69

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A PHARMACOLOGICAL STUDY OF ACUTE BLADDER NOCICEPTION

Hypothesis / aims of study

Drugs that reduce afferent activity represent an attractive therapeutic approach for pharmacologic interventions for the treatment of overactive bladder because of well-known side effects of the most common pharmacotherapy, antimuscarinic agents. However, pharmacology studies of sensory targets by recording afferent neuron activity have been limited by technical difficulties and the low productivity. Recently, cardiovascular and visceromotor responses to urinary bladder distention (UBD) in anesthetized rats were reported to be reliable measures of acute bladder nociception (1). The purpose of this study was to compare the effects of mu opioid receptor agonist, morphine, sodium channel blocker, mexiletine, the muscarinic receptor antagonist, oxybutynin, and the nonsteroidal anti-inflammatory drug, naproxen, in the rat UBD model.

Study design, materials and methods

Isoflurane anesthetized female Sprague-Dawley rats were acutely instrumented with needle electrodes into the abdominal musculature along with jugular venous, carotid arterial and bladder cannulas. The pressor and visceromotor (abdominal contractile as quantified by abdominal electromyography activity) responses to phasic UBD (20 s) by saline injection were recorded under light anesthesia (1% isoflurane).

Results

Enhanced pressor and visceromotor responses were observed to increased intensities of graded UBD from 10 to 80 mmHg (n=14). The intravesical pressure threshold for activating the pressor and visceromotor responses was 30 mmHg. Furthermore, the reflex responses to repeat noxious UBDs (n=14, 60 mmHg or 80 mmHg, at 3-minute intervals) initially increased. After an initial period of sensitization, the pressor and visceromotor responses became reproducible with repeat noxious UBD. Drug effects on the pressor and visceromotor responses to repeat noxious UBD were evaluated 2 min following accumulative intravenous administrations. All but naproxen inhibited the nociceptive responses in a dose-dependent manner. The rank order of potency of the drugs tested was morphine > mexiletine ≥ oxybutynin. At a cumulative dose of 1 mg/kg, analgesic morphine inhibited the pressor and visceromotor responses to 50.00 ± 5.91 % (n=5) and 8.53 ± 5.23 % of control (n=5), respectively ($p<0.05$). The mean ID50 values on the pressor and EMG responses were 1.06 ± 0.09 mg/kg and 0.70 ± 0.21 mg/kg, respectively. Mexiletine also produced antinociceptive effect, at 10 mg/kg, inhibiting the pressor and visceromotor reponses to 54.36 ± 4.30 % (n=4) and 24.88 ± 15.18 % (n=5) of control, respectively ($p<0.05$). The mean ID50 values on the pressor and visceromotor responses were 10.39 ± 0.88 mg/kg and 2.93 ± 0.51 mg/kg, respectively. The antimuscarinic agent, oxybutynin acts on the detrusor muscle, decreasing the ability of the bladder to contract. In this study, oxybutynin moderately attenuated reflex responses to noxious UBD at 10 to 30 mg/kg (n=4), confirming its contribution of inhibitory effects in bladder-afferent pathways. In contrast, naproxen was ineffective to attenuate pressor response up to 10 mg/kg intravenous administration, but weakly inhibited visceromotor response to 72.78 ± 8.82 % of control to UBD (n=3).

Interpretation of results

Current appraisal of diverse classes of drugs under standardized test conditions in the rat UBD model agrees with the basic research and clinical experience of analgesics (morphine and mexiletine) that have been administrated to humans to effectively inhibit nociceptive transmission.

Concluding message

The utility of the reflex responses to UBD prove useful to screen drugs which target the bladder sensory pathway.

References

1. THE JOURNAL OF UROLOGY, 165, 968–974, 2001

FUNDING: **NONE**
DISCLOSURES: **NONE**
ANIMAL SUBJECTS: **This study followed the guidelines for care and use of laboratory animals and was approved by The Institutional Animal Care and Use Committee of GlaxoSmithKline Pharmaceuticals, King of Prussia, PA**