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BK CHANNEL OPENERS CAN ACT SELECTIVELY ON THE BLADDER

Aims of Study

Activation of K^+ channels to relax bladder smooth muscle has been evaluated as a therapeutic approach to bladder overactivity. Although K_{ATP} channel openers relax bladder smooth muscle both in vitro and in vivo, they are more potent against vascular smooth muscle. Recently, a number of reports have implicated the large conductance Ca^{2+}-activated K^+ channel (BK) in the functioning of urinary bladder smooth muscle [1,2].

Little data is available on the relative bladder and vascular effects of BK channel openers. NS-8 (2-amino-3-cyano-5-(2-fluorophenyl)-4-methylpyrole) appears to activate the BK channel [3]. We evaluated the effects of NS-8 on vascular and urinary bladder smooth muscle to determine whether this class of compounds may offer an advantage over the K_{ATP} channel openers for the treatment of overactive bladder.

Methods

Urinary bladder and portal vein were removed from male Sprague-Dawley rats. Segments of bladder (bisected longitudinally) and portal vein were allowed to equilibrate under a resting tension of 1 g at 37°C for 1 h in a physiological salt solution bubbled with 95% O_2, 5% CO_2. Data were recorded and analysed using a PC based system (Biopac) using AcqKnowledge 3.5.7 software. Portal vein segments contracted spontaneously; bladder strips were stimulated by the addition of 15 mM KCl . Following equilibration (20 min), increasing concentrations of test compounds were added cumulatively. EC_{50}'s were determined from the area under the curve.

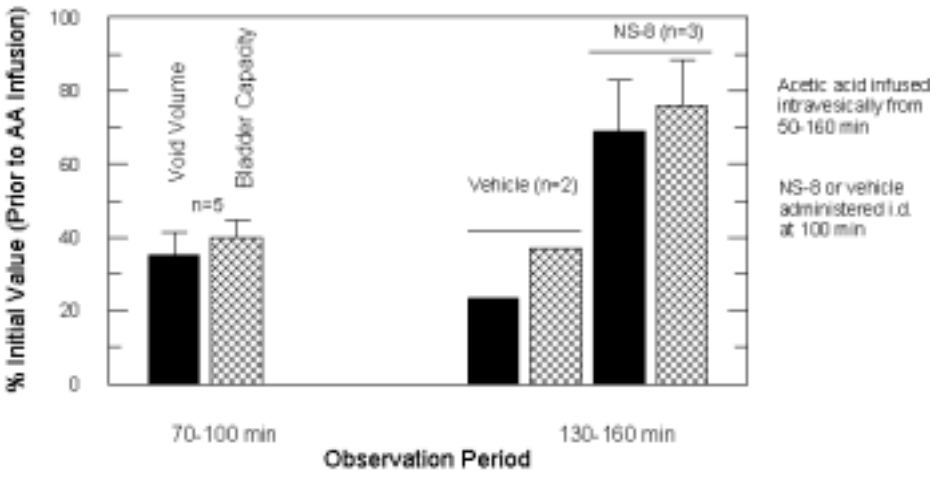
Female Sprague-Dawley rats (310-380 g) were anaesthetized with urethane (1.0 g kg^{-1} i.v.) and the urinary bladder and carotid artery cannulated. Saline was infused into the bladder (0.077 ml min^{-1}) until evoked micturition reflexes were consistent (approximately 5 voids). The bladder was manually emptied following each micturition to allow determination of residual volume. Acetic acid (0.5 %, pH 3.0) was then introduced intravesically to produce bladder irritation. When the micturition response stabilized NS-8 (3 mg kg^{-1} i.d.) or vehicle (10 % Gelucire i.d.) was administered and parameters recorded.

Results

NS-8 was more potent against bladder than portal vein. The opposite selectivity profile was observed for levcromakalim and pinacidil, which were 7 to 9-fold more potent in portal vein vis-a-vis urinary bladder.

Compound	EC_{50} (Bladder)	EC_{50} (Portal Vein)	Ratio
NS-8	940±480 nM	2900±1300 nM	0.3
Levcromakalim	197±29 nM	28±8 nM	7.0
Pinacidil	1400	150	9.3

NS-8 (3 mg kg^{-1} i.d.) approximately doubled bladder capacity and void volume in the bladder-irritated rats, with no effect on micturition pressure, mean arterial blood pressure or heart rate.



Conclusions

In contrast to the vascular-selective K_{ATP} channel openers, NS-8 selectively relaxes bladder smooth muscle. NS-8 also was able to reverse the bladder hyperactivity induced by acetic acid, at doses not affecting blood pressure or bladder emptying pressure.

In many animal models, the muscarinic antagonists decrease micturition pressure and increase residual volume. NS-8 appears to increase the ability of the bladder to store urine, without either of these deleterious effects or blood pressure reduction. Hence, BK channel openers such as NS-8 may offer a benefit over current therapies for overactive urinary bladder.

References

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