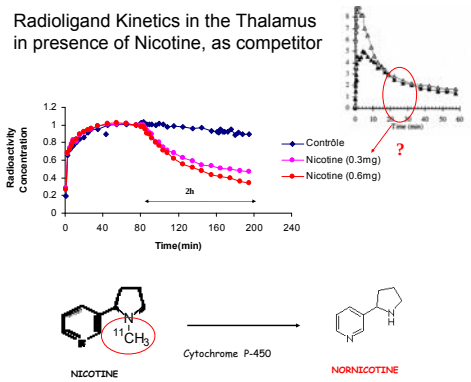
Results

Cerebral Kinetics of the ligand 18F-A85380



Results

Radioligand Kinetics in the Thalamus in presence of Nicotine, as competitor



Data Analysis for the Cerebral Kinetics

➢Studied in each specific brain region of interest, at precise level of the anatomical structures.

➢The kinetics of [18F]Fluoro-A-85380 in a specified region is as a distribution curve obtained from the analysis of the images obtained after the PET.

➢The concentration of radioactivity is expressed as a percentage of **the injected dose per milliliter of tissue**

%D.I./mL

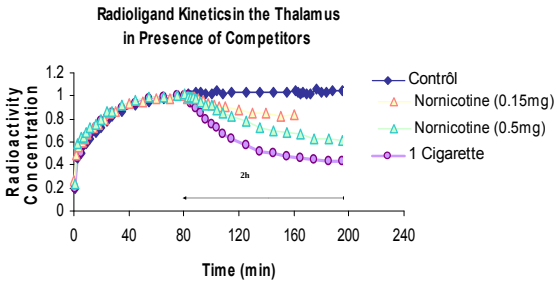
➢The results obtained from the controls are used to obtain the kinetics curve of reference for our specific radioligand.

➢The curves were normalised by the value obtained at 80min.

➢The calculation of the percentage of the displacement of the tracer by the competitor molecules studied is it performed at time T0 +190 - 200 min, by subtraction of the tracer's concentration curves values obtained in presence of different competitions from the control curve values of the same radiolingand, as in the equation:

Depl (%)=(C-D)/C

➢C and D represent the average values of the tracer fixation in the control study and in presence of competitors where the displacement takes place.



Kinetics of [18F]Fluoro-A-85380 in presence of competitors: nicotine, tabacco and nornicotine.

Six competition studies were performed: four with the nicotine, two with the nornicotine and two with the tabacco.

Two doses of nicotine (0.3 and 0.6 mg) and two doses of nornicotine (0.15 and 0.5 mg) were injected by i.v. to the baboons; the tabacco was given by successive inhalation of 1 cigarette.

Conclusions

➢The PET results show that the cerebral ditribution the the radioligand is correlated with the localisation of the α4β2 nicotinic receptors in the brain.

➢The nicotine, the nornicotine and the cigarette smoke are competing with the radioligand [18F]Fluoro-A-85380 for the same fixation sites of the α4β2 nicotinic receptors.

➢The results obtained open a new view on the role of the nornicotine (a nicotine metabolite) on the mechanism induced by the nicotine in the brain.

References

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Acknowledgements

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