

INHIBITION OF CASPASE-1 ACTIVITY INCREASES HIPPOCAMPAL CELL MIGRATION IN AGED RATS

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Impairment in learning and memory is a pathological feature that accompanies numerous neurological disorders. It is now a strong belief that central inflammatory events contribute significantly to the progression of several neurodegenerative disease, as well as, to the aging processes. For instance, in aged rats there is an increase in Interleukin-1 β (IL1 β) that has been implicated in declines of synaptic plasticity in the hippocampus and performance on cognitive tasks. IL β is a proinflammatory cytokine synthesized as an inactive precursor that is cleaved to generate the biological active 17kDa form by a protease named caspase-1. We have shown that inhibition of caspase-1 with Ac-YVAD-CMK (10 pmol), reverses age-related hippocampal dependent memory deficits in contextual fear conditioning. Impairment in age-related cognition may be linked to the decrease in neurogenesis that is observed in the hippocampus of aged humans and animals. Interestingly, it has been shown that the administration of a potent inflammatory agent, as well as, a potent inducer of IL1 β , lipopolisaccharide (LPS), strongly decreases hippocampal neurogenesis. It was our hypothesis that inhibiting the production of IL1 β in aged rats may lead to an increase in neurogenesis in the hippocampus. In the present study we inhibit the production of IL1 β using a specific inhibitor of Caspase-1 (Ac-YVAD-CMK, 10 pmol) in both old (22 months) and young (4 months) rats. Ac-YVAD-CMK was delivered for 28 days icv through a brain infusion cannula connected to an osmotic minipump (Alzet, Model 2004 pumping rate, 0.25 μ l/h; total volume 200 μ l) implanted subcutaneously. Animals were intraperitoneally injected with BrDU (50mg/kg) for 5 days and sacrificed 10 days after the last injection. Chronic infusion of a specific Caspase-1 inhibitor in aged rats resulted in an increase in cell migration in the granule cell layer, suggesting that IL1 β plays a critical role in age-related pathophysiological functions.