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EFFECTS OF SOLIFENACIN SUCCINATE ON LEARNING AND MEMORY: A COMPARATIVE STUDY.

Hypothesis / aims of study

Antimuscarinic drugs are widely used in the treatment of overactive bladder (OAB). However, as adverse effects associated with antimuscarinic drugs the risk of cognitive impairment is concerned. Solifenacin is a new muscarinic receptor antagonist and used as a treatment for OAB in Europe and the USA. There, however, have been few reports on its effects on the central nervous system. Thus, we examined effects of solifenacin on learning and memory using the passive avoidance task in rats, compared with those of other antimuscarinics oxybutynin, propiverine, tolterodine and darifenacin.

Study design, materials and methods

Male Wistar rats aged 8 weeks were used. A two-compartment, step-through, passive avoidance apparatus consisting of illuminated and dark compartments attached to an electrified grid floor and separated by a guillotine door was used. In the habituation trial, a rat was placed in the illuminated compartment and the door was raised. After entering into the dark compartment, the rat was returned to its home cage. In the acquisition trial 60 min after habituation trial, the rat was again placed in the illuminated compartment. When the rat entered the dark compartment, the guillotine door was closed and the rat was delivered scrambled electrical shocks of 0.8 mA for 4 sec through the grid floor using a shock generator. The drugs were intravenously administered 10 min before acquisition trials. In the retention trial, made 24 hr after the acquisition trial, the rat was placed again in the illuminated compartment and the response latency to enter the dark compartment was measured. Steel's test was used for statistical analysis and $p<0.05$ was considered significant.

Results

Solifenacin (0.3-3 mg/kg iv) and darifenacin (0.1-1 mg/kg iv) showed no effects on the retention latency. In contrast, oxybutynin (0.1-1 mg/kg iv) and propiverine (1-10 mg/kg iv) shortened the latencies in a dose-dependent manner with significant differences at doses of 0.3 mg/kg iv and more and 10 mg/kg iv, respectively. Tolterodine (0.1-1 mg/kg iv) tended to shorten the latency at a dose of 1 mg/kg iv (P value = 0.054).
The obtained results, compared with previously published inhibitory effects on carbachol-induced intravesical pressure (IVP) elevation, are summarized in the following Table.

Table. Inhibition doses on learning and memory and on carbachol-induced intravesical pressure (IVP) elevation

Drug	Inhibition dose of learning and memory (mg/kg iv)	ID_{30} of IVP elevation [1,2] (mg/kg iv)	Ratio (Inhibition dose of learning and memory/ID_{30} of IVP elevation)
Solifenacin	> 3	0.023	> 130
Oxybutynin	0.3	0.027	11.1
Propiverine	10	0.68	14.7
Tolterodine	> 1	0.010	> 100
Darifenacin	> 1	0.0098	> 102

Interpretation of results

Solifenacin and darifenacin did not affect rat learning and memory even at doses of 3 and 1 mg/kg iv, respectively. These doses were 130- and 102-fold higher than the effective doses, respectively, in carbachol-induced IVP elevation study.
Oxybutynin and propiverine impaired rat learning and memory at doses of 0.3 mg/kg iv and more and 10 mg/kg iv, respectively. The dose ratios of these drugs for effects on learning and memory and carbachol-induced IVP elevation were 11.1- and 14.7-fold, respectively.
Tolterodine tended to impair rat learning and memory at a dose of 100-fold higher than the effective dose in carbachol-induced IVP elevation study.

Concluding message

The present results showed solifenacin had no impairment effects on learning and memory in rats. In contrast, oxybutynin and propiverine showed impairment of learning and memory. These results suggest that solifenacin may be useful drug with less effect on cognitive function in the treatment of OAB.

References

1. Eur. J. Pharmacol. (2004) 492: 243-250.
2. J. Pharmacol. Sci. (2005) 97 (Supp I):253P.

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