

ROLES OF PERIPHERAL AND CENTRAL NICOTINIC RECEPTORS IN THE MICTURITION REFLEX IN RATS

Hypothesis / aims of study

Nicotinic acetylcholine receptors (nAChRs) have been reported to be present in urothelium, sensory neurons in dorsal root ganglia (DRG) and primary afferent terminals in the spinal cord, suggesting the functional role of nAChRs for bladder afferent pathways in peripheral and central nervous systems (CNS) (1, 2). Therefore, We investigated the effects of activation of nAChRs in the bladder, spinal cord and brain on the micturition reflex in urethane anesthetized rats.

Study design, materials and methods

The effects of nAChRs activation on bladder activity were examined during continuous infusion cystometrograms (0.04 ml/min). Nicotine with or without mecamylamine, a nAChRs antagonist, was administered intravesically, intrathecally (i.t.) or intracerebroventricularly (i.c.v.) in normal or capsaicin pretreated rats. In addition, we examined the responses to nicotine in dissociated bladder afferent neurons from L6-S1 dorsal root ganglia (DRG) that were sensitive to capsaicin, using whole-cell patch clamp recordings.

Results

Intravesical injection of nicotine (1 to 10 mM) induced detrusor overactivity, as evidenced by a reduction in intercontraction intervals (ICI) in a dose-dependent manner followed by a desensitisation phase. Nicotine-induced detrusor overactivity was abolished by intravesical co-application of mecamylamine (3 mM) as well as capsaicin pretreatment. In patch clamp recording, 300 μ M nicotine evoked rapid inward currents in capsaicin-sensitive bladder afferent neurons that were antagonized by mecamylamine. On the other hand, i.t. and i.c.v. administration of nicotine (10 μ g) decreased and increased the ICI, respectively. Both effects were antagonized by pretreatments with mecamylamine (50 μ g). Also, the spinal excitatory effect was significantly reduced by pretreatment with intrathecal MK-801 (20 μ g), an NMDA receptor antagonist. see Fig.1

Interpretation of results

These results indicate that activation of nAChRs in capsaicin sensitive C-fiber afferents in the bladder can induce detrusor overactivity. In the CNS, nAChRs activation in the spinal cord and brain can have excitatory and inhibitory effects on the micturition reflex, respectively. Also, the excitatory effect of nicotine in the spinal cord may be mediated via enhancement of glutamatergic transmission.

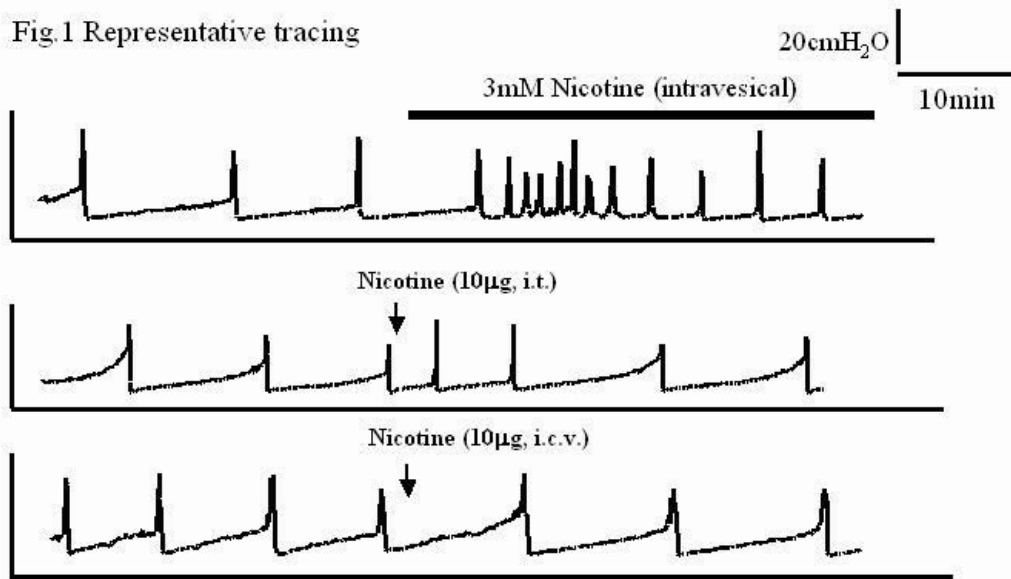
Concluding message

It is likely that nAChRs have an important role in the modulation of bladder afferent excitability and voiding. At the local (bladder) and spinal levels, nAChRs mediate excitatory effects rather than inhibition on the micturition reflex while at the supraspinal level, they mediate inhibitory effects on micturition reflex. Thus, detrusor overactivity induced by intravesical nicotine is likely to be a useful model for the study of lower urinary tract dysfunctions induced by the activation of bladder C-fiber afferents. In addition, these findings raise the possibility that modulating nAChRs in the bladder and/or CNS could be effective for treating detrusor overactivity and/or bladder pain in various pathological conditions.

References

1. Neurosci abstract, 538, 2002.
2. J Comp Neurol 467: 44-59, 2003.

Fig.1 Representative tracing



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