References.

[1] Drugs & Aging 6: 243-262 (1995)

[2] Current Topics in Pharmacology (Research Trends) 4: 239-250 (1998)

[3] J.Pharmacol.Exp.Ther. 255: 1148-1157 (1990)

[4] J.Pharmacol.Exp.Ther. 215: 176-185 (1980)

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Title (type in CAPITAL LETTERS, leave one blank line before the text):
BIOLOGICAL CHARACTERIZATION OF ADENOSINE RECEPTORS IN RAT DETRUSOR SMOOTH MUSCLE

Aims of Study: The function of detrusor smooth muscle is mainly regulated by cholinergic and adrenargic receptors in normal conditions. However, non-cholinergic and non-adrenergic regulators of the detrusor function have not been fully elucidated. The present study was undertaken to investigate the biological role of adenosine receptors in the regulation of detrusor function.

Methods: Detrusor muscle strips of 10 x 2 mm of Male Sprague-Dawley rats (weighning 250 to 300 grams) were mounted in an organ bath containing Krebs-Henseleit solution and gassed with 95% O_2, 5% CO_2 and maintained at 37 centigrade. A resting tension of 1 g was applied to the muscle strips and was equilibrated for 60 minutes. The isometric effects of adenosine agonists on detrusor contraction induced by calbachol were measured by force transducer. To measure intracellular cyclic AMP contents, muscle strips were incubated in an organ bath containing Krebs-Henseleit solution and gassed with 95% O_2, 5% CO_2 at 37 centigrade for 30 minutes. Drugs were added and the incubation were given for 5 minutes. After incubation with drugs, muscle strips were rapidly frozen with liquid nitrogen. Frozened muscle strips were added 2 ml of 6% trichroloacetate and homogenized. Afetr samples were centrifuged at 3000g for 10 minutes at 4 degree, the supernatant was removed and added 6 ml of diehtylether. Its content was measured using cyclic AMP assay kit.

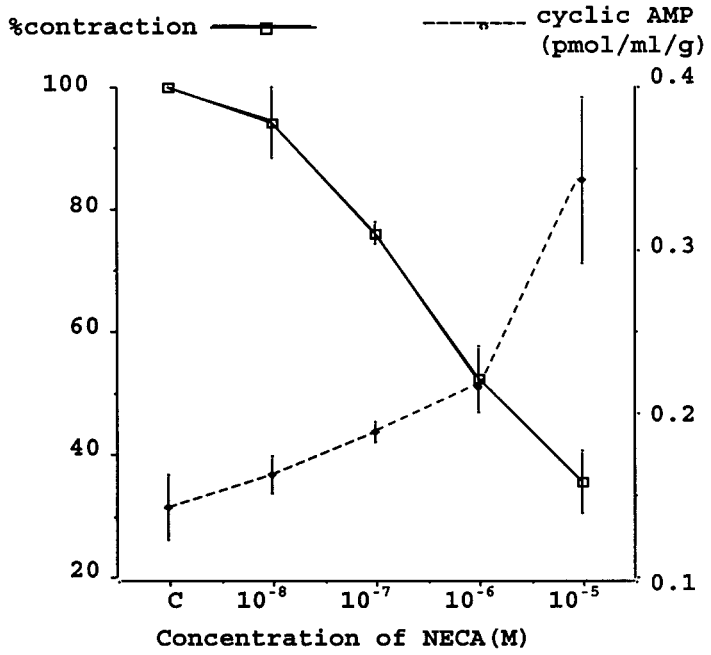
Drug: N6cyclo-pentyl-adenosine (CPA), 5N-ethylcarboxamide-adenosine (NECA), N^6cyclo-pentyl-adenosine (CPA), N^6-3-iodo-bendyl-adenosine-5N-methyluronamide (IB-MECA), 8-phenyl-theophylin (8-PT), carbachol chloride (CCh), Forskolin.

Results: The preincubation of 5N-ethylcarboxamide-adenosine (NECA), an adenosine A2 agonist, of 0.01 to 10 mM inhibited the contraction of the muscle strips induced by carbachol in a dose-dependent manner. NECA also produced significant increases in intracellular cyclic AMP levels of the muscle strips in a dose-dependent manner(Fig.1). The relaxation of the muscle strips and the elevation of intracellular cyclic AMP levels induced by 0.1 mM NECA were significantly inhibited
by 1 mM 8-phenyl-theophyline, an adenosine receptor antagonist. On the other hand, N^6cyclo-pentyl-adenosine, an adenosine A1 agonist, and N^6-3-iodo-bendyl-adenosine-5N-methyluronamide, an adenosine A3 agonist, at a concentrated range of 0.01 to 10 mM did not have any effects on the contraction of the muscle strips induced by carbachol.

Conclusions: These data demonstrate that the adenosine A2 agonist significantly inhibited the detrusor contraction induced by the cholinergic

reaction through the elevation of an intracellular cyclic AMP. It is possible that the modulation of adenosine receptors may have clinical application for bladder dysfunction in the future.

(Fig.1)Muscle relaxation and cyclic AMP contents induced by NECA



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Rec 15/3079: A NOVEL PRE AND POSTSYNAPTIC 5-HT_{1A} RECEPTOR ANTAGONIST ACTIVE ON THE LOWER URINARY TRACT.

AIMS OF STUDY

In previous studies (1) we have shown that 5-HT_{1A} receptor neutral antagonists influence central control of lower urinary tract function, decreasing the frequency of bladder voiding contractions and increasing bladder capacity. Several compounds with pre and postsynaptic 5-HT_{1A} antagonistic properties have been synthesized and, among them, Rec 15/3079 was selected for exploratory development and tested in relevant models of bladder activity. Since 5-HT_{1A} antagonists are claimed to be endowed with anxiolytic and/or antidepressant activity (2), Rec 15/3079 was also tested in several different experimental models detecting sedative, analgesic, anxiolytic or antidepressant activity, in order to evaluate its "uroselectivity".

METHODS

Affinity of Rec 15/3079 for human recombinant 5-HT_{1A} receptors and its displacing activity for about 70 different native or recombinant binding sites, as well as its effects on [^{35}S]GTPγS binding in HeLa cells