

PLASTICITY OF SUBVENTRICULAR ZONE (SVZ) NEURAL PRECURSOR RESPONSE TO THE PARKINSONIAN NEUROTOXIN MPTP: CORRELATION WITH NIGROSTRIATAL DENERVATION AND REINNERVATION

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The subventricular zone (SVZ) located in the lateral walls of the lateral ventricles is a specific brain region that retains the capacity to generate new neurons throughout the entire life. Neuroblast born in the adult SVZ migrate along the rostral migratory stream (RMS) to the olfactory bulb (OB) where they become interneurons. The fate of SVZ stem cells and their early progeny is regulated by a specialized microenvironment, referred as the "germinal niche" dictating when and where a cell will proliferate, migrate or differentiate (1). The neurotransmitter dopamine has been reported to stimulate endogenous adult neurogenesis in the SVZ by activating D2-like receptors. Neural precursor cells (NPC) in the adult SVZ are embedded in a rich network of dopaminergic (DA) afferents arising from the substantia nigra pars compacta (SNpc). Dopamine depletion in Parkinson's disease (PD) significantly reduces NPC proliferation in the SVZ, with yet unknown functional consequences. To gain further insights into the SVZ response to DA ablation, male C57BL mice received four i.p. injections of MPTP (20 mg/kg) 2 h apart in one day and were killed 1-42 days (d) after the last MPTP injection. Serial brain coronal sections throughout the SVZ were processed for immunofluorescence histochemistry coupled to confocal laser microscopy and changes in SVZ glial fibrillary acidic protein-positive (GFAP⁺) astrocytes (type-B cells), polysialylated neural cell adhesion molecule-positive (PSA-NCAM⁺) migrating neuroblasts (type-A cells) numbers and proliferation assessed with proliferation cell nuclear antigen (PCNA), were correlated with tyrosine hydroxylase (TH⁺) and dopamine transporter (DAT⁺) striatal innervation. Coincident with an almost 80% loss of TH⁺ and DAT⁺ nigrostriatal fibers innervating the SVZ already apparent 1 d after MPTP discontinuation and lasting for 14 d, a marked disruption of SVZ neurogenic niche was revealed by a dramatic alteration of GFAP⁺ astrocyte morphology and behaviour within SVZ and RMS along with a selective depletion of PSA-NCAM⁺ migrating neuroblasts (-68%) and a global reduction (-45%) in PCNA⁺ cell. Remarkably, starting from 21 d and continuing through 32-42 d, a gradual recovery of TH⁺ and DAT⁺ nigrostriatal innervation positively correlated with a significant increase in PSA-NCAM⁺ migrating neuroblasts and a return of PCNA⁺ cells to saline-injected controls. Thus, in the acute MPTP rodent model of PD, impaired neurogenesis is a transient phenomenon positively correlated with nigrostriatal denervation and reinnervation. An understanding of the underlying mechanism(s) and their significance can be exploited in therapeutical strategies for treatment of Parkinson's disease. Martino G and Pluchino S. 2006. *Nature Neurosci.* 7:395-406