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EFFECTS OF ANTI-MUSCARINIC AGENTS ON ACETIC ACID-PREPARED RAT MODEL OF INCREASED URINARY FREQUENCY

Hypothesis / aims of study

In spinal cord-lesioned humans, neurogenic detrusor overactivity is likely to be mediated by capsaicin-sensitive C-fiber afferents. Capsaicin has been used for the treatment of neurogenic bladder overactivity in patients with spinal cord injury or multiple sclerosis [1]. As anti-muscarinic agents act mainly during the storage phase, allowing an increase in bladder capacity, they may exert an inhibitory effect on bladder afferent nerves. This study was done to determine whether the effects of anti-muscarinics depend on the suppression of C-fiber bladder afferent nerves. An acetic acid-induced increase in urinary frequency in rats is used as a model of an urination disturbance due to overactive C-fiber afferents [2]. Therefore we evaluated the effect of oral administration of anti-muscarinic agents on this rat model.

Study design, materials and methods

Female CD (SD) rats (11-week-old) were used for the experiment. Under diethyl ether anesthesia, a polyethylene catheter was inserted into the bladder dome for cystometry. Seven days after the operation, the following urodynamic parameters were measured cystometrically in the conscious animals: intravesical pressure, urinary frequency, voided volume, and intercontraction interval. Saline was infused into the bladder continuously at the rate of 0.05 mL/min. After a preset period, an anti-muscarinic agent (propiverine hydrochloride, tolterodine tartrate or solifenacin succinate) was administered orally, and infusion of bladder with acetic acid at a concentration of 0.3 % in saline was started at the same time. The cystometry was done for 2.5 h, starting 30 minutes after the drug administration. The effects of agents were compared between agent and control groups. To induce desensitization of C-fiber bladder afferent nerves, capsaicin at the dose of 125 mg/kg was injected subcutaneously. The effect of desensitization was evaluated under the same measurement conditions.

Results

Intravesical infusion of 0.3 % acetic acid significantly reduced the intercontraction interval and voided volume compared with the saline infusion. Capsaicin-mediated desensitization blocked the increase in urinary frequency induced by acetic acid. Oral administration of only propiverine, at the dose of 30 mg/kg, significantly prolonged the intercontraction interval and increased the voided volume compared with the valves obtained for the control group.

Interpretation of results

Propiverine given in orally blocked the increase in urinary frequency induced by acetic acid. We propose that propiverine has not only anti-muscarinic activity but also atropine resistance–inhibitory activity (Ca2+ antagonistic or/and purinergic antagonistic effect).

Concluding message

Anti-muscarinic agents given by oral administration were evaluated for their effects on the acetic acid-induced increase in urinary frequency in conscious rats. This model was considered useful for predicting clinical effects because the oral route is the one used clinically. The increase in urinary frequency caused by acetic acid was reduced by only propiverine. Propiverine may be effective against increased urinary frequency and urgency by reducing the activity of C-fiber afferents. It is possible that propiverine has Ca2+ antagonistic activity to cause inhibition of the bladder contractions elicited by ATP. Although anti-muscarine agents increase the bladder capacity during storage phase, our results suggest that agents that have not only an anti-muscarinic effect but also atropine resistance–inhibitory activity are desirable in the treatment of pollakiuria due to overactive C-fiber afferents.

References

[1] J. Urol., 157, 585-589, 1997
[2] J. Neurophysiol., 86, 2276-2284, 2001

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