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Oxybutynin disrupts learning and memory in the rat passive avoidance response

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Abstract *Background*: oxybutynin, a drug for pollakisuria and urinary incontinence, has a potent antimuscarinic activity. This study was aimed to determine whether this drug disrupts learning and memory in rats, because antimuscarinic activity in the central nervous system is considered to cause amnesia in humans. *Methods*: male Wistar rats were given oxybutynin or scopolamine as a reference drug, and subjected to the acquisition trial of step-through passive avoidance response (PAR). Twenty-four hours later the retention test for each rat was performed and the latency time in the PAR was measured. *Results*: oral administration of oxybutynin at 30 mg/kg or higher and intraperitonial injection of scoplamine at 0.5 mg/kg caused a significant decrease in the latency time in the retention test. *Conclusions*: oxubutynin caused a decrease in the retention time of the PAR in a manner similar to scopolamine, indicating that oxybutynin may cause disruption of learning and memory.

Key words Oxybutynin · Urinary incontinence · Step-through passive avoidance response · Central nervous system · Memory

Introduction

Oxybutynin has been used clinically in the treatment of pollakisuria and urinary incontinence. It reduces unstable detrusor contractions and increases functional bladder capacity through its antimuscarinic and direct smooth muscle relaxation actions [1–3].

Drugs with antimuscarinic activity generally cause peripheral adverse side effects including dry mouth, mydriasis and constipation. In addition, the antimuscarinics permeable into the central nervous system (CNS) have long been known to disrupt learning and memory [4, 6, 7]. In particular, scopolamine, a CNS permeable antimuscarinic, impairs the retention of a passive avoidance response (PAR) in rats and mice when administered before the acquisition trial [8].

In spite of the potent anticholinergic activity of oxybutynin, there have been few reports on its effects on the CNS. In the present study, we investigated the effects of oxybutynin on the retention of memory in rats in a step-through PAR and compared them with those of scopolamine.

Methods

Male Wistar rats weighing 130–170 g were housed in groups of four or five in a room maintained at 21–25°C and relative humidity (45%–65%) with a controlled light–dark cycle (light on from 08:00 to 20:00). Water and food were given ad libitum.

The PAR of rats was examined in the step-through situation, as described previously [9]. Briefly, on day 1, the rats were adapted for 5 min to the apparatus, which consisted of a dark compartment equipped with an electrifiable grid floor and an illuminated Plexiglas compartment. The two compartments were separated by a solenoid-operated guillotine-type door. On day 2, the adaptation was followed by a single acquisition trial in which the animals were placed in the illuminated compartment and after a 30-s delay allowed to enter the dark compartment by raising the guillotine door. When the rat moved completely into the dark compartment, the door was closed and it received a foot shock (75 V) for 3 s delivered by an electric generator through the grid floor. Immediately after receiving the shock, the rat was removed from the dark compartment and returned to its home cage.

A retention test was given on day 3. It was conducted in a manner similar to the acquisition trial except that the guillotine door did not close when the rat entered the dark compartment and the shock was not applied to the grid floor. The time spent (latency time) without moving into the dark compartment after the guillotine door had been raised was measured. During the retention test, the rats were provided access to the dark compartment for 300 s.

Oxybutynin was kindly provided by Hoechst Marion Roussel (Kansas City, Mo) and scopolamine hydrochloride was purchased from Sigma Chemicals (St Louis, Mo). They were dissolved in physiological saline. Oxybutynin was administered p.o.

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1 h before, and scopolamine i.p. 15 min before the acquisition trial.

Statistical analyses of the latency time between multiple groups were made using the Kruskal-Wallis H-test followed by the Wilcoxon rank sum test.

Results

Oral administration of oxybutynin at doses higher than 30 mg/kg caused behavioral changes, including hypermotor activity and restlessness. Scopolamine 0.5 mg/kg (i.p.) caused behavioral changes similar to those caused by oxybutynin. These behavioral changes were not observed 24 h after drug administration.

During the acquisition trial, the mean latency time of groups treated with saline as a control or treated with drugs was less than 10 s and there were no significant differences between groups, indicating that neither oxybutynin nor scopolamine affected the latency time in the acquisition trial.

In the retention test trial (Fig. 1), the mean of the step-through latency time of the control animals was about 285 s. In contrast, the latency time of animals treated with oxybutynin 1 h before the acquisition trial was decreased in a dose-dependent manner and was statistically significant at doses of 30 mg/kg or higher. Scopolamine at 0.5 mg/kg caused a significant decrease in latency time in the retention test.

Discussion

In the present study, oxybutynin as well as scopolamine disrupted the retention of the PAR. PAR is referred to as a one-trial learning procedure and the procedure is well suited for the evaluation of the effects of drugs on the acquisition and consolidation of memory. The effect of scopolamine on the retention of the PAR has been previously reported [9] and the decrease in latency time caused by scopolamine could be demonstrated to be centrally mediated because of the lack of any amnesic effect of methyl scopolamine, a CNS-impermeable muscarinic antagonist [10]. Spencer and Lal [12] proposed that scopolamine may interfere with the processes of encoding (storing in a retrievable form).

Oxybutynin has antimuscarinic activity by blocking the muscarinic receptors as well as a weak calcium antagonistic activity [1, 2, 3, 5], and it is reported to be permeable into the CNS [13]. Of the muscarinic receptor subtypes, the M1 subtype is considered to be mainly responsible for learning and memory processes in the CNS. Oxybutynin is reported to have higher affinity for the M1 and M3 subtypes than for the M2 subtype [14–16]; therefore, the amnesic action of oxybutynin may be attributable to the blockade of M1 receptors in the CNS.

We observed significant disruption of the retention of PAR by oral administration of oxybutynin at 30 mg/kg or higher. The drug reportedly causes an increase in bladder capacity in rats as determined by cystometrography, a method closely approximating the clinical test for urinary bladder function; however, the effect was significant only at a dose of 0.1 mg/kg, i.e. at doses higher or lower than 0.1 mg/kg oxybutynin produced no increase in bladder capacity [17]. In another urological study using rats [18], oxybutynin in a dose-dependent manner inhibited the spontaneous bladder contractions caused by increasing the intravesical volume, and the effect was significant at 1 mg/kg or higher. Taken together, these results suggest that oxybutynin affects the bladder function of rats at doses of around 1 mg/kg (administered orally), whereas the dose required to induce amnesia (30 mg/kg, p.o.) is some 30-fold higher. Present findings strongly suggest that oxybutynin at high doses may disrupt memory and learning by blocking muscarinic receptors in the CNS.

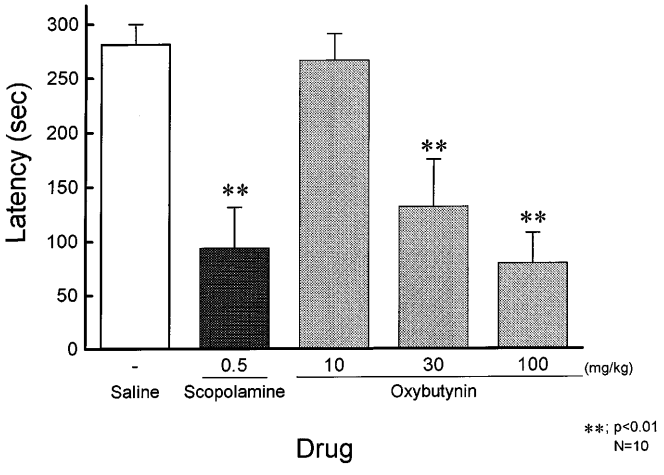

Fig. 1 Effect of oxybutynin and scopolamine on latency time in the retention test for the passive avoidance response in rats. Oxybutynin was administered p.o. 1 h before and scopolamine i.p. 15 min before the acquisition trial. Ten animals were used for each group

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ANNOUNCEMENTS

1999

3. International Symposium on Uro–Oncology "Advances in diagnosis and therapy of bladder cancer" 5–6 November 1999, Marburg, Germany

Topics: Pathology and molecular genetics of pediatric and adult bladder tumors; Diagnosis and staging of bladder cancer; Management of superficial bladder cancer; Therapy of muscle invasive bladder cancer (surgical demonstrations); Management of advanced bladder tumors

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2000

Urolithiasis 2000 The IXth International Symposium on Urolithiasis 13–17 February 2000, Cape Town, South Africa

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