Role of interleukin-1 receptor antagonist (IL-1ra) in neurogenesis: A new potential target for brain repair

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Recent reports suggest that there is a synergy between the immune system and neural stem cells (NSC) to promote functional recovery since immune cells help to maintain neurogenesis in germinial centres of the adult central nervous system (CNS) even under non-pathological conditions (Molina-Holgado and Molina-Holgado, 2010). Evidence is emerging that the interleukin-1 receptor antagonist (IL-1ra), an endogenous antagonist for the actions of IL-1 in the brain, is a potent signal that induces neural stem cell proliferation and migration. NSC cultures cells were prepared from the cortex of embryonic day 16 (E16) C57BL6 mice (wild type, WT). NSC were exposed to recombinant murine (rm) IL-1ra (20, 40, or 60ng/ml, t=7days, n=10), the specific CB1 antagonist AM251 (1 μM, t=7days), or to the CB2 antagonist AM630 (1 μM, t=7 days) for cell proliferation (serial dilution) assays. The regression slopes after plotting the initial cell number vs. number of neurospheres formed were (R²=0.9238) 42±1.5 for control cultures; (R²=0.9157) 363±6.5 for IL-1ra 60ng/ml; (R²=0.9249) 96±1.5 for IL-1ra 40ng/ml and (R²=0.9253) 44±2.5 for IL-1ra 20ng/ml). In addition we study the effects of IL-1ra (60ng/ml, t=24h) on BrdU incorporation. Experiments were performed using a pulse of BrdU (10 μM, t=6h) after 24 of culture passage. NSC proliferation rate was significantly increased after exposure to IL-1ra (40% increases, P<0.001 vs. control). NSC were exposed for 24 hours to IL-1ra alone or in combination with the inhibitor of diacylglicerol lipase (DAGL) activity RHC-80267 (5μM). We show that NSC self-renewal is controlled by bi-directional cross-talk between the endocannabinoid system and the IL-1ra signalling pathway. Using a specific IL-1 neutralizing antibody (10 μM, t=72h), we demonstrate that the IL-1 signalling is critical for the differentiation of NSC. In contrast, the observed IL-1ra proliferative effect on NSC is mediated by the endocannabinoid system as demonstrated with the pharmacological blockade of CB1/CB2 cannabinoid receptors using specific antagonist (AM250 or AM630) or the DAG lipase inhibitor RHC80267. AM250, AM630 or RHC80267 abolished the observed proliferative effects of IL-1ra. Overall these data suggest a novel mode of action for the endocannabinoid system in NSC proliferation that is coupled to IL-1ra signalling and that may be of therapeutic interest in the emerging field of brain repair.


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