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The Role of Beta-Adrenergic Receptor Blockers in Alzheimer's Disease: Potential Genetic and Cellular Signaling Mechanisms

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Abstract

According to genetic studies, Alzheimer's disease (AD) is linked to beta-adrenergic receptor blockade through numerous factors, including human leukocyte antigen genes, the renin–angiotensin system, poly(adenosine diphosphate-ribose) polymerase 1, nerve growth factor, vascular endothelial growth factor, and the reduced form of nicotinamide adenine dinucleotide phosphate. Beta-adrenergic receptor blockade is also implicated in AD due to its effects on matrix metalloproteinases, mitogen-activated protein kinase pathways, prostaglandins, cyclooxygenase-2, and nitric oxide synthase. Beta-adrenergic receptor blockade may also have a significant role in AD, although the role is controversial. Behavioral symptoms, sex, or genetic factors, including Beta 2-adrenergic receptor variants, apolipoprotein E, and cytochrome P_{450} *CYP2D6*, may contribute to beta-adrenergic receptor blockade modulation in AD. Thus, the characterization of beta-adrenergic receptor blockade in patients with AD is needed.

Keywords

beta-adrenergic receptor blocker, Alzheimer's disease, dementia, beta-adrenergic receptor antagonism

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly individualsand is associated with progressive memory loss and cognitive dysfunction. The AD is associated with beta-adrenergic receptors. In the brain, beta-adrenergic receptors are widely distributed in different regions, including the frontal, parietal, piriform, and retrosplenial cortices, medial septal nuclei, olfactory tubercle, midbrain, striatum, hippocampus, and thalamic nuclei.[1,2] The adrenergic receptors (or adrenoceptors) are a class of G-protein-coupled receptors that are targets of the catecholamines, especially norepinephrine (noradrenaline) and epinephrine (adrenaline). Many cells possess adrenergic receptors, and the binding of a catecholamine to these receptors will generally stimulate the sympathetic nervous system. There are 2 main groups of adrenergic receptors, α and β. Beta receptors have the subtypes $beta_1$, $beta_2$, and $beta_3$. All 3 beta subtype receptors are linked to G_s proteins (although $beta_2$ also couples to G_i), which in turn are linked to adenylate cyclase. Agonist binding thus causes a rise in the intracellular concentration of the second messenger cyclic adenosine monophosphate (cAMP). Downstream effectors of cAMP include cAMP-dependent protein kinase (PKA), which mediates some of the intracellular events following hormone binding. Amyloid beta peptide (Aβ) induces subtle alterations in the synaptic function in AD. The Aβ interacts with $beta_2$ adrenergic receptors in the central noradrenergic system to regulate synaptic functions in the prefrontal cortical neurons and induces the internalization and degradation of the $beta_2$-adrenergic receptor that results in the impairment of adrenergic and glutamatergic activities.[3,4] $Beta_2$-adrenergic receptors play an important role in AD. Compared with the thalamus of control brains, the thalamus of the brains with dementia had a lower total concentration of beta-adrenergic receptors. Compared with the control brains, brain with dementia have significantly lower concentrations of $beta_1$-adrenergic receptor in the hippocampus and higher concentrations in the nucleus basalis of Meynert (NbM) and cerebellar hemisphere, whereas brains wirh dementia have lower concentrations of $beta_2$-adrenergic receptor concentrations in the thalamus, NbM, and cerebellar hemispheres and higher concentrations in the hippocampus and putamen.[5] Compared with non-AD patients, patients with AD have lymphocytes that have lower $beta_2$-adrenergic receptor levels and lower levels of $beta_2$-adrenergic-stimulated cAMP.[6] Fibroblasts isolated from patients with AD have a reduced $beta_2$-adrenergic receptor response.[7] Karczewski et al[8] demonstrated the presence of agonistic autoantibodies directed at adrenergic receptors in the circulation of patients with mild-to-moderate Alzheimer's and vascular dementia. Beta-adrenoceptors mediate the ability of

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norepinephrine (NE) to differentially modulate $A\beta_{1-42}$-induced immune responses. The NE suppresses $A\beta_{1-42}$-mediated cytotoxicity and monocytic chemotactic protein 1 secretion but enhances Aβ-mediated IL-1β secretion via beta-adrenoceptor activity combined with the activating of cAMP/protein kinase A pathway and cAMP response element binding in human microglia-like THP-1 cells.[9] In addition, reduced levels of NE are associated with behavioral phenotypes observed in a TgCRND8 mouse model of AD.[10] The NE promotes murine microglial uptake and degradation of Aβ.[11] Moreover, the $beta_3$-adrenergic receptor agonist (CL316243), but not the $beta_2$-adrenergic receptor agonist, rescued this Aβ-induced memory loss.[12] The $beta_2$-adrenergic agonist clenbuterol improved the performance of many of the young and aged rats and monkeys that had performed poorly under control conditions.[13] The degeneration of locus ceruleus neurons and reduced levels of NE potentiated Aβ-induced cortical inflammation.[14] Moreover, patients with cognitive impairment who were on $beta_2$-adrenergic receptor blockers had poorer delayed memory retrieval.[15] However, compared with both nonaggessive patients with AD and control participants, agrressive patients with AD had small but significant increases (approximately 25%) in $beta_1$- and $beta_2$-adrenergic receptors of the cerebellar cortex.[16] Patients with AD have larger total numbers of $beta_2$- and $beta_1$-adrenoceptors in the hippocampus. By contrast, in the AD putamen, where $beta_1$-receptors were highly expressed, the total numbers of beta- and $beta_1$-receptors were significantly reduced with no consistent change in the number of $beta_2$-receptors.[17] Furthermore, compared with cerebellar AD and control tissues, the hippocampal has higher total beta adrenoceptor density.[18] The AD has significantly higher total number of beta receptors of the cerebral microvessels and numbers of $beta_2$-receptors, which is the type that is predominately expressed in microvessels.[19] Activation of the $beta_2$-adrenergic receptor stimulates γ-secretase activity and accelerates amyloid plaque formation. The $beta_2$-adrenergic receptor-selective antagonist ICI 118,551 reduced Aβ peptide production,[20,21] suggesting that blockade of $beta_2$-adrenergic receptor function might be effective in the prevention and treatment of AD. The use of $beta_2$-adrenergic receptor antagonists correlated with a decreased incidence of AD among patients with hypertension.[22-24] Propranolol reduced aggression and agitation in patients with senile dementia.[25-28] Propranolol also restored cognitive deficits and improved amyloid and tau pathologies in a senescence-accelerated mouse model.[29,30] Carvedilol, a nonselective beta-adrenergic receptor blocker, demonstrated a neuroprotective effect in colchicine- and aluminum chloride-induced cognitive dysfunction and oxidative damage.[31,32] Carvedilol also significantly attenuated brain oligomeric beta-amyloid content and cognitive deterioration in 2 independent AD mouse models.[33] In addition, nebivolol is highly tolerable and safe and can significantly reduce amyloid neuropathology in the brain, which could be one of the most important parameters for primary prevention of AD.[34] These findings suggested that beta-adrenergic receptor blockade may play a role in AD. Thus, we discuss the potential role of beta-adrenergic receptor blockers in AD.

Genetic Factors Associated With Beta-Adrenergic Inhibition and AD

Genetic studies provide an excellent opportunity to link molecular variations with epidemiological data. Variations in DNA sequences such as polymorphisms exert modest and subtle biological effects. Receptors play a crucial role in the regulation of cellular function, and small changes in their structure can influence intracellular signal transduction pathways.

Previous studies have suggested that *human leukocyte antigen (HLA)* genes are located in the *major histocompatibility complex (MHC)* class II loci and that several genes in the MHC region promote susceptibility to AD. Previous studies showed that HLA-DR1 was associated with enhanced cumulative recall ability, and conversely, HLA-DR5 was associated with a diminished delayed verbal recall and spatial recall abilities on cognitive abilities in an older nondemented population.[35] Brains with AD have increased MHC class II glycoprotein expression on microglial cells.[36-39] Furthermore, the AD retina has a significantly increased level of MHC class II expression.[40] HLA-DR was abnormally expressed in the neutrophils and monocytes of patients with AD.[41] Moreover, the postmortem brains of patients with AD had increased numbers of HLA-DR and interleukin 2 (IL-2)-receptor-positive cells, which were correlated with the number of senile plaques.[42] Shalit et al[43] observed a slight increase in HLA-DR levels in the mild stage of AD without changes in CD4, CD8, and IL-2 levels. In the moderately severe stage of AD, however, HLA-DR and CD4 levels increased, and CD8 levels slightly increased, suggesting that the peripheral immune reaction in AD may be correlated with the clinical stage of the disease. Furthermore, following long-term therapeutic immunization of an AD mouse model carring the *DRB1*1501* allele, Aβ were effectively cleared from the brain parenchyma, and brain microglial activation was reduced.[44] These results suggested that *HLA-DR* alleles are directly associated with specific Aβ T-cell epitopes with highly immunogenic properties of the abundant *DRB1*1501* allele in this mouse model of AD. Moreover, *HLA-DR* and *HLA-DQ* gene polymorphisms may be correlated with the anti-beta-receptor antibodies in familial cardiomyopathy.[45] Cardiac beta-adrenergic receptors and adenylate cyclase activity in dilated cardiomyopathy are modulated by circulating autoantibodies against the cardiac $beta_1$-adrenoceptor, the presence of which is regulated by the HLA-DR.[46] In addition, propranolol abrogated the interferon-gamma-induced increases in HLA class II expression and interleukin-1beta (IL-1β) secretion.[47] The lymphocytes of carvedilol-treated chronic heart failure (CHF) patients have significantly reduced HLA-DR expression.[48] These findings suggested that beta-adrenergic receptor blockers might affect AD via the suppression of MHC class II antigen expression.

The primary function of the renin–angiotensin system (RAS) is to maintain fluid homeostasis and regulate blood pressure. Several components and receptors of the RAS have been identified in the central nervous system (CNS),[49-52] suggesting that the RAS might be involved in brain activity. Increasing evidence suggests that specific components of the RAS may have a crucial role in learning and memory processes. Angiotensin-converting enzyme

(ACE) activity was reported in the homogenates of postmortem brain tissue from patients with AD and was correlated with Aβ plaque load.[53] The increased binding of radioactively labeled ACE inhibitor to ACE was demonstrated in AD temporal cortices.[54] Another report also demonstrated elevated neuronal and perivascular ACE immune-reactivity in AD parietal cortices.[55] Recently, ACE activity was found to be increased in the peripheral blood of patients with late-onset AD; however, ACE activity was not correlated with the level of Aβ in peripheral blood.[56] Thus, the role of ACE in AD remains controversial as well as the role of beta-adrenergic receptor antagonisms in AD; ACE inhibits Aβ aggregation and lowers the levels of secreted Aβ in living cells, an effect that is blocked with ACE inhibitor.[57,58] By contrast, in another study, the ACE inhibitor did not have an effect on cerebral Aβ levels and plaque deposition in vivo.[59] Although short-term treatment with ACE inhibitors failed to increase Aβ formation in the brain, long-term treatment enhanced the Aβ deposition in aged amyloid precursor protein (APP) transgenic mice.[60] Moreover, treatment with RAS blockers modulated serum adipocytokines and glucose homeostasis, thereby potentially slowing the cognitive decline in patients with AD.[61] The angiotensin receptor blocker losartan also exerted direct neuroprotective effects via its Aβ-reducing and anti-inflammatory effects in the CNS.[62] Furthermore, the renin inhibitor aliskiren conferred neuronal resistance to Aβ toxicity in primary rat cortical cultures.[63] The *ACE I/I* genotype and *I* allele showed an increased risk of AD,[64,65] but the *D/D* genotype was associated with a reduced risk.[66] Compared with the *D/D* genotype, the *I/I* genotype is linked to smaller volumes of the hippocampus and the amygdala[67] and has increased brain $A\beta_{42}$ load.[68] Moreover, catecholamines altered the release of AT II (Angiotensinogen II). Ming et al[69] demonstrated that isoproterenol enhanced the stimulatory effect of dexamethasone on *AT* gene expression via β_2-adrenergic receptors in mouse hepatoma cells. In addition, isoproterenol promoted an increase in the release of AT II from isolated perfused mesenteric arteries, and this release was blocked by propranolol treatment.[70] In other studies, isoproterenol increased the secretion of AT II in neuronal cultures, cultured bovine aortic endothelial cells, and the brachial arteries of patients with hypertension.[71-73] Compared with nontreated patients, patients with cirrhosis had reduced plasma renin activity (PRA) and AT I, AT II, and AT-(1-7) expression in the portal vein and periphery due to propranolol treatment.[74] Prevention or modification of certain vascular risk factors and proper management of cardiovascular disease may prevent the development or progression of dementia, including AD.[75] Protein homeostasis plays a role in the development of numerous disorders. Misfolded proteins are central in the pathophysiology of neurodegenerative diseases, such as AD, and play a role in the pathophysiology of common human cardiac diseases such as pathologic cardiac hypertrophy and dilated and ischemic cardiomyopathies.[76] In addition, cardiac surgery with cardiopulmonary bypass caused a profound cerebral inflammatory response, which was accompanied by increased postoperative cerebrospinal fluid (CSF) levels of the AD biomarker $A\beta^{1-42}$.[77] Carvedilol inhibited basal and stimulated ACE production in human endothelial cells[78] and exhibited beneficial effects on ACE activity and PRA levels in patients with CHF .[79] In addition, proliferating infantile hemangiomas expressed 2 essential components of the RAS, namely ACE and the AT II receptor, which are responsible for the propranolol-induced accelerated involution of large proliferating infantile hemangiomas.[80-82] Taken together, the RAS is activated in AD and the impact of beta-adrenergic receptor blockade on this system will affect AD.

Poly(ADP-ribose) polymerase 1 (PARP-1) is a nuclear protein that contributes to both neuronal death and survival under stressful conditions. The residual PARP activity found in PARP-1-deficient cells has been recently attributed to a novel DNA damage-dependent PARP.[83] The PARP cleavage is enhanced in the peripheral blood mononuclear cells of patients with mild cognitive impairment.[84] Enhanced PARP activity has been reported in AD and may be a marker for AD.[85] Poly-ADP-ribose polymers increase with age in the brains of an Alzheimer's mouse model, and Aβ-activated poly-ADP-ribose polymers induced astrocytic metabolic failure and neuronal death in response to oxidative stress. Inhibition of either PARP or the nicotinamide adenine dinucleotide phosphate oxidase prevented the appearance of poly-ADP-ribose polymers and the mitochondrial depolarization.[86] The *PARP-1* polymorphism modified the risk of AD in both an independent manner and through an interaction with the proinflammatory factor IL-1A.[87] The *PARP-1* gene is also highly associated with AD susceptibility. Both *Ht3-TT* and *Ht4-CC,* which are the *PARP* haplotypes, were significantly associated with an increased risk of AD, whereas the *Ht1-TC* haplotype showed a protective effect against AD when compared with control participants.[88] Moreover, rabbits treated with ketamine exhibited reduced left ventricular ejection fractions, ventricular conduction velocity, and increased susceptibility to ventricular arrhythmia, which were prevented by metoprolol treatment. The expression of Parp-1 and apoptosis-inducing factor increased after ketamine treatment and sharply decreased after metoprolol administration.[89] Propranolol treatment markedly suppressed PARP activation in skeletal muscle biopsies from pediatric patients with burn.[90] Propranolol also protected against staurosporine-induced DNA fragmentation and PARP cleavage in SH-SY5Y neuroblastoma cells.[91] Furthermore, the nonselective β-receptor blocker carvedilol significantly inhibited apoptosis and suppressed activated PARP-1 cleavage in human cardiac tissue.[92] Carvedilol significantly reduced ischemia–reperfusion-induced poly- and mono-ADP-ribosylation in heart perfusion and rheological models.[93] Carvedilol also reduced PARP activity in the hippocampus and protected neurons against death after transient forebrain ischemia.[94] Metipranolol reduced the sodium nitroprusside-induced breakdown of PARP-1 in the eyes and retinas of rats.[95] These findings suggested that PARP-1 is activated in patients with AD and that beta-adrenergic receptor antagonists may affect AD through the suppression of PARP-1.

Angiogenesis is a complex process that involves the coordinated steps of endothelial cell activation, proliferation, migration, tube formation and capillary sprouting. In addition, angiogenesis requires the participation of several intracellular

signaling pathways. Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis. Pathological angiogenesis may be a key event in the pathogenesis of AD. The abnormal regulation of VEGF expression has been reported in AD pathogenesis. Brain homogenates of APP23 mice, a transgenic model of AD, induced the formation of new vessels during in vivo angiogenesis and was blocked by a VEGF antagonist.[96] Compared with control participants, patients with AD had higher expression levels of angiopoietin 2 and VEGF in the microcirculatory system.[97] Clusters of reactive astrocytes showed enhanced VEGF immunoreactivity in the neocortex of patients with AD but not in elderly control participants.[98] Increases in the VEGF levels in the CSF were also observed in patients with AD and vascular dementia but not in healthy controls.[99] These findings suggested that angiogenic changes occur in the microcirculation of the brain with AD and may contribute to disease pathogenesis. The VEGF interacts with Aβ and co-localizes with Aβ in the brains of patients with AD.[100] The Aβ also inhibits VEGF-induced migration of endothelial cells as well as VEGF-induced permeability in an in vitro model of the blood–brain barrier.[101] The *VEGF* gene variability may be a genetic factor that influences lifespan in a cohort of Italian patients.[102] The *VEGF* polymorphisms are associated with AD in Italian, Han Chinese, and Tunisian populations.[103-106] A number of mechanisms might link cancer with AD and other neurodegenerative diseases.[107] Roe et al[108] used population-based data from the Cardiovascular Health Cognition study to confirm the negative correlation between cancer and AD but not vascular dementia in Caucasian adults. Results from the Framingham Heart Study also had the same conclusion.[109] Moreover, the beta-adrenergic receptor agonist isoproterenol significantly increased VEGF protein levels in human choroidal endothelial cells.[110] The NE treatment increased VEGF levels in cultured nasopharyngeal carcinoma (NPC) tumor cells, and this increase was inhibited by propranolol treatment. Norepinephrine also induced invasiveness in all NPC cell lines in a dose-dependent manner, and this induction was blocked by propranolol treatment.[111] Moreover, propranolol significantly reduced VEGF activity in a phorbol myristate acetate (PMA)-activated human leukemic cell line.[112] This drug also repressed gastric cancer cell growth via its downstream effects on VEGF.[113,114] Alternatively, NE increased VEGF expression, and these effects were inhibited by propranolol treatment in pancreatic cancer cells.[115,116] In addition, epinephrine enhanced the VEGF expression in colon adenocarcinoma cells, and the stimulatory action of epinephrine on colon cancer growth was blocked by treatment with atenolol and ICI 118 551, which are $beta_1$- and $beta_2$-selective antagonists, respectively.[117] $Beta_2$-adrenergic receptor blockade regulated VEGF production in a mouse model of oxygen-induced retinopathy.[118] Hypoxia-inducible factor 1α and VEGF messenger RNA and protein expression were both upregulated in a rat model of volume-overload heart failure; carvediol treatment reversed these abnormalities.[119] These findings suggested that beta-adrenergic receptor antagonists modulated VEGF expression in AD.

The reduced form of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzyme complex mediates critical physiological and pathological processes including cell signaling, inflammation and mitogenesis, by generating reactive oxygen species (ROS) from molecular oxygen. The NOX is widely expressed in various immune cells, including microglia, macrophages, and neutrophils. In AD, NOX is activated in microglia, resulting in the formation of ROS that are toxic to neighboring neurons.[120] The Aβ induces mitochondrial dysfunction and oxidative stress in astrocytes and neural death via NOX activation.[121,122] The NOX expression and activity are specifically upregulated in vulnerable brain regions of mildly cognitive impaired patients.[123] The NOX is also upregulated in the frontal and temporal cortices and contributes to AD progression.[124] The inhibition of NOX or the gene deletion of its functional $p47^{phox}$ (phox: phagocyte oxidation) subunit promotes alternative and anti-inflammatory microglial activation during neuroinflammation.[125] Moreover, nebivolol, a third-generation selective $beta_1$-adrenoceptor, improved left ventricle dysfunction and survival immediately after myocardial ischemia and inhibited cardiac NOX activation.[126] Nebivolol treatment has been associated with improvements in insulin resistance, reduced proteinuria, and reduced NOX activity as well as the production of ROS in the kidneys and skeletal muscle tissue of transgenic TG(mRen2)27 rats (Ren2).[127,128] Moreover, nebivolol also improved diastolic relaxation, fibrosis, and remodeling in obese Zucker rats and also reduced NOX-dependent superoxide production.[129] Carvedilol attenuated the increased expression of NOX subunits in the hearts and kidneys of rats after daunorubicin-induced cardiotoxicity and nephrotoxicity.[130] Activity of NOX in whole blood and isolated neutrophils was inhibited by nebivolol in a dose-dependent manner, whereas atenolol, metoprolol, and carvedilol were markedly less effective in Watanabe heritable hyperlipidemic rabbits.[131] Celiprolol, a specific $beta_1$-receptor antagonist with weak $beta_2$-receptor agonistic activity, suppressed NOX $p22^{phox}$, $p47^{phox}$, gp91phox, and Nox1 expression in the left ventricle of deoxycorticosterone acetate-salt hypertensive rats.[132] Taken together, these findings suggested that beta-adrenergic receptor antagonists play a role in AD through the suppression of NADPH expression.

The Role of Beta-Adrenergic Blockers in Alzheimer's Disease

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are responsible for remodeling the extracellular matrix and regulating leukocyte migration through the extracellular matrix. This migration is an important step in inflammatory and infectious pathophysiology. The MMPs are produced by many cell types, including lymphocytes, granulocytes, astrocytes, and activated macrophages.[133] Increasing evidence suggests that MMPs play an important role in the pathogenesis of AD. Leake et al[134] identified an approximately 50% increase in the cortical levels of MMP-1 in AD. This finding is consistent with the presence of an inflammatory state within the brain in AD and contributes to the blood–brain barrier dysfunction observed in AD. Plasma MMP-3 was also significantly elevated in patients with AD.[135] The MMP-3 was expressed predominantly in the brain white

matter and was also expressed in senile plaques in the cortices of patients with AD.[136] Compared with the control participants, patients with AD had significantly elevated plasma MMP-9 levels.[137] In the brain tissue of patients with AD, MMP-9 expression was found in the cytoplasm of neurons, neurofibrillary tangles, senile plaques, and vascular walls.[138] In addition, there were inverse correlations between the Global Cognitive and Mini-Mental State Examination scores and MMP-9 activity.[139] The Aβ is a potent stimulator of MMP-9 and MMP-2 activity in mixed hippocampal astrocyte cultures.[140] The interaction of Aβ and RAGEs induces MMP-2 expression in brain endothelial cells.[141] The *MMP* genotypes may influence the risk of dementia, and *MMP* gene polymorphisms have been reported to associate with vascular dementia and AD.[142] The *MMP-3* variants are associated with changes in the Aβ levels in humans and an increased risk of dementia.[143,144] Treatment with an MMP-9 inhibitor improved the Aβ-mediated cognitive impairment and neurotoxicity in mice.[145] These findings further suggested that MMP-9 plays a causal role in Aβ-induced cognitive impairment and neurotoxicity. Moreover, propranolol inhibited human brain endothelial cell tubulogenesis and MMP-9 secretion.[146] A selective $beta_3$-adrenoceptor agonist prevented human myometrial remodeling and MMP-2 and MMP-9 activation in an in vitro model of chorioamnionitis.[147] The NE treatment increased MMP-2 and MMP-9 levels in cultured NPC cells, and these increases were inhibited by propranolol treatment. The NE also induced the invasiveness of all the NPC cell lines in a dose-dependent manner, and this effect could be blocked with an MMP inhibitor and propranolol treatment.[111] Propranolol significantly reduced MMP-2 activity in a PMA-activated human leukemic cell line.[112] Propranolol-induced growth inhibition has been associated with arrest at both G_0/G_1 and G_2/M and repressed gastric cancer cell growth via the downstream inhibition of MMP-2 and MMP-9.[113] NE increased MMP-2 and MMP-9 expression, and these effects were inhibited by propranolol treatment in pancreatic cancer cells.[115,116] Epinephrine upregulated MMP-9 activity in human colon adenocarcinoma HT-29 cells, and this effect was blocked by $beta_1$- and $beta_2$-selective receptor antagonists, atenolol, and ICI 118,551.[117] These studies suggested that beta-adrenergic receptor antagonists might play an important role in the pathological process of PD via the regulation of tissue inhibitor of mettaloproteinase levels and the downregulation of MMPs.

The mitogen-activated protein kinase (MAPK) signaling pathways provide a key link between membrane-bound receptors that receive cues from signaling molecules and changes in the patterns of gene expression, which include the extracellular signal-regulated kinases cascade, the stress-activated protein kinases/c-Jun N-terminal kinase (SAPK/JNK) cascade, and the p38 MAPK/RK/HOG cascade.[148] An increase in the activation and expression levels of MKK6, one of the upstream activators of p38 MAPK, has been observed in AD brain tissue.[149] Patients with AD had increased levels of p38 MAPK phosphorylation associated with Aβ plaques and neurofibrillary tangle-bearing neurons.[150,151-152] There is a link between Aβ-induced oxidative stress, activation of stress kinases SAPK/JNK and p38, and tau hyperphosphorylation, which was suggested in neurites surrounding amyloid plaque.[151] Strong protein kinase of 38-kDa (p38-P) immunereactivity was observed in about 50% to 70% of neurons with neurofibrillary tangles and in dystrophic neurites of senile plaques in AD.[152] In vitro activation of MKK6-p38 MAPK pathway resulted in tau phosphorylation at Ser-396, which suggested that MAPK pathway has a functional role in microtubule binding. Abnormal phosphorylation at Ser-396 was demonstrated in AD brain but not in normal functioning adult brain.[153] In addition, AD hippocampal isolated from post-mortem human brains showed co-immunopreciptate of MKK6 and phosphorylated tau protein, and such studies also showed that APP co-immunoprecipitated with both ASK-1 and MKK6.[154] Moreover, Aβ stimulated glial cell cultures and activate p38 MAPK,[155] contributing to the loss of neurons observed in neurodegenerative disease. A novel p38 α-MAPK inhibitor (MW01-2-069A-SRM) suppressed brain proinflammatory cytokine upregulation and attenuated synaptic dysfunction and behavioral deficits in an AD mouse model.[156] Inhibition of p38 MAPK with SB203580 decreased IL-1β-induced tau phosphorylation in vitro in neuronal cultures,[157] thus highlighting the importance of p38 MAPK as a target for combating neuro-inflammation. Moreover, beta-adrenoceptor stimulation activated the cAMP/PKA and MAPK pathways in pancreatic cancer cells. $Beta_2$-adrenergic receptor antagonists suppressed invasion and proliferation via the inhibition of both cAMP/PKA and Ras, which regulate MAPK pathway activation.[116] The NE stimulated pancreatic cancer cell proliferation, migration, and invasion via the beta-adrenergic receptor-dependent activation of the p38/MAPK pathway. These stimulatory effects were completely abolished by treatment with propranolol or the p38/MAPK inhibitor SB203580.[158] Propranolol exerts its suppressive effects on hemangiomas via the hypoxia-inducible factor-1α-VEGF-A angiogenesis axis, with effects mediated by the PI3K/Akt and p38/MAPK pathways.[159] Taken together, these findings suggested that beta-adrenergic receptor antagonists may play a role in AD via suppression of the MAPK pathway.

Inflammation is thought to be integral to the pathogenesis of AD. Prostaglandins (PGs) play a role in inflammatory processes.[160] Cyclooxygenase (COX) participates in the conversion of arachidonic acid (AA) into PGs. The AA and its various metabolites, including PGs, thromboxanes, and leukotriene B4, induce a significantly higher secretion of both $A\beta_{40}$ and $A\beta_{42}$ peptides.[161] COX-2 and PGE_2 synthesis are induced by $A\beta_{1\text{-}42}$ in astrocytic cells via a nuclear factor-κB-dependent mechanism.[162] The PG receptors are expressed in the hypothalamus, thalamus, and limbic system,[163] and COX-2 is expressed by excitatory neurons at postsynaptic sites in the rat cerebral cortex.[164] Overexpression of COX-2 is observed in the perinuclear, dendritic, and axonal areas of pyramidal neurons as well as in subregions of the hippocampal formation in AD.[165,166] Moreover, COX-2 potentiated Aβ protein generation via mechanisms that involve γ-secretase activity.[167,168] Long-term treatment with nonsteroidal anti-inflammatory drugs has shown beneficial effects, including the improvement in AD progression.[169,170] The COX-2 was abnormally expressed in neutrophils and monocytes in patients with AD.[41] The *COX-2 G/G* genotype is associated with AD.[171]

Moreover, epinephrine increased the release of PGE_2 in human colon adenocarcinoma HT-29 cells, and this release was blocked by treatment with COX-2 inhibitors or atenolol and ICI 118 551 ($beta_1$- and $beta_2$-selective adrenergic antagonists, respectively).[117] $Beta_2$-adrenergic receptor antagonists suppressed COX-2 expression in pancreatic cancer cells.[116] Propranolol inhibited cell proliferation and repressed gastric cancer cell growth via the downstream COX-2 pathway.[113,114] In addition, the administration of propranolol and a COX-2 inhibitor, applied perioperatively in most patients with cancer with minimal risk and low cost, counteracted several immunological and endocrinological perturbations and improved recurrence-free survival rates in mice undergoing primary tumor excision.[172,173] These findings suggested that beta-adrenergic receptor antagonists play a role in modulating the inflammatory process in AD.

The ROS have been implicated in the pathogenesis of neuronal death in AD. Increased levels of ROS have been reported in AD.[174,175] Oxygen-free radical injury causes some AD-type molecular abnormalities in human neuronal cells.[176] Oxidative stress is a sign of AD pathology and may be an early event in the progression of the mild cognitive impairment that leads to AD.[177] Cultured skin fibroblasts from patients with AD exhibited increased superoxide dismutase activity, and these cells were more susceptible to free radical damage.[178,179] Mitochondria-derived ROS resulted in enhanced amyloidogenic amyloid precursor protein (APP) processing, and Aβ itself led to mitochondrial dysfunction and increased ROS levels.[180] Moreover, myocardial tissue sections displayed increased ROS levels after traumatic brain injuries. Treatment with propranolol lowered cardiac ROS levels.[181] D-propranolol attenuated lysosomal iron accumulation and oxidative injury in endothelial cells.[182] Carvedilol modulated ROS-induced signaling. Carvedilol also significantly reduced ischemia–reperfusion-induced free radical production and NAD^+ catabolism, lipid peroxidation, and red blood cell membrane damage, as determined by free malondialdehyde production in heart perfusion and rheological models.[93] Carvedilol also protected against colcichine- and aluminum-induced neurotoxicity in rats by attenuating oxidative stress, including lipid peroxidation, nitrite concentration and restored reduced glutathione, superoxide dismutase, catalase, and glutathione S-transferase activity. Carvediol also improved the memory of rats in the Morris water maze test.[31,32] Furthermore, nebivolol improved diastolic dysfunction and myocardial remodeling through reductions in oxidative stress in transgenic (mRen2) rats.[183] These findings suggested that beta-adrenergic receptor antagonists modulate oxidative stress in AD.

Nitric oxide synthase (NOS) generates nitric oxide (NO), which is a critical signaling molecule involved in synaptic plasticity and memory.[184,185] Endothelial NO (eNO) plays an important role in modulating APP expression and processing within the brain and cerebro-vasculature. Brain tissue from $eNOS^{-/-}$ mice had statistically higher APP and BACE1 protein levels, as well as increased BACE1, beta-site APP-cleaving enzyme1, enzyme activity and $A\beta_{1\text{-}42}$ wild-type control.[186] Prolonged NO treatment resulted in tau aggregation in SH-SY5Y cells.[187] Studies have reported that the leukocytes and brain microvessels of patients with AD had significantly increased NOS activity.[188,189] Moreover, NOS may contribute to the pathogenesis of AD. In AD and APP transgenic mice, astrocytes with high NOS levels were associated with Aβ protein deposits.[190] In AD-like mice, NOS deficiency also protected against premature mortality, cerebral plaque formation, increased Aβ protein levels, astrocytosis, and microgliosis.[191] Moreover, metipranolol suppressed NO-induced lipid peroxidation in the eyes and retinas of rats.[95] Nebivolol prevented vascular NOS III uncoupling in experimental hyperlipidemia,[131] and propranolol suppressed hemangioma growth via inhibition of eNOS protein expression and the subsequent production of NO.[192] Furthermore, celiprolol activated eNOS through the PI3K-Akt pathway via oxidative stress-induced $NF\text{-}_kB$ activity.[132] These findings suggested that beta-adrenergic receptor antagonists play a role in AD via the inhibition of NOS expression.

Conclusion

Beta-adrenergic receptor blockade may play a role in AD. Genetic studies have identified proteins that link beta-adrenergic receptor antagonism to the pathology of AD, including *HLA* genes, the RAS, PARP-1, NGF, VEGF, and the reduced form of NADP. Beta-adrenergic receptor inhibition also affects AD via nongenomic mechanisms, including MMPs, MAPK pathways, PGs, COX-2, and NOS. The beta-adrenergic receptor blockades are contradicted in patients with asthma and CHF and cautioned to nursing women. Depression has been associated with lipophilic beta-adrenergic receptor blockades, such as propranolol. Serious CNS adverse effects, including agitation, confusion, and hallucinations, are rare. However, the most interesting side effect of beta-adrenergic receptor blockade is hypotension or symptoms associated with hypotension. The role of beta-adrenergic receptor blockade in AD is still controversial. It is still unclear whether behavioral symptoms, sex, or genetic factors, including $beta_2$-adrenergic receptor variants, *apoliporotein E* (*apoE*), and cytochrome P_{450} CYP2D6 participate in the beta-adrenergic receptor blockade modulation in AD. Various behavioral abnormalities appear to be present in subgroups of patients with AD.[193,194] Compared with both nonaggressive patients with AD and control participants, aggressive patients with AD had small but significant (approximately 25%) increases in concentrations of $beta_1$- and $beta_2$-adrenergic receptors in the cerebellar cortex.[16] There was also an apparent sex difference in cerebral amyloid plaque formation. Compared with the males, transgenic female *Tg2576* mice had more $A\beta_{40}$ and $A\beta_{42}$ in the brain.[195] Ni et al[20] reported that female mice had more amyloid plaques than age-matched males among the control mice. These authors also revealed that female mice appeared to be more sensitive to chronic treatment with beta-adrenergic receptor agonist than the male mice. $Beta_2$-adrenergic receptor polymorphisms contributed to AD pathology.[196,197] The ApoE is a major cholesterol carrier that supports lipid transport and injury repair in the brain. The *ApoE* polymorphic alleles are the main genetic determinants of AD risk; individuals carrying the ε4 allele are at increased risk of AD compared with those carrying the more common *ε3* allele, whereas the *ε2* allele decreases risk.[198] The *apoE ε4* allele frequency was

significantly higher in the AD groups compared with the control group.[199] Carvedilol reduces the severity of atherosclerosis in apoE-deficient mice via reducing superoxide production.[200] The *CYP2D6B* allele is associated with AD.[201,202] The *CYP2D6* allele frequency is known to vary among racial/ethnic groups. In general, the frequency of the functional group of predominant alleles in European caucasians is 71%. In Asians, the functional alleles represent only ~50% of the frequency of *CYP2D6* alleles.[203] Moreover, genetic polymorphism of *CYP2D6* results in altered pharmacokinetics of beta-adrenergic receptor antagonistic medications.[204-207] However, substantial reservation regarding these findings need to be noted. It is not entirely clear whether the direct action of beta-adrenergic receptor antagonists in brain has been separated from the impact of beta drugs on the cardiovascular system, which, in turn, affects AD. Thus, further studies on the relationship between beta-adrenergic receptor antagonists and AD are warranted.

Declaration of Conflicting Interests

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