210

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THE SHORT-TERM EFFECT OF AMANTADINE HYDROCHLORIDE ON MICTURITION IN 6-HYDROXYDOPAMINE TREATED PARKINSON'S DISEASE MODEL RATS

Hypothesis / aims of study

Amantadine hydrochloride is an antiviral agent with activity against various strains of influenza virus. In1968, amantadine hydrochloride was serendipitously found to relieve parkinsonian symptoms. Then it was begun to be used in treatment of motor dysfunction of Parkinson's disease(PD). However, whether amantadine hydrochloride has effect on autonomic dysfunction of PD was not well known. In particular, effect of amantadine hydrochloride on lower urinary tract dysfunction (LUTD) in PD was not reported previously. We evaluated short-term effect of a single dose of amantadine hydrochloride on LUTD in PD by using 6-hydroxydopamine treated Parkinson's disease model rats.

Study design, materials and methods

Experiments were performed on adult male Sprague-Dawley rats (8-9 weeks, weighting about 250-300g) in standardized environmental conditions. 4 weeks before studies, bilateral injections of 6-hydroxydopamine (PD model, n=8) or saline (vehicle) (Sham model, n=8) were performed in substantia nigra stereotaxically. Three days before studies, a polyethylene tube (PE-50) was inserted into the bladder from the bladder dome with midline abdominal incision to monitor bladder activity and another tube was placed into jugular vein to inject drug or vehicle under nembutal anesthesia. Then, animals were attached on harness with external tube, and kept in metabolic cages in order to settle in to study's condition. Studies were performed in the daytime. Urodynamic evaluation was performed without any anesthesia. Saline at room temperature was infused into the bladder at a rate of 12ml/h. Interval of void (time), number of void, and urine volume per void were measured. After achievement of equilibration and 60 minutes' baseline recording, a single dose of amantadine hydrochloride (0.3, 3, 30, 100 μM) or saline (vehicle) was administrated intravenously. And recording was continued for over 60 minutes after each administration. The data obtained in each condition were compared with each other.

Results

In saline-administrated sham and PD model rats, interval between voids (time) and urine volume per void almost unchanged from the base line. In amantadine hydrochloride -administrated sham rats, mean interval of void (time) and mean urine volume per void also almost unchanged from the base line. Compared with these models, in PD model rats, 0.3 and 3 μM amantadine hydrochloride (low dose) induced prolongation of mean interval of void (time) and increase in mean urine volume per void dose-dependently ($p<0.05$). However, 30 and 100 μM amantadine hydrochloride (high dose) induced shortening of mean interval of void (time) and decrease in mean urine volume per void dose-dependently ($p<0.05$).

Interpretation of results

In sham model rats, amantadine hydrochloride had no effect on micturition. In PD model rats, low dose (0.3, 3 μM) of amantadine hydrochloride inhibited micturition reflex, however high dose (30, 100 μM) of amantadine hydrochloride stimulated micturition reflex.

Concluding message

Amantadine hydrochloride had biphasic effects on lower urinary tract function only in PD model rats. Therefore low dose of amantadine hydrochloride seems to be useful for ameliorating not only motor dysfunction but also storage urinary dysfunction in PD. In contrast, high dose of amantadine hydrochloride can be useful to voiding dysfunction in PD. These effects may be related with presumable neurotransmitter changes by amantadine hydrochloride. Amantadine hydrochloride can become a new drug candidate in treating both motor and urinary disorders of PD.

References

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