501

Yamada S[1], Yoshida A[1], Maruyama S[1], Tsukada H[2], Ito Y[1]
1. *University of Shizuoka,* ***2.*** *Hamamatsu Photonics*

IN VIVO ANALYSIS OF BRAIN MUSCARINIC RECEPTOR OCCUPANCY AFTER ADMINISTRATION OF ANTIMUSCARINIC AGENTS IN RATS BY USING POSITRON EMISSION TOMOGRAPHY (PET) AND QUANTITATIVE AUTORADIOGRAPHY (ARG)

Hypothesis / aims of study

Antimuscarinic agents such as oxybutynin, darifenacin and imidafenacin are widely used for the treatment of overactive bladder (OAB). While antimuscarinic agents have proven the efficacy in patients with OAB, they are also associated with anticholinergic side effect of dry mouth, constipation and blurred vision. Especially, the agents that can cross the blood brain barrier (BBB) and bind to muscarinic receptors in the brain have the risk of causing central nervous system (CNS) dysfunction including cognitive impairment. Therefore, this study was undertaken to characterize *in vivo* muscarinic receptor occupancy in brains of rats after systemic administration of oxybutynin, darifenacin and imidafenacin by using positron emission tomography (PET) and quantitative autoradiography (ARG).

Study design, materials and methods

After the administration of oxybutynin (0.1-1.0 mg/kg, i.v.), darifenacin (0.1-1.0 mg/kg, i.v.) and imidafenacin (2-20 mg/kg, p.o.), rats were received intravenously (+)*N*-[^{11}C]Methyl-3-piperidyl benzilate ([^{11}C](+)3-MPB), highly selective muscarinic receptor radioligand. In PET study, PET scan was performed for 60 min using Clairvivo PET (Shimazu, Kyoto, Japan). Regions of interest were placed on cerebral cortex, striatum, and cerebellum, and the time-activity curves were calculated. These image data were analyzed by the kinetic analysis of which reference region is cerebellum, and binding potential of [^{11}C](+)3-MPB in the cortex and striatum was calculated. In ARG study, at 30 min after the injection of [^{11}C](+)3-MPB, rats were scarified and the brain were rapidly removed and cut into 2 mm thick coronal sections. The imaging plate exposed by the sections for 10 min were scanned with a bio-imaging analyser. Regions of interest were placed on the cerebral cortex, striatum, hippocampus, amygdale, thalamus, hypothalamus, pons and cerebellum, and then the specific binding of [^{11}C](+)3-MPB was defined as the difference of radioactivity between each brain region and cerebellum.

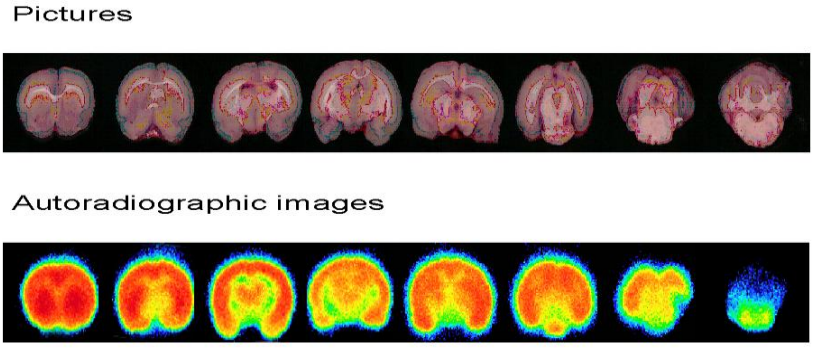

Fig. 1 Representative autoradiographic images (distribution of radioactivity) in the brain region of rats received i.v. injection of [^{11}C](+)3-MPB.

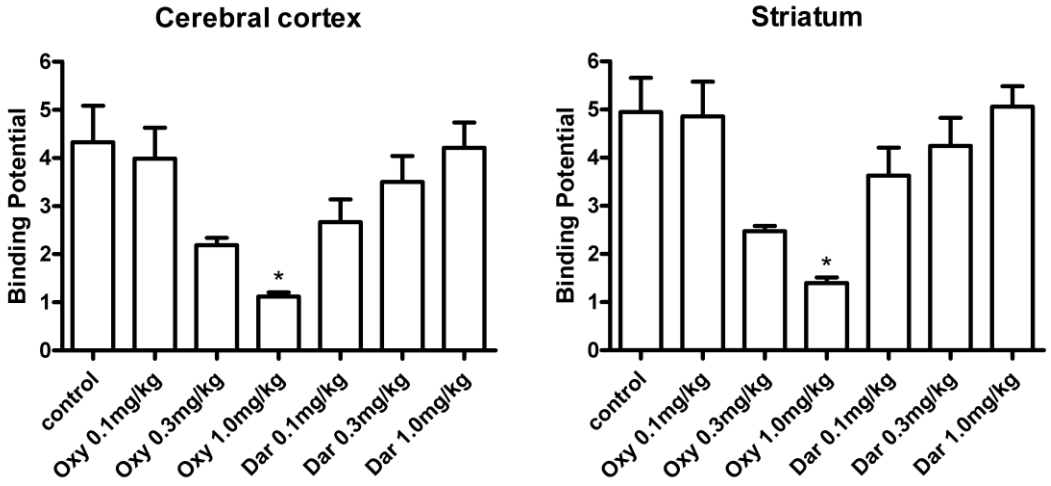

Fig. 2 Effect of oxybutynin and darifenacin on binding potential of [^{11}C](+)3-MPB in the cerebral cortex and striatum of anesthetized rats analyzed by positron emission tomography (PET).

Results

In both PET and ARG study, the highest radioactivity of [^{11}C](+)3-MPB was detected in the striatum and the lowest value was seen in the cerebellum (Fig 1). As shown in Fig. 2, following the i.v. injection of oxybutynin (0.1-1.0 mg/kg), there was significant and dose-dependent decrease in binding potensial of [^{11}C](+)3-MPB in cerebral cortex and striatum compared with control values. In the case of darifenacin (0.1-1.0 mg/kg), slight decreases in binding potential of [^{11}C](+)3-MPB were observed, but they were not significant. Similarly, in ARG study, oxybutynin (0.1-1.0 mg/kg, i.v.) significantly and dose-dependently decreased specific [^{11}C](+)3-MPB binding in brain regions. On the other hand, the dose-dependent inhibition of specific [^{11}C](+)3-MPB binding was not observed after the administration of darifenacin (0.1-1.0 mg/kg, i.v.) and imidafenecin (2-20 mg/kg, p.o.).

Interpretation of results

This study could evaluate *in vivo* muscarinic receptor binding in rat brain after the systemic administration of oxybutynin, darifenacin and imidafenecin used to treat OAB. The results have suggested that oxybutynin could cross the BBB more easily than darifenacin and imidafenacin to bind the brain muscarinic receptors.

Concluding message

In vivo analysis of brain muscarinic receptor occupancy by using PET and ARG could provide pharmacological basis for the feasibility of CNS side effects of antimuscarinic agents used to treat OAB. Oxybutynin but not darifenacin and imidafenacin has been shown to have a high risk of CNS side effects.

Specify source of funding or grant	**None**
Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**This study was done in accordance with recommendations of the US National Institutes of Health and also the guidelines of Central Research Laboratorym, Hamamatsu Photonics and the Experimental Animal Ethical Committe of the University of Shizuoka.**