

THE ROLE OF SPINAL ADENOSINE A₁ RECEPTORS IN DETRUSOR OVERACTIVITY INDUCED BY CYCLOPHOSPHAMIDE

Hypothesis / aims of study

The antinociceptive effects of systemic and spinal administration of adenosine, adenosine analogs or adenosine kinase inhibitor have been widely studied in various nociceptive paradigms, such as thermal thresholds, inflammatory and neuropathic pain tests (1, 2). Therefore, we examined whether detrusor overactivity caused by cyclophosphamide (CYP) could be suppressed by intravenous (i.v.) and intrathecal (i.t.) adenosine, N⁶-cyclopentyladenosine (CPA, selective adenosine A₁ receptor agonist), CGS-21680 (selective adenosine A_{2A} receptor agonist) and ABT-702 (adenosine kinase inhibitor). We also examined whether adenosine A₁ receptor antagonist DPCPX can suppress the effects of above adenosine related compounds.

Study design, materials and methods

Continuous cystometrograms (CMG, 0.1 ml/min infusion rate) 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.) 24 hours before CMG. Injection of adenosine (i.v. at 0.1 to 3.0 mg/kg and i.t. at 10 to 100 µg/rat), CPA (i.v. at 0.03 to 0.3 mg/kg and i.t. at 0.03 to 0.3 µg/rat), CGS-21680 (i.v. at 0.3 and 1.0 mg/kg and i.t. at 0.1 and 1.0 µg/rat) or ABT-702 (i.v. at 0.1 to 1.0 mg/kg and i.t. at 0.1 to 3 µg/rat) with or without DPCPX (i.v. at 1mg/kg and i.t. at 10 µg/rat) were performed and CMG was recorded in CYP as well as control groups during saline infusion.

Results

Bladder capacity (BC) in the CYP group (0.14±0.03ml) was significantly lower than in the control group (0.71±0.09ml). I.v. as well as i.t. injected adenosine, CPA and ABT-702 but not CGS-21680 significantly and dose-dependently increased the BC in the CYP group (see Figure 1). Adenosine and CPA, but not ABT-702, at the highest dose slightly but significantly increased the BC in the control group. Percent increase in BC in the CYP group was higher than that in the normal group (p<0.05). I.v. and i.t. administered DPCPX itself significantly decreased BC and also suppressed the increasing effects of adenosine, CPA and ABT-702 on the BC in the CYP group without changing the BC in the control group.

Interpretation of results

These results indicate that exogenous adenosine or augmentation of endogenous adenosine by inhibition of adenosine kinase increased the bladder capacity in CYP treated rats, at least in part, mediated via spinal adenosine A₁ receptors. Also, adenosine A₁ receptor antagonist decreased bladder capacity in CYP treated rats, suggesting that adenosine A₁ receptors are endogenously activated in this model.

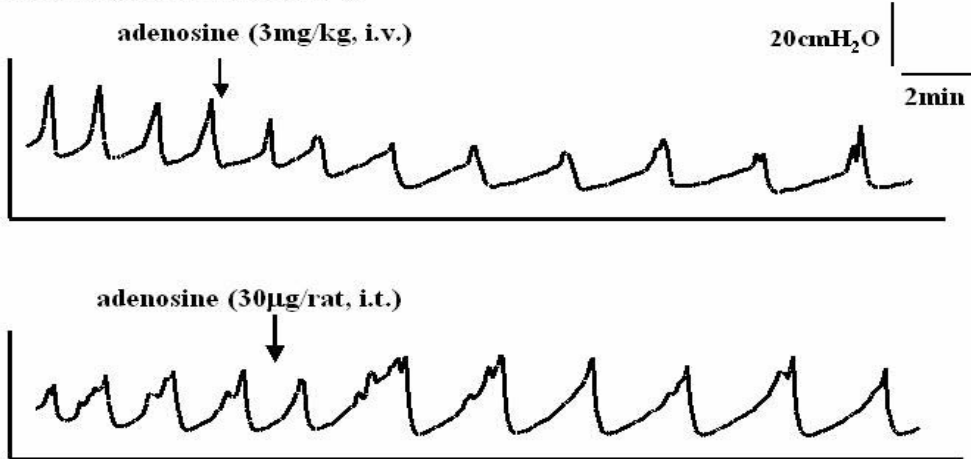
Concluding message

Our results suggests that activation of the adenosine A₁ receptor in the spinal cord may inhibit afferent transmission involved in the emergence of detrusor overactivity and provide a possible basis for the use of adenosine related compounds for the treatment of detrusor overactivity.

References

1. Pain 74: 235-245, 1998
2. Neurosci Letters 328: 241-244, 2002

Fig.1 Representative tracing



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