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

Hypothesis / aims of study
Zonisamide (ZNS) is an antiepileptic discovered in Japan. Recently, it was reported that ZNS ameliorated movement disorder in patients with Parkinson disease (PD), and ZNS was notified as a new anti-parkinsonian drug. However, there were few reports to evaluate effect of ZNS on autonomic dysfunction, especially on lower urinary tract dysfunction in PD patients. In only one clinical case report, it was reported that urinary frequency was improved by ZNS for movement disorder in one of their PD patients.
We evaluate short-term effect of ZNS on lower urinary tract function in PD by using 6-hydroxydopamine treated PD model rats.

Study design, materials and methods
Experiments were performed on adult male Sprague-Dawley (SD) rats (Age, 8 weeks: Body weight, 200-250g) in standardized environmental conditions. 4 weeks before studies, bilateral injections of 6-hydroxydopamine (PD model) or saline (sham model) were performed in substantia nigra stereotaxically. Four days before studies, a polyethylene tube (PE-50) was inserted into the bladder from the bladder dome with midline abdominal incision. Three days before studies, 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. Water cystometry during storage and voiding phase was performed in awake and free moving state, and number of micturition per 60 minutes, micturition interval, urine volume per void, and maximum bladder pressure during voiding were observed. After achievement of equilibration and over 60 minutes' baseline recording, a single dose of ZNS (0.1, 1, 10, 100 μM) or the same volume of saline was given intravenously, and recording was continued for over 60 minutes after drug administration. The data obtained in each condition were compared with each other.

Results
In 60 minutes' baseline recording before administrating a drug, comparing with sham model rats, number of micturition per 60 minutes increased, and micturition interval and urine volume per void decreased in PD model rats.
In saline-administrated PD and sham model rats, number of micturition per 60 minutes, micturition interval and urine volume per void unchanged from the base line. In ZNS-administrated sham rats, number of micturition per 60 minutes, micturition interval and urine volume per void unchanged from the base line. In contrast, in ZNS-administrated PD model rats, number of micturition per 60 minutes, micturition interval, and urine volume per void in 0.1 and 1 μM unchanged. However, 10 and 100 μM ZNS induced a decrease in the number of micturition per 60 minutes and an increase in micturition interval and urine volume per void, particularly at 100 μM. Maximum bladder pressure during voiding was unchanged in any status.

Interpretation of results
In PD model rats, micturition reflex was accelerated, indicating that lower urinary tract dysfunction during storage such as detrusor overactivity occurred. Moderate and high dose of ZNS ameliorated this abnormal micturition reflex without impairment of voiding function in PD models, but not induced suppression of normal micturition reflex in sham models.

Concluding message
ZNS has beneficial effects on not only motor disorder but also lower urinary tract (storage) dysfunction of PD model rats at moderate and high dose. ZNS may become a new drug target for the treatment of lower urinary tract (storage) dysfunction in PD.

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