

EFFECTS OF INTRATHECAL CHOLINESTERASE INHIBITOR APPLICATION ON BLADDER OVERACTIVITY INDUCED BY CYCLOPHOSPHAMIDE AND ACETIC ACID

Hypothesis / aims of study

A variety of studies have implicated spinal cholinergic systems being involved in modulation of painful stimuli (1). Intrathecal (i.t.) administration of oxotremoline-M (OXO-M), a muscarinic receptor agonist, reportedly has an inhibitory effect on the normal micturition reflex in the rats (2). Therefore, we examined whether bladder overactivity caused by cyclophosphamide (CYP) or acetic acid could be modulated by activation of spinal muscarinic or nicotinic receptors using i.t. injected neostigmine, a cholinesterase inhibitor, OXO-M, or epibatidine, a nicotinic agonist.

Study design, materials and methods

Continuous cystometrogram (CMG, 0.1ml/min) was performed in female Sprague-Dawley rats under urethane anesthesia (1.2g/kg., s.c.). Some rats received single intraperitoneal injection of CYP (200 mg/kg.) 24hours before CMG (CYP group). In another group, following baseline CMG recordings with saline (0.1ml/min for 60min), 0.25% of acetic acid was infused (0.1ml/min for 60min) (acetic acid group). Increasing doses of neostigmine (0.01-1 μ g), OXO-M (0.01-0.3 μ g) or epibatidine (0.01-0.1 μ g/rat) were administered i.t. and CMG was recorded in CYP and acetic acid groups as well as the control group with saline infusion. To evaluate pharmacological characteristics of the activity, muscarinic receptor antagonists (atropine, M₁ antagonist pirenzepine, M₂ antagonist methoctramine and M₃ antagonist 4-DAMP) or a nicotinic receptor antagonist, mecamylamine, were administered i.t. before neostigmine (1 μ g) was administered. In some cases, pretreatment with MK-801 (20 μ g/rat), a NMDA receptor antagonist, was administered i.t. to investigate the involvement of glutamate receptors in the spinal nicotinic pathway.

Results

Bladder capacity (BC) in CYP (0.17 \pm 0.03ml) and acetic acid (0.37 \pm 0.05ml) groups was significantly lower than that in control (0.71 \pm 0.11ml) rats. I.t. injected neostigmine increased BC and pressure threshold in all groups dose-dependently. Percentage increase in BC after 1 μ g neostigmine in normal, CYP and acetic acid groups was 87.3 \pm 9.2%, 119 \pm 9.8% and 214.7 \pm 15.2%, respectively, when compared with preinjection capacity. Percentage increase in BC in CYP and acetic acid groups was higher than that in the normal group (p <0.05). In all groups, pirenzepine (1 μ g) and atropine (3 μ g) almost completely inhibited the inhibitory effects of neostigmine (1 μ g) on the micturition reflex and 4-DAMP (3 μ g) partially antagonized the effects. However, methoctramine (10 μ g) and mecamylamine (10 μ g) did not antagonize the effects of neostigmine. In addition, i.t. injected OXO-M increased BC and pressure threshold in all groups dose-dependently, and percentage increase in BC caused by OXO-M (0.3 μ g, i.t.) in CYP and acetic acid groups was higher compared with the normal group (p <0.05), which were similar to the results of neostigmine treatment. In contrast, i.t. injected epibatidine significantly decreased BC in all groups dose-dependently. These stimulatory effects were significantly suppressed by pretreatment with i.t. injected mecamylamine (10 μ g) or MK-801 (20 μ g).

Interpretation of results

These results indicate that intrathecal cholinesterase inhibitor application suppresses micturition reflexes induced by mechanoreceptive and nociceptive stimuli due to activation of spinal muscarinic receptors, especially the M₁ subtype. In addition, direct spinal muscarinic receptor activation has an inhibitory effects on micturition reflex, while spinal nicotinic receptor activation has an excitatory effects, at least in part, mediated via activation of spinal glutamate pathways.

Conclusion message

Our results suggest that endogenous acetylcholine in the spinal cord can suppress detrusor overactivity induced by excitation of bladder afferent pathways due to activation of the muscarinic M₁ receptor subtype and could provide a basis for the use of cholinesterase inhibitors for the treatment of detrusor overactivity.

References

1. Neuropharmacol 37: 1515-1525, 1998.
2. J. Pharmacol. Exp. Ther 297: 933-939, 2001.

Fig. 1 Effects of intrathecal (i.t.) administration of (a) neostigmine, (b) epibatidine or (c) OXO-M on the detrusor overactivity caused by CYP

