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EPIBATIDINE-DERIVATIVES: LIGANDS FOR THE NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR

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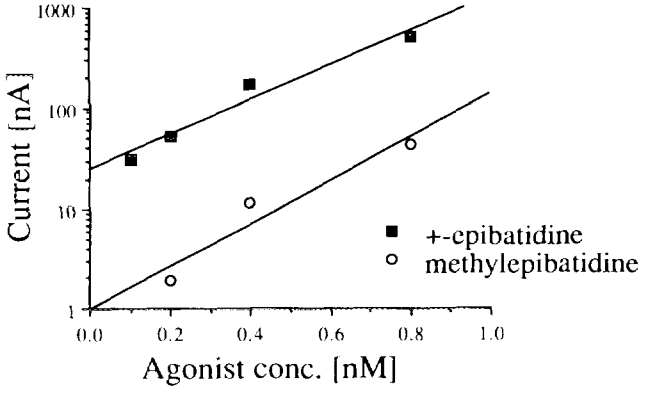
Epibatidine, isolated from the Ecuadorian frog Epipedobates tricolar, has been synthesised. ^{11}C-N-methyl derivate is investigated as useful nicotinergic receptorligand by electrophysiological methods and in vivo mice experiments.

Epibatidine is an azabicycloheptane alkaloid which had been first isolated from the skin extracts of the ecuadorian frog Epipedobates tricolor (1). The total synthesis of this substance was performed by several groups (2,3,4,5,6). Both stereoisomers of epibatidine show a very high affinity and selectivity to brain nicotinic receptors. It has been shown that the N-methyl derivative shows a similar pharmacological behaviour as the mother compound (7).

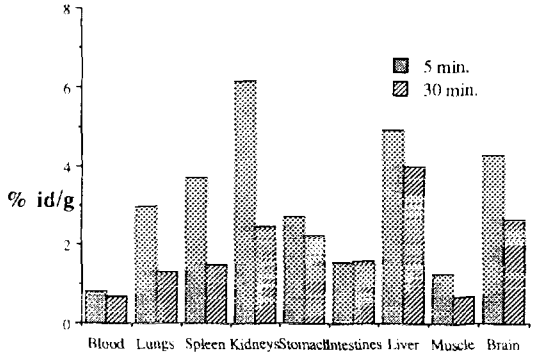
N-Methyl epibatidine may have possibilities as a compound which maps the neuronal nicotinic receptor. To enable a PET investigation of the kinetics of receptor binding *in vivo* and to develop a brain receptor tracer for the nicotinic system we have prepared [^{11}C]N-methylepibatidine in a remotely controlled system by methylation of epibatidine with ^{11}C-MeI.

The sensitivity of nAChR towards this derivative was compared with +-epibatidine by electrophysiological methods. The receptor was reconstituted in *Xenopus* oocytes with the major brain subunits $\alpha 4\beta 2$, the most sensitive nAChR to this class of compound.



The sensitivity of nAChR to methylepibatidine is four times lower than that towards +-epibatidine.

We studied the biodistribution in mice.



Uptake of the compound was highest in the brain, except for the liver and kidneys: % of the injected dose /g after 5 min. (mean of 3 animals): brain 4.29%, blood 0.82%, liver 4.95%, kidneys 6.17%, spleen 3.70%, lungs 2.96%, heart: 1.29%, stomach: 2.70%, GI-tract 1.55%, muscle 1.27%. Blood/brain ratio 5.2.

N-[^{11}C]Methylepibatidine is a promising nAChR PET ligand.

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