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Review

Roles of β-adrenergic receptors in Alzheimer's disease: Implications for novel therapeutics

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ABSTRACT

Alzheimer's disease (AD), the most common cause of age-related dementia, is a progressive neurodegenerative disorder with an enormous unmet medical need. In recent years, several unexpected longitudinal and cross-sectional epidemiological studies reveal that beta-blockers treatment reduces the prevalence of AD in patients suffering from hypertension. Now, a newly population-based study of individuals with incident AD demonstrates that beta-blockers are also associated with delay of functional decline. Furthermore, accumulated convincing evidences from cell culture experiments and animal studies have also suggested that β-adrenergic receptors (β-ARs) may involve in the AD pathogenesis through effects on amyloid-β (Aβ) production or inflammation. This review explores clinical and experimental studies that might help to explain the roles of β-ARs in the AD pathogenesis and the potential underlying mechanisms and whether treatment with β-ARs antagonists provides a new therapeutic option for AD.

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1. Introduction

Alzheimer's disease (AD) is the most common cause of progressive dementia in aging human populations, and one of the most devastating diagnoses that patients and their families can receive. It is a chronic neurodegenerative disorder characterized by progressive disturbances of cognitive functions including memory, judgement, decision-making, orientation to physical surroundings and language [64]. The neuropathological hallmarks of AD include selective neuronal and synaptic losses, extracellular neuritic plaques comprised of aggregated amyloid-β (Aβ) peptides, and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated forms of the tau protein in characteristic brain regions [57].

β-Adrenergic receptors (β-ARs) are G protein-coupled receptors (GPCRs) that mediate physiological responses to adrenaline and noradrenaline. There are three receptor subtypes in this family: β1-adrenergic receptor (β_1-AR) is found at its highest levels in

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the heart and brain [26], β2-adrenergic receptor (β_2-AR) is more widely expressed [17], and β_3-adrenergic receptor (β_3-AR) is found at its highest levels in adipose tissue [20]. All three receptors couple primarily to Gαs to stimulate adenylyl cyclase, but can also couple to Gαi in some cells under certain conditions [12,82,94]. Both β_1-AR and β_2-AR play important roles on cognition functions and stress behaviors [59,68]. In recent years, several unexpected longitudinal and cross-sectional epidemiological studies reveal that beta-blockers treatment reduce the prevalence of AD in patients suffering from hypertension [32,45,76]. Furthermore, accumulated convincing evidences from cell culture experiments and animal studies have also suggested that both β_1-AR and β_2-AR, especially β_2-AR, may involve in the AD pathogenesis through effects on amyloid-β (Aβ) production or inflammation [39,43,50,63].

2. Brain noradrenaline system, cognition and AD

The involvement of the noradrenergic nervous system in AD is often overlooked, but the ability of the noradrenergic nervous system to modulate cognitive and behavior function is so profound. Central noradrenaline neurons are suggested to have a crucial role in regulating cognitive and behavioral functions [68], and can influence some symptoms which accompany dementia, such as depression, aggression, agitation, and psychosis [36]. Noradrenaline containing neurons can be found throughout the nervous system, and the majority of these neurons in the brain are located in the locus coeruleus (LC), a brain structure that can influence many vital brain functions, including attention, sleep, arousal, mood regulation, learning, and memory [3]. The LC is a primary source for an extensive noradrenaline network in the forebrain and takes almost exclusively care of the noradrenaline supply of amygdala, hippocampus and neocortex [89], the main brain regions involved in AD [87]. A deficiency in the noradrenergic system of the brain, originating largely from cells in the nucleus, is theorized to play a critical role in the progression of a family of neurodegenerative disorders that includes AD [31,54,99]. Earlier post-mortem histological and autoradiographic studies have indicated a reduction of cell numbers in the LC and a corresponding decrease in noradrenaline transporter (NET) in brains obtained from Alzheimer's disease (AD) patients as compared to age-matched healthy controls [99]. Recent positron emission tomography (PET) imaging studies, using the novel selective PET radioligand for NET (S,S)-[18F]FMeNER-D2, for diagnostic considerations, have also reported that significant decreases of NET densities can be demonstrated with the radioligand in both the LC and the thalamus in AD as compared to age-matched controls. The decreases in AD correlate with the progress of the disease as indicated by Braak grades [31].

β-ARs stimulation has been known to play a critical role in long-term memory consolidation in the amygdale and hippocampus. For example, blockade of β-ARs with agents such as propranolol attenuated the emotional enhancement of memory in both rodents and human volunteers, whereas infusion of a β-AR agonist improves memory consolidation [5]. Similarly, β-ARs stimulation in the dentate gyrus can induce long-term potentiation [8] and is involved in the late phase of memory consolidation in the hippocampus [77]. In contrast, a more recent study suggests that propranolol or betaxolol treatment does not have a significant effect on hippocampal memory consolidation but impairs the retrieval of intermediate-term contextual and spatial memories through the β_1-AR in the hippocampus in the absence of an increase in corticosterone [62]. Similarly, Ramos et al. show that endogenous activation of β_1-AR, as can occur with stress, impairs prefrontal cortex (PFC) cognitive function [69]. In this study, blocking the β_1-AR improved working memory performance following either direct PFC infusion in rats, or systemic administration in monkeys.

3. Brain noradrenaline system, stress and AD

Stress has been recently appreciated to be a risk factor for AD [25,58,72,92]. Stress can elevate the concentration of the endogenous β-AR ligands epinephrine and noradrenaline [24], then brain noradrenaline system may involve in the pathogenesis of AD by the pathway of stress [4,63].

Clinical studies have suggested that chronic stress, accompanied by hypersecretion of glucocorticoids (GCs), the primary stress hormones, also involved in the pathogenesis and/or progression of AD [18,33,93]. Significantly, experimental studies found that stress and GC promote amyloid deposition and tau accumulation in mouse transgenic models of AD [29,40] and chronic stress was found to trigger the mis-processing of APP [6]; moreover, GC themselves can trigger neuronal atrophy and apoptosis [7,11]. Recently, Sotiropoulos et al. reported that GC could trigger APP mis-processing and tau hyperphosphorylation and accumulation, while increasing the vulnerability of neurons to the toxic actions of Aβ [83]. It is also known that glucocorticoids increase noradrenaline turnover in the brain [13]. Extensive findings also suggest that β-adrenoceptor-cyclic adenosine monophosphate (cAMP) pathway may be essential in regulating glucocorticoid effects on the brain in influencing different aspects of cognitive function [73–75]. Additionally, both the glucocorticoid-induced enhancement and impairment of memory functions require the integrity of the basolateral amygdala and the noradrenergic system [19,74]. Recent evidence from both animal and human studies suggests that blockade of β_2-ARs with propranolol prevented glucocorticoid-induced different memory functions deficits [14,74]. In view of these data, it is reasonable to induce that β-ARs antagonists could be potential drugs for the treatment of AD by interrupting the process of stress.

4. Roles of β-ARs in AD from clinical observations

Noradrenaline assumes critical physiological roles in regulating cellular signaling and in governing compensatory and protective mechanisms that determine neuronal function and survival in the brain. It plays an important role in regulating cognitive and behavioral functions [70], and can influence some symptoms which accompany dementia, such as depression, aggression, agitation, and psychosis [36]. Previous studies have indicated propranolol, a long-acting β-ARs antagonist, to be an effective treatment for aggression and agitation in patients with dementia who have been unsuccessfully treated with conventional therapies [65,80]. A recent double-blind, placebo-controlled randomized trials of propranolol in people with AD was conducted to evaluate the efficacy of the propranolol for treatment-resistant disruptive behaviors and overall behavioral status in nursing home residents with probable or possible AD [67]. The results showed that propranolol appeared modestly effective and well tolerated for overall behavioral status in nursing home residents with probable or possible AD complicated by disruptive behaviors. Both the total Neuropsychiatric Inventory (NPI) score and the Clinical Global Impression of Change (CGIC) significantly favored propranolol. It was also supported by the greater number of moderately and markedly improved subjects in the propranolol condition, and the willingness of nursing home personnel to allow propranolol subjects to continue in the study longer than placebo subjects.

According to several longitudinal and cross-sectional studies, hypertension appears to increase the incidence of AD [46,60,81]. Antihypertensive drug treatment, according to preliminary evidence, may serve to reduce the rates of such events [66]. Several observational and experimental studies have therefore evaluated the potential of antihypertensive (AH) medications for modification of the risk of AD. Beta-adrenergic receptor blockers (beta-blockers)