ALPHA-SYNUCLEIN/SYNAPSIN III INTERPLAY ORCHESTRATES THE LOCOMOTOR RESPONSE TO PSYCHOSTIMULANTS SUCH AS COCAINE AND METHYLPHENIDATE

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Background: Dopaminergic nigrostriatal neurons loss and fibrillary α-synuclein (α-syn) aggregation in Lewy bodies (LB) characterize Parkinson's disease (PD). We recently found that Synapsin III (Syn III), a phosphoprotein regulating dopamine (DA) release with α-syn, localizes within LB fibrils and mediates α-syn aggregation and toxicity.
Cocaine and methylphenidate (MPH), two psychostimulants inhibiting monoamine reuptake, can bind α-syn and/or regulate Syn III. While cocaine stimulates Syn III-dependent DA release in the absence of α-syn, MPH, which can counteract PD-associated freezing of gait, controls α-syn-mediated DA overflow and presynaptic compartmentalization. This notwithstanding, whether cocaine- or MPH-induced locomotor response can be affected by α-syn/Syn III interplay is still unknown.

Methods: Here, we studied α-syn/Syn III co-deposition and longitudinal changes of α-syn, Syn III and DA transporter (DAT) striatal levels in nigrostriatal neurons of aged human C-terminally truncated (1-120) α-syn transgenic (SYN120 tg), C57BL/6J wild type (wt) and C57BL/6JOlaHsd α-syn null mice. We then analyzed the locomotor response of these animals to an acute administration of cocaine, MPH (d-threo) or the selective DAT blocker GBR-12935along aging.

Results: We found that cocaine stimulated a Syn III-dependent hyperactivity response only in aged α-syn null mice with elevated Syn III expression, but not in SYN120 tg mice. Instead, MPH over-stimulated a Syn III-dependent locomotor activity, that was independent of DAT inhibition, in aged SYN120 tg animals showing α-syn/Syn III co-aggregates.

Conclusions: Our observations unveil that α-syn/Syn III interplay regulates the motor response to cocaine and MPH. In particular, the effect of MPH can be positively fostered in the presence of α-syn/Syn III co-aggregates when these proteins are markedly elevated as occurs in the brain of PD patients. These findings own significant implications for PD therapeutics development.