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DOPAMINE D1 AGONIST INHIBIT THE BLADDER CONTRACTION AND CHANGE THE ACTIVITY OF STRIATAL BLADDER RELAXATION PHASE RELATED NEURON IN CATS.

Hypothesis / aims of study
It is common that patients with Parkinson’s disease (PD) show various micturition symptoms and many patients with PD are suffering from overactive bladder (OAB) symptoms. Since, PD is caused by striatonigral dopaminergic neuronal loss, striatonigral dopaminergic nervous system might be one of the suprapontine higher micturition centre.

We have previously reported that the severity of micturition symptoms are significantly correlated with the striatal dopaminergic neuronal loss in PD patients (1), and identified the bladder contraction/relaxation related neurons in the ventral striatum in normal cats (2). Pharmacological studies suggested that stimulation of dopamine D1 receptor suppress the bladder contraction in animal, whereas dopamine D2 receptor stimulation causes facilitation of the bladder contraction in both animal and human (3). Although dopamine D1 receptor agonist is not available in human, pharmacological studies suggested that D1 agonist might be effective in treating OAB symptoms in PD patients. We therefore aimed to examine the effect of D1 receptor stimulation on both the bladder contraction and the activity of bladder contraction/relaxation related neuron in the ventral striatum.

Study design, materials and methods
Experiments were done on 12 adult male cats under anesthesia with ketamine. The continuous periodic bladder contraction/relaxation cycles were induced by infusing saline volume into the bladder slightly exceeding a threshold volume (20-50ml). After the continuous periodic bladder contraction/relaxation cycles were generated, we stereotaxically inserted microelectrode into the ventral striatum to examine the neuronal activity of the bladder contraction/relaxation related neuron. Neurons were defined as bladder relaxation phase-related neurons if their mean firing frequencies in the contraction phase were significantly higher than those in the contraction phase during a period of three urinary cycles or more, and as bladder contraction phase-related neurons if their mean firing frequencies in the contraction phase were significantly higher than those in the relaxation phase during a period of three urinary cycles or more. After the bladder contraction/relaxation phase related neuron was identified in the ventral striatum, we intravenously administered dopamine SKF38393 (dopamine D1 agonist) 3mg/kg to evaluate the change in the bladder contraction and the activity of the striatal bladder contraction/relaxation phase related neuron, respectively.

Results
Intravenous administration of SKF38393 markedly suppressed the bladder contraction and significantly prolonged average intercontraction interval from 116 s to 262 s (Figure 1). We identified five neurons activating during bladder relaxation phase in the ventral striatum and found that two neurons increase the neuronal firing during bladder contraction phase after SKF38393 administration (Figure 2). The mean firing frequency during bladder contraction phase significantly increased from 1.86 Hz to 8.91 Hz after SKF38393 administration. The mean firing frequency during bladder relaxation phase remained unchanged. The effect of SKF38393 on the bladder contraction and the ventral striatal neuronal activities were obtained separately.

Interpretation of results
The present study revealed that the systemic administration of dopamine D1 agonist significantly inhibits the bladder contraction in cat, which is consistent with previous studies using normal rat. We also showed that the ventral striatal neuron activating during bladder relaxation phase tend to increase the neuronal firing during bladder contraction phase after SKF38393 administration. The striatal neuron activating during bladder relaxation phase might be responsible for inhibiting bladder contraction during relaxation phase and the decreasing of the neuronal firing of these neuron might induce bladder contraction. Therefore increased neuronal firing during bladder contraction phase might lead to suppression of the bladder contraction. The present result suggested that SKF38393 suppressed bladder contraction by increasing the activity of striatal bladder relaxation phase related neuron during bladder contraction phase.

Concluding message
Intravenous administration of the dopamine D1 agonist markedly suppressed bladder contraction probably via changing the activity of bladder relaxation phase related neuron in the ventral striatum.

Figure 1
Intravenous administration of SKF38393 3mg/kg markedly suppressed the bladder contraction.

Figure 2

This neuron is bladder relaxation phase related neuron. Intravenous administration of SKF38393 3mg/kg significantly increased the neuronal firing in the bladder contraction phase.

References
2. Neurourol Urodyn. 2009 Epub ahead of print

Specify source of funding or grant
- Grant-in-Aid for Young Scientists(B), Japan

Is this a clinical trial?
- No

What were the subjects in the study?
- ANIMAL

Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?
- Yes

Name of ethics committee
- Chiba University, Chiba, Japan