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Title: EFFECTS OF INTRATHECAL OXOTREMORINE-M ON BLADDER HYPERACTIVITY INDUCED BY ACETIC ACID IRRITATION IN AWAKE RATS

Aims of study

C-fiber, unmyelinated afferent fibers in the lower urinary tract, have been involved in the pathogenesis of bladder hyperreflexia[(1)]. These indicate that C-fiber afferents in the bladder are potentially an important target for drug therapy in the treatment of hyperactive bladder disorders. Previous experiments revealed that certain drugs can differentially affect C-fiber afferent and that analgesic drugs which suppress vesical nociceptive pathways do not necessarily affect C-fiber afferent[(2)]. We reported that Oxotremorine-M (OXO-M), a nonselective muscarinic agonist, alters the afferent rather than the efferent limb of the micturition reflex pathway in the spinal cord that control voiding function and suppresses vesical nociceptive pathways in awake rats[(3)]. The present studies were undertaken to determine whether OXO-M would influence the spinal processing of C-fiber input from bladder. Several studies described that intravesical instillation of acetic acid, which influence the spinal processing of C-fiber input from bladder, induced bladder hyperactivity under urethane anaesthesia[(4), (5)]. We determined the effects of intravesical instillation of acetic acid in awake rats then compared with the effects of intrathecal administration of OXO-M between intravesical instillation of acetic acid and that of physiological saline in conscious rats.

Methods

In normal female S-D rats (250-300g) anaesthetised with halothane, a catheter was inserted through the bladder dome and an intrathecal cannula to the L-6 level of the spinal cord was inserted. After the surgery, rats were allowed to conscious restrained state. Saline was infused into the bladder at a constant rate (0.1 ml/min.) and after saline infusion, 0.1 % of acetic acid was infused at a constant rate (0.1 ml/min.). Control cystometrogram (CMG) in saline infused rats were recorded at least for one hour and then that in acetic acid infused rats were recorded at least for 30 minutes. Increasing doses of OXO-M (0.001-1 μg /rat. i.t.) were injected and CMG was recorded in acetic acid infused conscious rats. As a control group, increasing doses of OXO-M (0.001-1 μg /rat. i.t.) were adopted in saline infused rats instead of acetic acid infused rats.

Results

Pressure threshold (PT), maximal voiding pressure (MVP) and post-voiding intravesical pressure (PVIP) before OXO-M injection in acetic acid infused group (n=7) were 18.0 cm H_2O, 50.3 cm H_2O and 17.4 cm H_2O respectively and these were significantly higher than those in saline infused group (n=7; PT; 12.7 cm H_2O, MVP; 39.9 cm H_2O, PVIP; 10.1 cm H_2O). Bladder capacity before acetic acid infusion was 0.36 ml and that after acetic acid infusion was 0.14 ml. Both amplitude pressure (AP; acetic acid infused group; 32.9 cm H_2O, saline infused group; 29.7 cm H_2O) and voiding efficiency (AP; acetic acid infused group; 88.0%, saline infused group; 89.5%) before OXO-M injection was not different between two group. Neither dose of OXO-M changed AP in any group. Voiding efficiency after OXO-M injection was not different between two group.

Bladder capacity after 0.1μg and 1μg of OXO-M injection increased 87% and 170% when comparing with pre-injection. In saline infused group, bladder capacity after 0.1μg and 1μg of OXO-M injection increased 85% and 179% when comparing with pre-injection. Moderate dose (0.1μg) of OXO-M did not change PT, MVP, PVIP, AP and voiding efficiency in both group when comparing with pre-injection.

Conclusions

Acetic acid infusion decreased bladder capacity in conscious rats. These indicate that acetic acid infusion irritates C-fiber afferent limb in conscious rats as well as urethane anaesthetised rats. Acetic acid infusion did not change AP or voiding efficiency, which indicate that acetic acid infusion does not influence efferent limb. Acetic acid infusion increased PT, MVP and PVIP without influencing AP or voiding efficiency. These results suggest that evidence of an efferent function of afferent nerves or the afferent mediate neuroepithelial interaction. The present study revealed that OXO-M caused same degree of increases on bladder capacity in two groups. Moderate dose of OXO-M increased bladder capacity without changing every pressure and voiding efficiency, which were not different between two group. These results indicate that OXO-M alters the afferent limb rather than the efferent limb of the micturition reflex and depress the spinal processing of activity in C-fiber bladder afferents. On a higher dose OXO-M also depresses reflex-activity induced by Aδ-fiber bladder afferents.

References

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