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TEMPORAL CHANGES IN BLADDER FUNCTION IN AN ANIMAL MODEL OF PARKINSON'S DISEASE

Hypothesis / aims of study

Bladder dysfunction in patients with Parkinson's disease is generally attributed to central neurodegeneration caused by loss of dopaminergic neurons in the *substantia nigra*, resulting in disinhibition of bladder reflexes and detrusor overactivity. However, recent clinical and epidemiological evidence suggests that autonomic symptoms related to visceral organs, including lower urinary tract symptoms, may precede the onset of motor deficits and possibly the loss of nigrostriatal dopaminergic neurons. The pathologic aggregation of α-synuclein in Lewy bodies is a distinguishing feature of Parkinson's disease. Although α-synuclein has been implicated in several cellular processes including the trafficking and release of synaptic vesicles, the biologic function of this pre-synaptic protein is poorly understood. The expression and distribution of α-synuclein in the central nervous system is well described; however, its localization under physiologic and pathologic conditions in the bladder has not been defined. Therefore, the purpose of this study was to determine the time-dependent changes in bladder function and α-synuclein behaviour in an animal model of Parkinson's disease.

Study design, materials and methods

Mice lacking the murine α-synuclein gene but overexpressing human α-synuclein with a common familial mutation (A53T) were used in this study ($SNCA^{A53T}$). Mice that overexpress the wild-type human α-synuclein gene were used as controls ($SNCA^{WT}$). Bladders removed from both groups were cut longitudinally and placed in temperature controlled tissue baths. Resting tension was adjusted to 0.5 gram and tissue was equilibrated for an hour. The contractile response to electrical field stimulation (40 volts, 0.5ms, 10 seconds) over a range of frequencies (1-64 Hz) was determined in each group at 14, 28, 42 and 58 weeks of age. The expression of α-synuclein in the bladder was determined by western blot. The distribution of α-synuclein and its localization with neuronal markers (VAChT, synaptophysin) were examined by immunofluorescence/confocal imaging.

Results

At younger ages (14 weeks), the frequency-response curve generated after electrical field stimulation in the mutant transgenic group ($SNCA^{A53T}$) was similar to that of the wild type transgenic group ($SNCA^{WT}$). However, by 28 weeks of age, the neurogenic response was significantly higher in $SNCA^{A53T}$ mice compared to the response in $SNCA^{WT}$ mice. At 42 weeks, the frequency-response curves were similar between groups, while at 58 weeks of age, evoked responses were reduced in $SNCA^{A53T}$ mice compared to $SNCA^{WT}$ mice. Endogenous α-synuclein expression was detected in bladders from normal C57 mice in monomeric form and as a tetramer on western blot. Immunoreactivity of endogenous α-synuclein was distributed throughout the bladder wall and co-localized with VAChT.

Interpretation of results

Profound temporal changes in neurogenic contractions detected in an animal model of Parkinson's disease suggest that altered bladder function may occur at an early stage of disease progression. The localization of α-synuclein with excitatory nerve fibers is consistent with its potential role in peripheral neurotransmission in the bladder.

Concluding message

Transgenic mice overexpressing a human α-synuclein mutation is a promising model of bladder dysfunction in Parkinson's disease. Since α-synuclein appears to regulate local neurotransmission in the bladder, pathologic changes in its expression or aggregation may contribute to bladder dysfunction prior to the onset of centrally mediated deficits associated with Parkinson's disease.

Disclosures
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