Galanin: Neurobiologic Mechanisms and Therapeutic Potential for Alzheimer’s Disease

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ABSTRACT

The neuropeptide galanin (GAL) is widely distributed in the mammalian CNS. Several lines of evidence suggest that GAL may play a critical role in cognitive processes such as memory and attention through an inhibitory modulation of cholinergic basal forebrain activity. Furthermore, GAL fibers hyperinnervate remaining cholinergic basal forebrain neurons in Alzheimer’s disease (AD). This suggests that GAL activity impacts cholinergic dysfunction in advanced AD. Pharmacological and in vitro autoradiographic studies indicate the presence of heterogeneous populations of GAL receptor (GALR) sites in the basal forebrain which bind GAL with both high and low affinity. Interestingly, we have recently observed that GALR binding sites increase in the anterior basal forebrain in late-stage AD. Three G protein-coupled GALRs have been identified to date that signal through a diverse array of effector pathways in vitro, including adenylyl cyclase inhibition and phospholipase C activation. The repertoire and distribution of GALR expression in the basal forebrain remains unknown, as does the nature of GAL and GALR plasticity in the AD basal forebrain. Recently, GAL knockout and overexpressing transgenic mice have been generated to facilitate our understanding of GAL activity in basal forebrain function. GAL knockout mice result in fewer cholinergic basal forebrain neurons and memory deficits. On the other hand, mice overexpressing GAL display hyperinnervation of basal forebrain and memory deficits. These data highlight the need to explore further
the putative mechanisms by which GAL signaling might be beneficial or deleterious for cholinergic cell survival and activity within basal forebrain. This information will be critical to understanding whether pharmacological manipulation of GALRs would be effective for the amelioration of cognitive deficits in AD.