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MECHANISM OF LOWER URINARY TRACT DYSFUNCTION IN PARKINSON'S DISEASE; PARTICIPATION IN BASAL GANGLIA CIRCUITRY AND SENSORY AND AUTONOMIC/EMOTIONAL NERVOUS SYSTEMS

Hypothesis / aims of study

Parkinson disease (PD) often has not only parkinsonism (motor disturbance) but also lower urinary tract dysfunction (LUTD), and which is also characterised by 1) increased bladder sensation, 2) urgency, 3) detrusor overactivity (DO), and 4) impaired detrusor contraction. However, the detailed mechanism of LUTD in patients with PD is still unknown. The main pathologic feature of PD is a degeneration of the dopaminergic neurons in the substantia nigra (SNc). Experimental rats with a lesion of the SNc produced by 6-hydroxydopamine (6OHDA) exhibit parkinsonism such as involuntary movement and freeging/bradykinesia, and these are often used as a experimental model of PD. The mechanism of parkinsonism also has been investigated in this model, and the SNc lesion was found to result in dysfunction of the basal ganglia circuitry, particularly in the output via thalamus and pedunculopontine nucleus. The dysfunction of these nuclei has been reported to be a cause of both involuntary movement which occur because of the impairment of suppression and termination of unnecessary movement, and freeging/bradykinesia that result from the impairment of initiation of necessary movement. This PD model also has LUTD, which is similar to LUTD in patients with PD. We investigated the mechanism of LUTD in PD, by brain-mapping the expression of the Fos protein, a nonspecific marker of neuronal activation encoded by the immediate-early gene c-fos, using 6OHDA 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 operated 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 evening. As a task to half the each model rats, saline was infused into the bladder continuously for 2h without anesthesia and restriction. After the task, brains were quickly removed and the number of cells exhibiting Fos immunoreactivity was counted in various brain regions, particularly in the basal ganglia circuitry including striatum, globus pallidus, subthathalamic nucleus, thalamus, and pedunculopontine tegmental nucleus, and the other regions which have been reported to be involved in both the control of bladder function and associated with sensory and autonomic/emotional reactions (sensory cortex, anterior cingulate gylus, insula, hypothalamus, periaqueductal gray mater (PAG), and brainstem reticular formation).

Results

The PD model rats showed facilitation of micturition reflex which was defined by shortening of micturition interval and decrease in urine volume per void, and spontaneous non-voiding bladder contractions between voids.
The results of mapping c-Fos expression in the basal ganglia circuitry showed 1) during micturition in normal model rats with infusion, Fos immunoreactivity mainly decreased within the striatum and subthathalamic nucleus, thus resulting in an increase in Fos immunoreactivity in the thalamus and pedunculopontine tegmental nucleus, 2) in the groups with no infusion, Fos immunoreactivity in the PD model rats was different from that in the normal rats, 3) comparing with normal model rats, during micturition in PD model rats, Fos immunoreactivity mainly increased within the striatum and the subthathalamic nucleus, thus resulting in decrease in Fos immunoreactivity in the thalamus and pedunculopontine tegmantal nucleus. The results of mapping c-Fos expression in the other regions associated with sensory and related emotion showed 1) during micturition in normal model rats with infusion, Fos immunoreactivity increased within the various regions of interest, 2) in the groups with no infusion, Fos immunoreactivity in the PD model rats was not different from that in the normal rats. 3) during micturition in PD model rats, Fos immunoreactivity abnormally increased in the PAG, hypothalamus, insula and anterior cingulate gyrus.

Interpretation of results

Compared to the normal model rats, the Parkinson disease model rats with abnormal micturition showed dysfunction of the basal ganglia circuitry and the other regions associated with sensory and autonomic/emotional reactions. In particular, there was impaired activation in the thalamus and pedunculopontine tegmental nucleus and abnormal increased activation in the PAG and anterior cingulate gyrus.

Concluding message

These findings suggest that nigrostriatal dopaminergic lesion as main cause of PD, which is lesion of supra-pontine micturition center, may cause detrusor overactivity as the impairment of suppression and termination of unnecessary movement and impaired detrusor contraction as the impairment of initiation of necessary movement by the dysfunction of thalamus and pedunculopontine tegmental nucleus, and may produce urgency as the abnormal sensation and autonomic/emotional reactions by the abnormal activation of PAG and anterior cingulate gyrus tegmental nucleus. Thus, the reconstruction / plasticity of basal ganglia circuitry and the other regions associated with sensory and autonomic/emotional reactions may contribute LUTD in patients with PD.

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