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Effects of RO 61-8048 on Neurogenesis: Focus on Interleukin-1β Modulating Effect

Zaki Al Dubai, Francisco Molina-Holgado. University of Roehampton, Life Sciences, London SW15 4JD, UK

A growing body of evidence highlighted the negative contribution of Interleukin-1β (IL-1β) in the regulation of adult neurogenesis. In this regard, elevated levels of IL-1β have been reported in many neurodegenerative disorders concomitantly with reported overactivity of kynurenine pathway (KP). While the co-interaction between the two pathways is still not fully understood, a recent study suggested that Interleukin-1β may exert its detrimental effect on neurogenesis through up-regulation of the neurotoxic arm of the KP at the expense of the neuroprotective arm. As the neurotoxic arm of KP is mainly under the control of kynurenine 3-monoxygenase enzyme (KMO), we proposed that IL-1β silencing will potentiate the neuroprotective properties of the potent KMO inhibitor RO 61-8048. We studied the effects of RO 61-8048 on the proliferation of neural stem cells (NSC) from C57BL6/J wild type (WT) mice and IL-1β knockout (KO) mice, using the neurospheres-forming assay. Results showed that IL-1β silencing potentiated the inductive effect of RO 61-8048 as evident by the 2.4 folds increase in the proliferation rate in KO subgroups as compared to their WT counterparts ($P<0.01$). In the presence of activated microglia (BV2) , RO 61-8048 demonstrated neuroprotective properties as it increased the proliferation rate in BV2-treated NSC by 2.46 -3.29 folds as compared to NSC which treated with BV2 microglia only. While 10 µM RO 61-8048 associated with neuroprotective activity, 100 µM of RO 61-8048 associated with clear neurotoxicity and cell death. This reduction in the proliferative capacity of NSC accompanied with the emergence of some differentiated cells as shown under microscope. Similarly, this cytotoxic properties were observed ,as well, when microglial cells were treated with 100 µM of RO 61-8048 as evident by the 53% reduction in Bromodeoxyuridine incorporation (BrdU) as measured by spectrophotometry ($P<0.001$). The previous observations indicate that IL-1β exerts some of its detrimental effect on neurogenesis through up-regulation of the toxic arm of the KP. Hence, down-regulation of the toxic arm by RO 61-8048 associated with neuroprotective outcomes. However, higher concentrations of the inhibitor associated with neurotoxicity and cell death. Taken together, these findings suggested that inhibition of KMO enzyme in tandem with down-regulation of IL-1β is a promising therapeutic strategy to tackle neurodegenerative disorders.