INDUCTION OF THE WNT ANTAGONIST, DICKKOPF-1, IN THE SENESCENCE OF THE SAMP8 MICE MODEL

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Wnt pathway activation leads to inhibition of GSK-3β through a dissociation of the enzyme from a multiprotein complex involving β-catenin. This results in the stabilization of the non-phosphorylated form of β-catenin which translocates to the nucleus, where it regulates the expression of Wnt-responsive genes that promote cell survival. Increasing evidence suggests that inhibition of the Wnt pathway is implicated to the pathophysiology of neuronal damage in model of acute and chronic neurodegenerative disorders. Moreover, induction of Dickkopf-1 (Dkk-1), a protein that antagonizes the Wnt pathway by inhibiting LRP5/6 interaction with Wnt, is related to processes of neurodegeneration in a number of CNS disorders, including Alzheimer's disease. To ascertain the role of Dkk-1 in aging process, we studied the levels of Dkk-1 expression in an accelerated aging model that was established through phenotypic selection from a common genetic pool, the senescence-accelerated mouse prone 8 (SAMP8). The SAMP8 is a good animal model to investigate the fundamental mechanisms of age-related learning and memory deficits at gene and protein levels. Our results by Western blot show an increase in Dkk-1 protein levels, together with an activation of GSK-3β and reduced levels of Bcl-2 in these animals, indicating that an inhibition of the Wnt pathway is present in the process of neurodegeneration that accompanies aging. The results suggest the modulation of this route as a pharmacological target for neurodegenerative processes.

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