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Improvement of REM and NREM sleep by neuronal stem cell transplantation after bilateral Locus Ceoruleus lesion in rats

Vahid Pirhajati Mahabadi[1], Neda Eslahi[1], Mohammadhadi Fartookzadeh[1], Mansoureh Movahedin[2], Saeed Semnanian[2], Javad Mirnajafi-zadeh[2] and **Mehrdad Faizi[3]**
[1]Iran University of Medical Sciences, Iran
[2]Tarbiat Modares University, Iran
[3]Shahid Beheshti University of Medical, Iran

Neural stem cells (NSCs) as a heterogeneous multipotent and self-renewal population find in the different areas in the developing mammalian nervous system, as well as the sub-ventricular zone (SVZ) and the hippocampus of the adult brain. NSCs can give rise to neurons, astrocytes, and oligodendrocytes. between the noradrenergic-LC (NA-LC) in sleep regulation. Locus Ceoruleus (LC) plays an important role in the sleep-wake cycle. Noradrenergic cells in LC participate in the process of cortical activation and behavioral arousal. The aim of this investigation was the study of the effect of Neural Stem Cells (NSCs) transplantation on the sleep-wake cycle after bilateral lesion of the locus coeruleus in the rat. Fourty-two adult male Wistar rats weighing between 250-275 g, obtained from Pasteur Institute of Tehran, were used as subjects. The rats were categorized in seven groups [Control, Sham (cannula implantation), lesion, experimental 1 (intravenous transplantation of NSCs), experimental 2 (intravenous transplantation of noradrenergic-like cells (NACs)), experimental 3 (intraventricular transplantation of NSCs), experimental 4 (intraventricular transplantation of NACs)]. Neural stem cells were harvested from the SVZ of newborn rat brains. The cells were cultured in DMEM F12, B-27 supplemented with 20 ng/ml (hFGF) and 20 ng/ml (EGF) for 2 weeks. NSCs were differentiated in neurobasal medium, B-27 supplemented with BDNF (50 ng/ml) and GDNF (30 ng/ml) for 3 and 5 days. The animals received bilateral 6_hydroxydopamine (6_OHDA)[2µg/0.5µl in 0.1% ascorbic acid and 0.9% saline solution] lesion of the LC. For sleep-wake recording 3 EEG and 2 EMG electrodes were implanted respectively in the skull and dorsal neck muscle. After 7 weeks, following being anesthetized, brains were cut in 7µm serial sections and stained with cresyl violet. Cavity volume was evaluated through the stereological technique. In this study, Nestin and Sox2 were expressed in NSCs and neurospheres. NSCs were differentiated into noradrenergic-like cells (NACs) and Tyrosine hydroxylase was detected in these cells. Cavity volume caused by lesion was restricted to LC. A significant decrease ($P \leq 0.05$) was seen in NREM (Non-Rapid Eye Movement) and PS (Paradoxical Sleep) stages and a significant increase ($P \leq 0.05$) was seen in the wake and PS-A (Paradoxical Sleep without Atonia) in lesion group in comparison with control and sham groups. There were no significant differences in Wake, NREM, PS, PS-A between experimental groups. NSCs transplantation in experimental groups prevented of the decrease in PS and increase in PS-A So that a significant increase in PS and a significant decrease in PS-A in comparison with lesion group were seen in experimental groups ($P \leq 0.05$). The results of this study demonstrate NSCs have the ability to differentiate into noradrenergic cells using BDNF and GDNF growth factors and NSCs transplantation improved disruption of the sleep-wake cycle after bilateral lesion of LC.

vpirhajati.1@gmail.com