Sleep/wake activity in the Lewy bodies models of Parkinson's disease

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Résumé

Parkinson's disease (PD) is characterized by the loss of dopaminergic (DA) neurons of the substantia nigra pars compacta (SNc) and the presence of cytoplasmic inclusions named Lewy Bodies (LB) containing notably misfolded alpha-synuclein (a-syn). Although primarily a movement disorder, PD patients exhibit a myriad of non-motor symptoms. Sleep/wake alterations, such as rapid-eye movement (REM) sleep behavioral disorder (RBD), REM loss or increased day time sleepiness, may occur in the prodromal phase of PD. They are even considered as predictors of PD.
While neurotoxin-based experimental models recapitulate both motor and non-motor symptoms, their poor face validity with regard to the neurodegenerative process make them unsuitable for investigating the likelihood of a relationship between progression of neurodegeneration, progression of the a-syn pathology and occurrence of sleep/wake issues. We here take advantage of recently developed LB mouse and LB monkey models of parkinsonian degeneration to investigate the potential occurrence of sleep/wake deficits as the pathology develops.

Wild-type mice were injected with LB, containing pathological α-syn, extracted from the brain of PD patients leading to a progressive loss of DA neurons (LB mice). Control mice were injected with a fraction devoid of aggregated a-syn, extracted from the same patients (NoLB mice). Mice were implanted with a device recording both cortical neuronal activity (ElectroEncephaloGraphy, EEG) and neck muscles contractions (ElectroMyoGraphy, EMG) enabling the discrimination of sleep/wake cycle stages: wake, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Recording sessions were performed once a month for 48h over a 4-month period. Alteration of the sleep/wake cycles are detailed in both LB and NoLB mice with an emphasis put upon the changes in power band frequencies.

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Non-human primates were injected either with the same LB fractions injected to the mice (LB monkeys), or with sucrose (vehicle monkeys). They were then implanted with a device recording EEG, EMG and the electrical activity of the eye (ElectroOculoGraphy, EOG) enabling the discrimination of sleep/wake cycle stages: wake, NREM sleep (light and deep stages) and REM sleep. Alteration of the sleep/wake cycles are detailed in both groups of monkeys over a 8-month period.

Eventually, and considering the evidence that sleep plays an important role in protein clearance, sodium oxybate (SO), a small neuroactive molecule drug used to treat catalepsy and daytime sleepiness in patients affected by narcolepsy, was administered orally in a subset of LB monkeys for testing the possibility that increasing SWS would reduce the pathological burden.
Understanding if sleep disorders may serve experimentally as a surrogate marker of neurodegeneration or pathology progression could provide a way of early detection and lead to new therapeutic strategies to slow down its progression.

Mots-Clés: alpha, synuclein, sleep, neurodegeneration, mouse