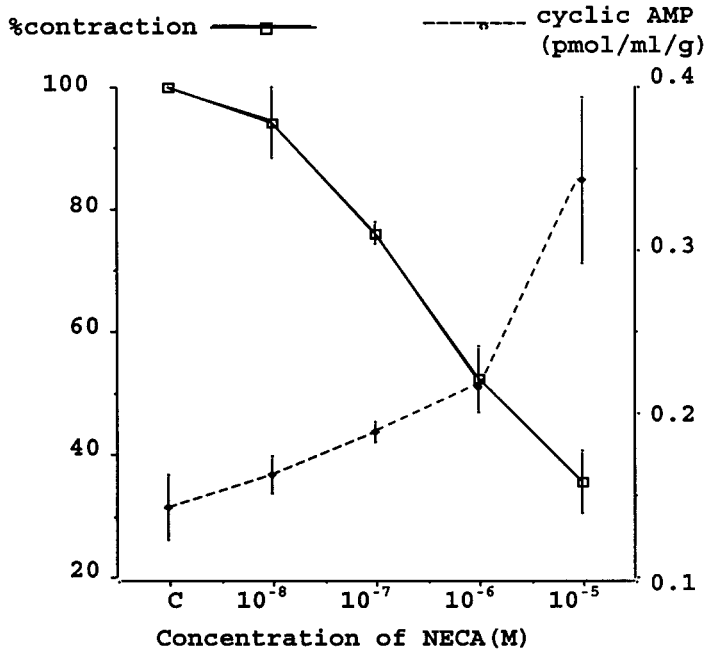
reaction through the elevation of an intracellular cyclic AMP. It is possible that the modulation of adenosine receptors may have clinical application for bladder dysfunction in the future.

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



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L. Guarneri, P. Angelico, C. Velasco, A. Leonardi and R. Testa.

Pharmaceutical R&D Division, RECORDATI S.p.A., Milano, Italy

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

stably expressing the cloned human 5-HT_{1A} receptors, were evaluated. The in vivo antagonistic activity on presynaptic and postsynaptic 5-HT_{1A} receptors was evaluated as antagonism of hypothermia induced in mice by 8-OH-DPAT, and inhibition of 8-OH-DPAT-induced fore-paw treading in rats, respectively.
At bladder level, the in vitro activity on rat bladder strips contracted by carbachol and on rabbit urethra strips contracted by noradrenaline was evaluated. Activity on isovolumic bladder voiding contractions in anesthetized rats and cystometrographic recordings in conscious rats and guinea-pigs, as well as cystometrographic recordings in conscious rats with irritated bladder were studied.
At CNS level, four plates test in mice and Vogel conflict test in rats were used to detect anxiolytic activity. Tail suspension test in the mouse was utilized to evaluate both anxiolytic and antidepressant activity, as well as behavioral despair test in the mouse. Hot plate and tail-flick tests in the rat were utilized to evaluate analgesic activity, and rotarod test in the rat to detect neurological deficits.

RESULTS
Rec 15/3079 showed very high affinity only for the 5-HT_{1A} receptor (Ki = 0.2 nM). It did not modify the basal [^{35}S]GTPγS binding to HeLa cells membranes stably expressing the human recombinant 5-HT_{1A} receptor, but shifted the activation isotherm of 5-HT to the right in a parallel manner, with pKb value of 10.5, indicating that it can be considered a neutral antagonist at this receptor. Accordingly, i.v. Rec 15/3079 potently antagonized 8-OH-DPAT-induced hypothermia in mice (ID_{50} = 20 μg/kg), a model of pre-synaptic antagonism, and 8-OH-DPAT-induced forepaw treading in rats (post-synaptic antagonism; ID_{50} = 36 μg/kg). In vitro studies demonstrated that Rec 15/3079 was only marginally active in antagonizing carbachol-induced bladder (pD'2 = 5.03) or noradrenaline-induced urethra (pD'2 = 4.72) contractions. In the (isovolumic) voiding contractions model (anesthetized rats) Rec 15/3079 (10-100 μg/kg i.v.) blocked the contractions with no effects on their amplitude. Its effects were antagonized by mesulergine and potentiated by citalopram. In conscious rats and guinea-pigs with bladder filled with saline, Rec 15/3079 increased bladder capacity (300-1000 μg/kg i.v.) without affecting bladder contractility. In conscious rats with bladder filled with diluted acetic acid, Rec 15/3079 (300 μg/kg i.v.) reversed the decrease of BVC induced by the acid. When tested in several different experimental models for CNS activity, Rec 15/3079 showed only a slight, non dose-dependent, decrease in the duration of immobility in the behavioral despair test (antidepressant) after i.v. administration of 1 mg/kg. No anxiolytic activity was observed after i.v. administration of doses up to 10 mg/kg. It had also no effects in the hot plate test, but it significantly increased the tail-flick latencies after i.v. administration of 3-10 mg/kg.

CONCLUSIONS
In conclusion, these studies demonstrate that Rec 15/3079 is endowed with favorable effects on bladder function (inducing increase of bladder capacity without derangement of bladder contractility) and it is devoid of unwanted side effects at the level of CNS at doses at least 10 fold higher than those active on the bladder. This new molecule can be considered an "uroselective" drug candidate for the care of urinary urge syndromes.

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Author(s):
R. Pehrson and K-E. Andersson #, O. Ishizuka and Y. Igawa §

Institution, city, country:
Dep. of clinical pharmacology, University of Lund, § Dep. of Urology, Shinshu University School of Medicine, Japan

Title (type in CAPITAL LETTERS, leave one blank line before the text):
5-HT1A RECEPTORS AND MICTURITION CONTROL IN NORMAL, CONSCIOUS RATS

AIMS OF STUDY: Serotonergic neurons originating in the raphe nuclei descend to the autonomic and somatic nuclei in the lumbosacral spinal cord in rats. There is evidence that these neurons may inhibit the micturition reflex. The receptors in the spinal cord through which this effect is mediated have not been established. 5-HT1A receptor agonists has previously been shown to stimulate micturition in rats when given systemically. 5-HT1A receptors