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IN VIVO ANALYSIS OF BRAIN MUSCARINIC RECEPTOR OCCUPANCY AFTER ORAL OXYBUTYNIN IN CONSCIOUS RHESUS MONKEY BY USING POSITRON EMISSION TOMOGRAPHY (PET)

Hypothesis / aims of study

Anticholinergic agents such as oxybutynin are widely used for the treatment of overactive bladder which is characterized by symptoms of increased frequency of micturition and urge urinary incontinence. However, chronic administration of anticholinergic agents in older patients is reported to result in a non-degenerative mild cognitive impairment [1]. The extent to which memory and other cognitive functions are disrupted by antimuscarinic agents used to treat overactive bladder depends on the ability of drugs to cross the blood-brain barrier and to bind to muscarinic receptors in the brain. Therefore, this study was undertaken to characterize *in vivo* muscarinic receptor occupancy of oxybutynin in rhesus monkey brains after oral administration by using positron emission tomography (PET).

Study design, materials and methods

This study included 5 young adult male rhesus monkeys. After receiving oral administration of oxybutynin (0.1 or 0.3 mg/kg), (+)*N*-[^{11}C]Methyl-3-piperidyl benzilate ([^{11}C](+)3-MPB) was intravenously injected, a mscarinic receptor radioligand , and PET scan was performed for 91min. Region of interests were identified (frontal, temporal and occipital cortices, cingulate gyrus, caudate, amygdala, putamen, hippocampus, thalamus, and cerebellum) according to MR images of individual monkey brain, and time-activity curves. These image data were analyzed by the Logan plot, and receptor occupancy was calculated by the distribution volumes of each region. Plasma concentrations of oxybutynin and its active metabolite, N-desethyl-oxybutynin (DEOB) were measured by LC/MS/MS.

Results

At 30 min after oral administration of oxybutynin (0.1mg/kg), plasma concentrations of oxybutynin and DEOB reached maximum levels. The Cmax values of oxybutynin and DEOB were 7.9±7.1 and 29.1±36.4 ng/mL, respectively. Respective values increased to be 21.9±10.9 and 63.1±53.6 ng/mL, when larger dose of oxybutynin (0.3 mg/kg) was administered. At 1 hr after oral administration of oxybutynin at doses of 0.1 and 0.3 mg/kg, muscarinic receptor occupancy in each brain region of conscious rhesus monkey was estimated to be about 40% and 60%, respectively (Fig.1). At 4 hr later, the *in vivo* receptor occupancy at each dose decreased (Fig.2).

Interpretation of results

The plasma concentration (Cmax value) in rhesus monkey after oral administration of oxybutynin at the dose of 0.1 mg/kg was closely associated with that in humans received immediate release tablet containing 5 mg oxybutynin [2]. Therefore, these data (plasma drug concentration and brain muscarinic receptor occupancy) in rhesus monkey may be responsible for those in humans. The interpretation of results is that oral oxybutynin (and also its metabolite, DEOB) crossed the blood-brain barrier and bound to muscarinic receptors dose-dependently in each brain region.

Concluding message

The present study has firstly demonstrated that orally-administrated oxybutynin occupies muscarinic receptors in the brain of conscious monkeys. Therefore, oxybutynin used to treat overactive bladder may have a risk of adverse effect on the central cholinergic neuronal system in the clinical condition.

References

[1] British Med J (2006) 24; Fed 06 on-line.
[2] Clin Pharmacokinet (2003) 42; 1243-1285.

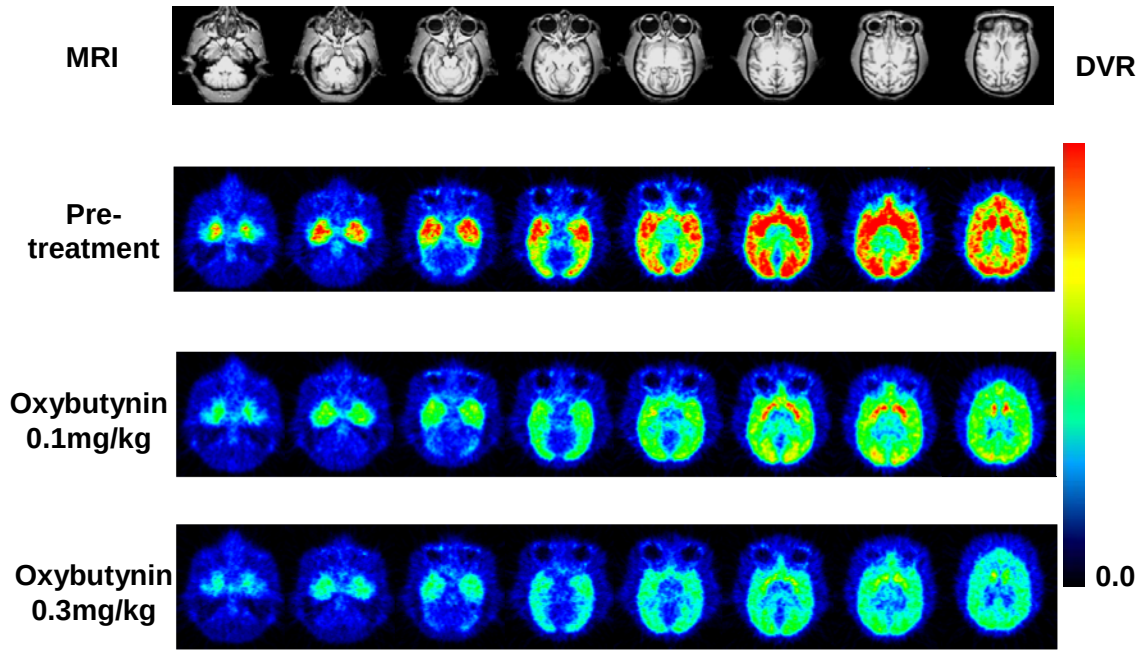

Fig.1 Dose effects of oral oxybutynin on [^{11}C](+)3-MPB binding to muscarinic receptors in the brain of conscious monkey as measured by PET.

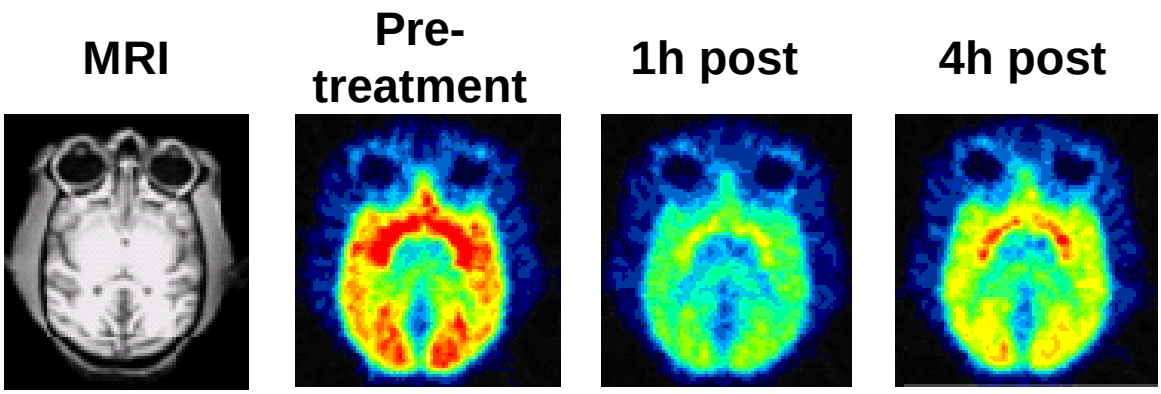

Fig.2 Time course effects of oral oxybutynin (0.3mg/kg) on [^{11}C](+)3-MPB binding to muscarinic receptors in the brain of conscious monkey as measured by PET.

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ANIMAL SUBJECTS: **This study followed the guidelines for care and use of laboratory animals and was approved by This study was done in accordance with recommendations of the US National Institutes of Health and also the guidelines of Central Research Laboratory, Hamamatsu Photonics and the Experimental Animal Ethical Committe of the University of Shizuoka**