

SIGNAL APOPTOTIC PATHWAYS IN HYPOTHALAMIC NEURONS IN AGING

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Our aim was obtaining factors which can regulate apoptosis of hypothalamic neurosecretory cells (supraoptic and paraventricular nuclei). We evaluated apoptosis rate by TUNEL and expression of p53, pin1, wrn (these genes play important role in aging) and p21 (transcriptional target of p53, cyclin-dependent kinase inhibitor 1A) using in situ hybridization, and caspase-8 expression by immunohistochemistry. We investigated senescent accelerated HER2/neu transgenic mice (with overexpression of oncoprotein HER2) and wild type (WT) mice, young and old groups. The apoptosis level, p53, wrn and caspase-8 expression increases in hypothalamic neurons of aged WT mice. We can conclude that age-related apoptosis is mediated by caspase-8 and p53 signaling pathways. However, these criteria are low in hypothalamic neurons of HER2 aged mice. We obtained augmentation of wrn mRNA in hypothalamus of aged WT mice, and significantly lesser wrn expression in aged HER2 mice. As is known, there is direct physical and functional interaction between p53 and wrn, and this interaction is necessary for regulation of p53 synthesis and functions. So, we propose that the possible reason of p53-mediated apoptosis suppression in neurons of HER2 mice is low expression of wrn, which regulates p53 synthesis and functions. Besides, misbalance of p21 and pin1 synthesis takes part in this suppression. So, both caspase-8 and p53 signaling pathways are suppressed by HER2 overexpression in transgenic mice. The result of it is low apoptosis level and, therefore, high level of carcinogenesis in aged transgenic mice. The work is supported by Russian Foundation of Fundamental Investigation (08-04-00032).