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Nishijima S[1], Sugaya K[1], Miyazato M[1], Ashimine S [1], Morozumi M[1], Ogawa Y[1]
1. University of the Ryukyus.

EFFECTS OF INTRAVENOUS OR INTRATHECAL NORADRENALINE AND/OR NAFTOPIDIL ON BLADDER ACTIVITY AND AMINO ACID NEURONAL ACTIVITIES IN THE LUMBOSACRAL CORD IN RATS

Aims of study

Benign prostatic hyperplasia (BPH) induces lower urinary tract symptoms (LUTS) that are both voiding and collecting disorders. Hypertension worsens LUTS, especially urinary frequency and nocturia, in BPH patients. Although adrenergic alpha-1 receptor antagonists improve both voiding and collecting disorders in BPH patients, naftopidil (an alpha-1D receptor antagonist) is superior for collecting disorders. Since intrathecal injection of naftopidil to the lumbosacral cord level transiently abolishes bladder contractions in rats, noradrenaline may facilitate afferent activity of the micturition reflex at the lumbosacral cord via alpha-1D receptor. Therefore, in order to clarify the influence of noradrenaline on micturition reflex activity, the effects of intravenous and/or intrathecal injections of noradrenaline or naftopidil on bladder activity and the changes of amino acid neurotransmitter levels in the lumbosacral cord were examined.

Materials and methods

Fifty-six female Sprague-Dawley rats were used. The rats were divided into two groups; 1) 24 rats for cystometry and 2) 32 rats for amino acid analysis. All rats were anesthetized by intraperitoneal and subcutaneous injection of urethane (1.2 g/kg). In rats for cystometry, a polyethylene catheter was inserted into the bladder through the urethra. The urethra was ligated to the catheter near the external urethral meatus, and bladder was filled with physiological saline (0.05 ml/min) to above the threshold volume to induce isovolumetric rhythmic contractions. After the bladder contractions had become stable, noradrenaline and/or naftopidil were injected intravenously and/or intrathecally at the sacral cord level, and the change of bladder activity was recorded. In rats for amino acid analysis, physiological saline, noradrenaline and naftopidil were injected intrathecally at the sacral cord level. After 5 min, these rats were sacrified and the lumbosacral cord was harvested. The spinal amino acid levels were measured by capillary electrophoresis system. Data were expressed as means±standard deviation.

Results

Intravenous injection of noradrenaline (0.1 mg) significantly shortened the interval (22% decrease, $p=0.027$) and decreased the amplitude of bladder contractions (33% decrease, $p<0.001$) and decreased the intravesical baseline pressure (31% decrease, $p=0.012$) when compared with those before injection. Intrathecal injection of noradrenaline (0.01-1 μg) also significantly shortened the interval of bladder contractions (maximally 33% decrease at dosage of 1 μg , $p=0.037$), while higher dose of noradrenaline (0.1-1 μg) transiently stopped bladder contractions before inducing high frequent bladder contractions, and intrathecal injection of 10 μg noradrenaline completely stopped bladder contraction over 30 min. The amplitude of bladder contractions and the intravesical baseline pressure was not changed by intrathecal injection of noradrenaline (0.1-1 μg). Simultaneous intravenous injection of noradrenaline (0.1 mg) and intrathecal injection of naftopidil (0.1 mg) did not change the interval of bladder contractions, but the amplitude of bladder contractions and the intravesical baseline pressure were decreased (30% and 26% decrease, respectively. $p=0.008$ and $p<0.001$). On amino acid analysis, intrathecal injection of noradrenaline (10 μg) increased the glutamate level (5% increase, $p=0.001$) and decreased the glycine and GABA levels (15% and 22% decrease, respectively. $p=0.001$ and $p<0.001$) in the lumbosacral cord when compared with those injected physiological saline (sham groups). While, intrathecal injection of naftopidil (50 μg) increased the GABA level (32% increase, $p=0.002$) in the lumbosacral cord when compared with those in sham groups.

Interpretation of results

Intravenous injection of noradrenaline shortened the interval of bladder contraction with decrease of the amplitude and intravesical baseline pressure, while intrathecal injection of noradrenaline also shortened the interval of bladder contraction without change of the amplitude and intravesical baseline pressure. The amino acid levels in the lumbosacral cord were changed after intrathecal injection of noradrenaline. These results suggest that noradrenaline directly inhibits the activities of the bladder smooth muscle cells and some of noradrenaline passes through the blood-brain barrier and activates excitatory glutamatergic neurons and inhibits inhibitory glycinergic and GABAergic neurons in the lumbosacral cord as a result. Simultaneous intravesical injection of noradrenaline and intrathecal injection of naftopidil did not change the interval of bladder contractions, and the GABA level in the lumbosacral cord was significantly decreased by intrathecal injection of naftopidil. So, naftopidil may block some of these noradrenergic influences in the lumbosacral cord caused by the decrease of inhibitory neurons activity. The mechanism that higher dose of noradrenaline transiently stopped bladder contractions is not known in this study, but this phenomenon may not involve in these amino acid neuronal activities.

Concluding message

Serum noradrenaline level may influence several amino acid neuronal activities in the lumbosacral cord and LUTS. Therefore, the adjustment of the blood pressure might be important to the improvement of LUTS.