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DIFFERENTIAL ROLES OF ADENOSINE RECEPTOR SUBTYPES A1 AND A2A ON THE MICTURITION REFLEX IN RATS

Hypothesis / aims of study

Adenosine is an endogenous neurotransmitter that exerts numerous physiological effects in many organs. Adenosine regulates physiological functions through activation of four types of receptors classified as A_1, A_{2A}, A_{2B}, and A_3, among which A_1 and A_{2A} receptors are considered to be the main targets for extracellular adenosine at physiological concentrations. Both animal and clinical studies demonstrate that adenosine has an important role in neuromodulations such as pain or respiratory control. To date, however, it is not fully clarified how adenosine receptors can regulate the micturition reflex. Therefore, we examined the role of adenosine A_1 and A2A receptors in bladder activity of normal and cystitis rats.

Study design, materials and methods

Female Sprague-Dawley rats were used. Continuous cystometrograms during saline or 0.2% acetic acid (AA) infusion (0.04ml/min) were recorded under urethane anesthesia. After a stabilization period, 2-chloro-N^6-cyclopentyladenosine (CCPA, adenosine A_1 receptor agonist) and ZM24138 (ZM, adenosine A2A receptor antagonist) were administered intravenously (iv), intrathecally (it), intracerebroventricularly (icv) or intravesically (after urothelial permeability was increased by DMSO retained in the bladder for 30 min). Micturition parameters (intercontraction interval [ICI] and maximum voiding pressure [MVP]) were recorded and compared before and after drug administration.

Results

In comparison to saline infusion, AA significantly reduced ICI by 67.8%. Iv, it or icv administration of CCPA significantly increased ICI in both saline and AA infusion groups while no change was detected in MVP. Moreover, during AA infusion, the inhibitory effects induced by iv and icv CCPA administration were significantly greater than those during saline infusion (post-CCPA ICI increase: 207.1±67.6 vs. 42.1±14.8% and 282.7±39.6 vs. 104.4±23.4%, respectively) (fig.1A). Intravesical administration of CCPA significantly increased ICI compared to the DMSO-only retained group although this effect lasted for only few minutes (fig.2).

Intravesical administration of ZM did not change any parameters. Iv, it or icv administration of ZM also significantly increased ICI in both saline and AA infusion groups while no change was detected in MVP. During AA infusion, the inhibitory effects induced by iv and it ZM administration were significantly greater than those during saline infusion (post-ZM ICI increase: 103.1±25.2 vs. 26.6±10.0% and 203.4±40.9 vs. 98.5±26.4%, respectively) (fig.1B).

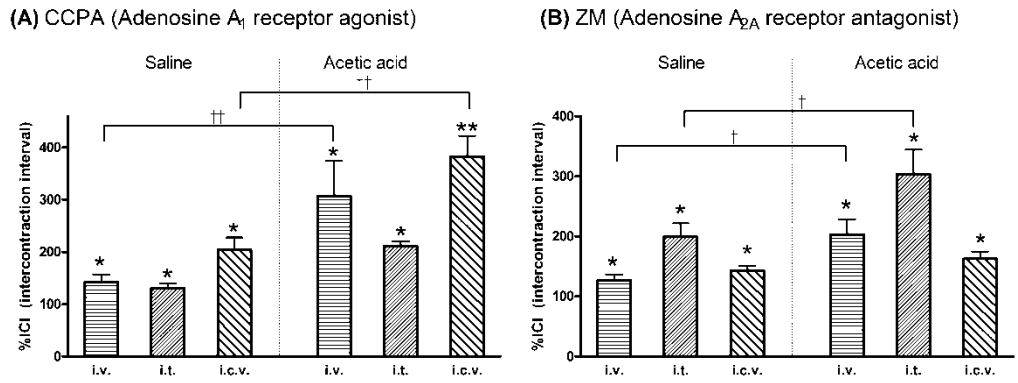

Fig.1 ICIs before and after drugs application were compared using absolute values (min) (* P<0.05, ** P<0.01 vs. pre-drug ICI), and then post-drug ICIs were converted to % values of pre-drug ICIs, which were compared between saline and AA infusion groups († P<0.05, †† P<0.01 vs. saline infusion group).

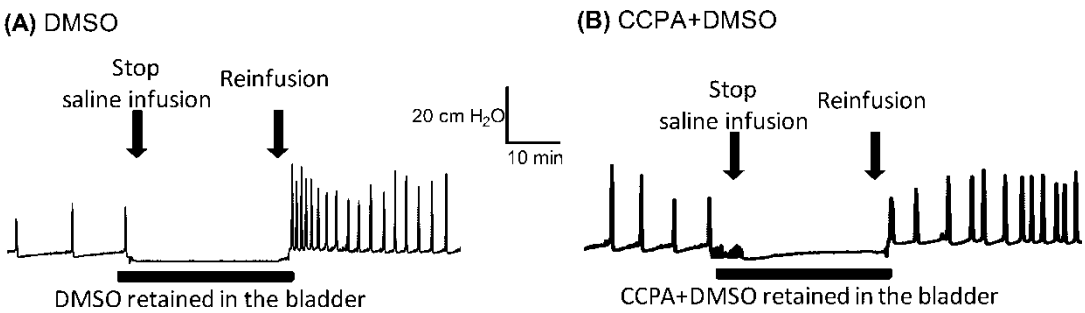

Fig.2 Effects of intravesical administration of vehicle (DMSO) (A) and CCPA (Adenosine A1 receptor agonist) and DMSO (B). Bar underneath the trace indicates the duration of drugs retained in the bladder.

Interpretation of results

During saline or AA infusion, both A_1 agonist and A2A antagonist increased ICI without affecting MVP, suggesting an action on bladder afferent rather than efferent pathways. Previous reports revealed that adenosine A_1 receptors are distributed more widely than A_{2A} receptors in the brain. Our findings suggest that as the the nociceptive signals from the bladder increase, brain A_1 receptors are more predominant than in the normal condition. Moreover, the A_1 receptor might also have a peripheral effect on the control of the micturition reflex. On the contrary, the inhibitory effect of an A2A antagonist was enhanced after AA infusion, which induces bladder overactivity mainly due to C-fiber bladder afferent activation. Thus it seems likely that the A2A receptor-mediated excitatory adenosinergic mechanism might be enhanced in the spinal cord following C-fiber afferent stimulation.

Concluding message

Adenosine A_1 receptor agonists and A_{2A} receptor antagonists could be effective for the treatment of overactive bladder and/or bladder hypersensitive disorders such as BPS/IC.

However, to avoid the central effects in the brain, the adenosine A_{2A} receptor antagonist, which has spinal cord-selective pharmacological properties, might be more preferable than the A_1 receptor agonists although intravesical administration of A_1 receptor agonists could be an alternative therapeutic option.

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**University of Pittsburgh Institutional Animal Care and Use Committee**