SÉMINAIRE DE L'AXE

Découverte et validation de cibles thérapeutiques

Vglut2 expression in dopamine neurons contributes to post-lesional striatal reinnervation

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A significant subset of adult ventral tegmental area (VTA) dopamine (DA) neurons expresses Vglut2, a vesicular glutamate transporter, and releases glutamate as a second neurotransmitter in the striatum, while only few adult substantia nigra (SN) DA neurons have this capacity. Recent works showed that cellular stress created by neurotoxins such as MPTP and 6-hydroxydopamine (6-OHDA) can upregulate Vglut2 in surviving DA neurons, suggesting the possibility of a role in cell survival, but also that a high level of overexpression could be toxic to DA neurons. Here we examined the level of Vglut2 upregulation in response to neurotoxins and what consequences this has on post-lesional plasticity. We first took advantage of an *in vitro* neurotoxin model of Parkinson's disease (PD) and found that this caused an average of 2.5-fold enhancement of Vglut2 mRNA in DA neurons. This could represent a reactivation of a developmental phenotype because using an intersectional genetic lineage-mapping approach, we find that more than 98% of DA neurons have a Vglut2-positive lineage. Expression of Vglut2 was detectable in most DA neurons at E11.5 and was localized in developing axons. Finally, compatible with the possibility that enhanced Vglut2 expression in DA neurons promotes axonal outgrowth and reinnervation in the post-lesional brain, using mixed-sex groups we observed that DA neurons in mice in which Vglut2 is conditionally removed, established fewer striatal connections 7 weeks after a neurotoxin lesion. Thus, we propose here that the developmental expression of *Vglut2* in DA neurons can be reactivated at postnatal stages, contributing to post-lesional plasticity of dopaminergic axons.