Exogenous EPO-Releasing Adult Mouse Neural Precursors transplantation in experimental Parkinson's disease

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Cell therapies have long been considered a feasible regenerative approach to compensate the loss of specific cell populations in neurodegenerative disorders, where symptoms can be ascribed to the degeneration of a specific cell type, such as the loss of Substantia Nigra (SN) dopaminergic neurons in Parkinson's disease (PD). Recently, we reported the existence of a subclass of SVZ-derived neural progenitors surviving after donor death. Such post mortem neural precursors (PM-NPCs) show a higher neural–like differentiation, and the process is likely dependent on autocrine erythropoietin (EPO) release, since it is prevented by the exposure to anti-EPO and -EPOR antibodies. In order to determine the therapeutic potential of PM-NPCs in a pre-clinical experimental model of PD, here we transplanted GFP PM-NPCs (2,5 x 10^5 cells/mouse), unilaterally into the striatum of symptomatic, and dopamine-depleted 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- exposed C57/bl mice. MPTP was applied at the dosage of 36 mg/kg i.p, then a second injection (i.p.) of MPTP at the dosage of 20 mg/kg stabilized the lesion. PM-NPCs (2,5 x 10^5/mouse) were administered by stereotaxic injection unilaterally in the striatum three days after the second MPTP administration. A large part (78,50 ±7,5%) of injected cells were still present 2 weeks after transplantation. The vast majority (69,56 ±4,5%) of GFP-positive transplanted PM-NPCs were within the striatum. Grafted PM-NPCs appeared rather differentiated with an oval soma and abundant neuritic processes. Moreover, we observed that grafted PM-NPCs migrated from the injection site trough the striatum. In 2 weeks PM-NPCs had migrated up to 3125,72 mm from the site of injection following a ventral direction. Furthermore, when transversal brain section were analyzed, we observed that PM-NPCs migrated beyond the borders of the striatum and reached SN pars compacta, ipsilaterally and controlaterally to the injection site. Close to the injection site a higher number of cells were positive to Nestin (precursor cell marker), while most migrated PM-NPCs resulted positively marked by anti-NeuN (81,88 ± 2,3%) and anti-MAP2 (62 ± 3,5%) antibodies (markers of neuronal differentiation), while a lower percentage of cells was positive to NG2 (38,77 ± 3,8%; marker of oligodendrocytes precursors) and Nestin (36± 2,9%). PM-NPCs promoted functional recovery and a massive survival of TH - positive neurons in both substantia nigra. When PM-NPCs were inoculated with co-administration of anti- EPO or anti-EPOR specific antibodies (3 μg/ml, respectively), the effects of transplanted cells was abolished. We used two behavioral tests: the vertical and horizontal grid tests. As a further control, we administered EPO through the same route. The administration of rh-EPO (1U/gr) in MPTP parkinsonian mice significantly improved their behavioral impairment as early as 3 days after injection, in full agreement with data obtained with both vertical and horizontal grid tests. The intrastriatal injection of anti-EPO and anti-EPOR antibodies alone did not modify the animal behavioral impairment caused by MPTP. These data suggest that the positive action of PM-NPCs in MPTP mice was likely due to EPO release by transplanted PM-NPCs. In conclusion, our findings suggest that PM-NPCs may represent a source for cellular therapy in neurodegenerative disorders such as PD.