Cellular and Molecular Mechanisms underlying Neurorehabilitation after Stroke in Aged Rats

Age-related brain injuries including stroke, are a major cause of physical and mental disabilities. Therefore studying the basic mechanism underlying functional recovery after brain stroke in aged subjected it is of considerable clinical interest.

Data from our lab and elsewhere indicate that behaviorally, Behaviorally, aged rats are more severely impaired by stroke than are young rats, and they also showed diminished functional recovery. Infarct volume does not differ significantly in young and aged animals, but critical differences are apparent in the cytological response to stroke, most notably an age-related acceleration of the establishment of the glial scar. The early infarct in older rats is associated with a premature accumulation of BrdU-positive microglia and astrocytes, persistence of activated oligodendrocytes, a high incidence of neuronal degeneration, and accelerated apoptosis. In aged rats, neuroepithelial marker-positive cells emanating largely from capillaries were rapidly incorporated into the glial scar, but these neuroepithelial-like cells did not make a significant contribution to neurogenesis in the infarcted cortex in young or aged animals. The expression of plasticity-associated proteins, such as MAP1B, was delayed in aged rats. Tissue recovery was further delayed by the upregulation of Nogo, ephrin-A5 and MAG, that exert a powerful negative effect on axonal sprouting, in the aged peri-infarct cortex and by an age-related increase in the amount of the neurotoxic C-terminal fragment of the β-amyloid precursor protein (Aβ) at 2 wks post-stroke.

At gene level, long-term downregulation of gene expression for stem cell-related genes in the contralateral hemisphere in conjunction with a premature expression of apoptosis-related genes and down regulation of anti-oxidants acting genes in the periinfarcted area in aged rats may contribute to diminished recovery in post-stroke aged rats. Our findings indicate that the aged brain has the capability to mount a cytoproliferative response to injury, but the timing of the cellular and genetic response to cerebral insult is accelerated in aged animals, thereby further compromising functional recovery. Elucidating the molecular basis for this phenomenon in the aging brain could yield novel approaches like long-term hypothermia, enriched environment or anti-inflammatory drugs treatment to neurorestoration in the elderly.