Exogenous EPO-Releasing Neural Precursors promote functional recovery in experimental Parkinson's disease

T. Giallongo[1*],S. Carelli[1*], C. Viaggi[2], F. Vaglini[2], F. Caremoli[1], E. Latorre[1], G.U. Corsini[2], A.M. Di Giulio[1], A. Gorio[1]

[1]Laboratories of Pharmacology, Dept. of Health Sciences, University of Milan, Milan, Italy
[2]Dept. di Ricerca Traslazionale e delle Nuove Tecnologie in Medicina e Chirurgia, Università di Pisa, Italia

*equal contribution

Parkinson's disease (PD) is the second most common neurodegenerative disease. Stem cells transplantation has emerged as a promising approach to replace lost neurons in order to restore dopamine levels in the striatum and reactivate functional circuits. Neural stem cells from the sub-ventricular zone of the forebrain, because of their proliferation and differentiation characteristics, are a good tool for tissue replacement therapies. We recently isolated a subclass of neural progenitors, capable of surviving the powerful ischemic insult caused by death. These cells were named Post Mortem Neural Precursor Cells (PM-NPCs). Earlier studies by our group showed that PM-NPCs blocked secondary degeneration in spinal cord injury in the mouse. The degeneration of dopaminergic neurons was obtained with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) at the dosage of 36 mg/kg i.p. The lesion was stabilized by a second injection (i.p.) of MPTP at the dosage of 20 mg/kg. 2,5 x 10^5 of PM-NPCs were administered to C57/BL mice by stereotaxic injection unilaterally in the striatum three days after the second MPTP administration. The effects of transplanted cells were determined by means of two performance tests aimed at detecting behavioral improvements. The horizontal grid test is made of a horizontal grid mesh (total size 12 cm2) mounted 20 cm above a hard surface. Once the mouse firmly grabbed on the grid with all four paws, the apparatus was inverted so that the mice were hanging upside down. The animal was videotaped for 30 s and the percentage of unsuccessful forepaw steps was determined. The vertical grid test is made of the vertically standing box. For this test, the mouse was placed 3 cm from the top of the apparatus, facing upward, and was videotaped while it turned around and climbed down. The score reported was the time required by the mouse to make a turn, climb down and reach the floor of the grid by its forepaw within 180s. Our results show that animals treated with PM-NPCs had a remarkable improvement of parameters measured by means of both horizontal and vertical grid tests starting within the third day after cells transplantation. The behavioral improvement was maintained throughout the study reaching values close to control in animals transplanted with PM-NPCs. The difference between the two groups was even more conspicuous, when their motor coordination ability was tested by the vertical grid test. At 3 days after transplantation, animals showed a significant improvement in the time required for turning and descending the grid, while the time employed by MPTP group was almost twice as long even worse than MPTP alone. For further confirmation of our findings, by means of HPLC we determined catecholamines and their metabolites levels into the *striata* of control, PM-NPCs or saline injected mice. MPTP exposure caused a 50% reduction of dopamine in both left and right striatum, such a loss was not modified by PM-NPCs transplantation. Thus, behavioral recovery promoted by PM-NPCs seems independent from the amount of dopamine remaining available in the striatum. DOPAC, HVA and 3-MT were also reduced bilaterally, and remained unaffected by treatment. Differently 5-hydrossitriptamine, 5-HIAA, and norepinephrine were not affected by both MPTP exposure and cell transplantation. In conclusion, the reparative action of PM-NPCs may not be mediated by the simple recovery of dopamine levels in the striatum but rather by different mechanisms that may lead to an enhanced efficacy of the synaptic dopaminergic transmission by surviving dopaminergic axon terminals. Moreover, the findings obtained from the behavioral tests suggest how PM-NPCs may represent a liable source for cellular therapy in neurodegenerative disorders such as PD.