

Effects of cholinergic enhancing drugs on cholinergic transporters in the brain of spontaneously hypertensive rats

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Hypertension has been related to the establishment of brain damage and is the main risk factor for the development of cerebrovascular disease. Abnormal regulation of cholinergic neurotransmission might contribute to cognitive impairment associated with adult-onset dementia disorders including Alzheimer's disease (AD) and vascular dementia (VaD).

Cholinergic transporters control cellular mechanisms of acetylcholine (ACh) synthesis and release at presynaptic terminals. The high-affinity choline uptake transporter (CHT) recaptures choline deriving from acetylcholine (ACh) hydrolysis by acetylcholinesterase (AChE). Choline is resynthesized into ACh by choline acetyltransferase. The neurotransmitter is loaded into synaptic vesicles by the vesicular ACh transporter (VAcHT). Abnormal regulation of cholinergic transporters might contribute to the cognitive impairments associated with neurodegenerative disorders.

This study has assessed the influence of 4 week treatment with the AChE/cholinesterase (ChE) with the AChE inhibitor galantamine or with the cholinergic precursor choline alfoscerate (alpha-glyceryl-phosphorylcholine, GPC) on spontaneously hypertensive rats (SHR) used as a model of cerebrovascular injury. In these rats an obvious cholinergic hypofunction is noticeable. They could therefore represent a model for investigating the effect of drugs on cholinergic system. Wistar Kyoto (WKY) rats which belong from the normotensive phenotype opposed to SHR were investigated as well. Analysis performed by immunohistochemistry and ELISA included frontal cortex, striatum, hippocampus and peripheral blood lymphocytes (PBL).

An increased expression of CHT and VAcHT was observed in brain areas investigated and in PBL of SHR. This increase probably represents an up-regulation to counter cholinergic deficit of SHR. Treatment with galantamine countered the increase of CHT and VAcHT. Treatment with GPC further increased CHT and to a greater extent VAcHT.

The effect of GPC is consistent with an increased synthesis of ACh it induces. This suggests that association between GPC and AChE/ChE inhibitors may represent a strategy worthwhile of being investigated in appropriate clinical trials.

Key words

Cholinergic enhancing drugs, vesicular acetylcholine transporter, choline uptake transporter, brain damage