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Implication of Central β_2 Adrenergic Receptor for the Development of Novel Drugs Against Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive onset of symptoms, including memory loss, accompanied by other neurological impairments. This progression is attributed to the deterioration of neuronal connections and a decrease in neurotransmission. Although this phenomenon has been extensively studied in the cholinergic system, it also affects other neurobiological pathways, particularly adrenergic transmission. In this context, the use of agonists, in particular, β_2-adrenergic receptor (β_2AR) agonists, may represent a promising therapeutic approach. After reviewing the main pharmacological aspects related to these receptors, we will first present the different existing modulators and their peripheral effects. We will then analyze the results of studies investigating their use in disease models. Finally, we will discuss the conditions and prospects for the development of a new treatment for Alzheimer's disease using a β_2AR agonist.

1 | Generalities of the β-Adrenergic System

βARs are involved in numerous physiological regulations. These receptors belong to the G protein-coupled receptors (GPCR) superfamily, which are receptors with seven transmembrane α-helical domains [1].

The structure of the βARs has been extensively studied, and one of the first human GPCR structures was determined from β_2AR following stimulation by an inverse agonist [2].

Since this discovery, the conformation of β_2AR has been extensively studies. Most GPCR can exist in two different conformations: active and inactive forms. The βARs tend to have an active conformation by coupling to different G proteins [2]. At the intracellular level, βARs can couple to stimulatory (Gs) or inhibitory (Gi) G proteins [3].

These receptors are mainly stimulated by the secretion of endogenous adrenaline and noradrenaline. Mainly secreted by adrenal glands and adrenergic neurons, adrenaline can stimulate βARs located in different organs such as the heart, lungs, blood vessels, adipose tissue, liver, gastrointestinal tract, uterus, bladder, brain, and eye. Adrenaline has a short duration of action (about 2 min), as it is rapidly metabolized by catechol-*O*-methyltransferases (COMT) in the majority, and by monoamine oxidases (MAO) in the minority [4, 5].

Stimulation of Gs-coupled βARs induces activation of the adenylate cyclase cascade. This leads to the release of cyclic adenosine monophosphate (cAMP). The increase in cAMP concentration allows the phosphorylation of protein kinase A (PKA). PKA can then phosphorylate various proteins in the target organs [3, 5].

There are three main subtypes of βARs: β_1, β_2 and β_3. These different βAR subtypes have different localizations and distributions in the central and peripheral nervous systems. They play an important role in cardiac contraction, smooth muscle and vascular relaxation, and neurotransmitter release.

1.1 | β_1 Adrenergic Receptors (β_1AR)

The β_1AR are predominant in the heart, accounting for around 80% of βARs. They are mainly coupled to the Gs protein, and their stimulation leads to activation of the adenylate cyclase cascade. The production of cAMP leads to phosphorylation of PKA substrates (calcium channels, troponin I, myosin...), inducing an increase of calcium ions. This results in positive inotropic and chronotropic effects, enhancing cardiomyocyte contractility [6, 7].

However, continuous β_1AR stimulation induces hypertrophy and promotes cardiomyocyte apoptosis (Figure 1) [8].

1.2 | β_3 Adrenergic Receptors (β_3AR)

Unlike the other βARs subtypes, the β_3AR have different physiological properties. This is due to the absence of a phosphorylation site at the C-terminus of the receptor. The β_1AR and β_2AR possess a phosphorylation site consisting of serine and threonine residues that are phosphorylated following overactivation of the receptor. Phosphorylation of the receptor leads to desensitization of β_1AR. In contrast, β_3AR are not sensitive to desensitization because they lack this phosphorylation site [5].

In addition, β_3AR activation requires a higher concentration of catecholamines than β_1AR and β_2AR. The response following β_3AR stimulation also lasts longer. This is related to the absence of the desensitization phenomenon on this type of receptor.

The β_3AR are mainly expressed in brown and white adipose tissue and are mainly coupled to the Gs protein [5, 6]. Their activation leads to lipolysis and promotes glycogenogenesis induced by insulin secretion. Antidiabetic and antiobesity effects have been observed.

In cardiomyocytes, stimulation of the Gs-coupled β_3AR induces inhibition of calcium channels and a decrease in the concentration of intracellular calcium ions, while stimulation of the Gi-coupled β_3AR leads to nitric oxide and cGMP production. Although these effects are controversial, a negative inotropic effect has been observed in animal and human models (Figure 1) [5, 8].

1.3 | β_2 Adrenergic Receptors (β_2AR)

β_2ARs are ubiquitously distributed in the body, with a higher concentration in the smooth muscles of the lungs. They are also present in hepatocytes and the smooth muscle of the bladder and uterus. Like β_1AR, they are coupled to Gs protein, and their stimulation leads to activation of the adenylate cyclase cascade. This leads to the phosphorylation of PKA, which in turn phosphorylates the proteins responsible for muscle tone. In addition, PKA promotes calcium entry into the cell, leading to smooth muscle relaxation. These molecular mechanisms result in the dilation of the bronchial blood vessels and relaxation of the walls of the bronchi, bladder, uterus and gastrointestinal tract [3].

In the heart, β_2AR are poorly represented (about 20%), and their stimulation causes increased contraction of the heart and dilation of the coronary arteries. However, with high catecholamines concentrations, β_2AR preferentially couple to the Gi protein. This activates the phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) cascades. This mechanism induces a slowdown in cell growth and counterbalances the overactivation of βAR receptors [3, 5, 8]. Moreover, the response to

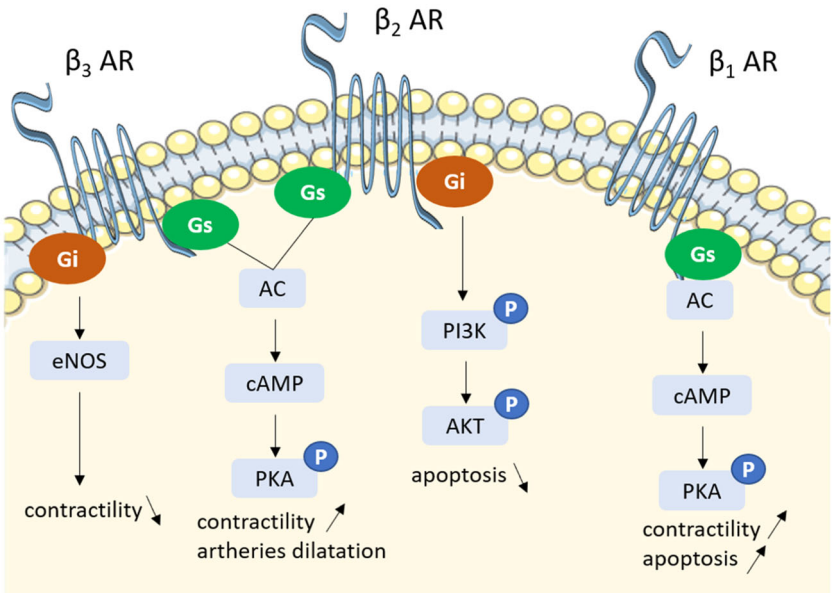


FIGURE 1 | The β-adrenergic receptor (βARs)-mediated signaling pathway in cardiomyocytes [8].

β_2AR stimulation remains local, unlike that of the β_1AR. This prevents exacerbation of the effects within the cell [9].

β_2AR are also present in the brain, notably in the hippocampus and cortex. Their stimulation leads to activation of the AKT cascade and PKA phosphorylation. PKA can activate signaling pathways involved in the processes of awakening, learning, and memory (Figure 1) [10].

Studies have shown that prolonged agonist stimulation of β_2AR leads to receptor phosphorylation by GRK (G-protein-coupled receptor kinase) and recruitment of β-arrestin. These lead to receptor desensitization (Figure 2). Once the receptor is coupled to β-arrestin, effectors are G-protein independent and other signaling pathways can be activated [11, 12].

Among the three βARs subtypes, the β_2AR have been extensively studied, both in terms of their protein structure and their various physiological properties [3]. Numerous studies have demonstrated the importance of targeting these receptors, particularly as they are involved in numerous metabolic regulations. For this purpose, the various pharmacological modulations of these receptors at the peripheral level have been listed.

2 | Peripheral Modulation of β_2AR

The main β_2AR modulators used clinically are agonists. There are several types of agonists, classified according to their duration of action: short-acting, long-acting, and ultra-long-acting (Table 1) [13, 14]. The selectivity ratios β_1AR versus β_2AR of molecules have been reported on the basis of Baker JG's team work [15] and the literature. According to these data, salmeterol is the most β_2AR selective molecule.

Modulation of peripheral β_2AR leads to a variety of physiological effects. Depending on the target organ, the expression of these receptors will change, as will the pharmacological profile of the ligand of interest. A nonexhaustive table summarizing the different types of β_2AR ligands, the peripheral organs targeted and the pharmacological effects has been compiled (Table 2).

β_2AR agonists appear to be relevant in the treatment of a multitude of pathologies, but the use of full agonists remains controversial. Indeed, receptor desensitization or conformational changes by coupling to the Gi protein show the limits of their use. These receptors are also widely distributed in the body, which may lead to "out-targeting" effects associated with the use of nonselective agonists.

Further, these receptors are also present in the central nervous system. They are involved in the learning and memory. Various correlation studies have been carried out to determine the effect of adrenergic receptors on the development of AD-type dementia, making these receptors an interesting therapeutic target for AD.

3 | Central Modulation of β_2AR and the Benefits in the Treatment of AD

AD is a neurodegenerative disorder characterized by progressive loss of memory and certain cognitive functions, which affects the daily life tasks of affected people. Complex pathophysiological mechanisms and many clinical signs have been identified, including the formation of amyloid aggregates and plaques, neurofibrillary tangles, tau protein hyperphosphorylation, neuroinflammation, and neurodegeneration. Among the neurons affected, a loss of adrenergic neurons was found in the locus cœruleus. In fact, the locus cœruleus is the main nucleus of noradrenergic neurons, projecting to the prefrontal cortex, parietal cortex, piriform cortex, retrosplenial cortex, hippocampus, thalamic nucleus, and amygdala. These regions are involved in memory, attention and stress, and are particularly affected in AD [41–43].

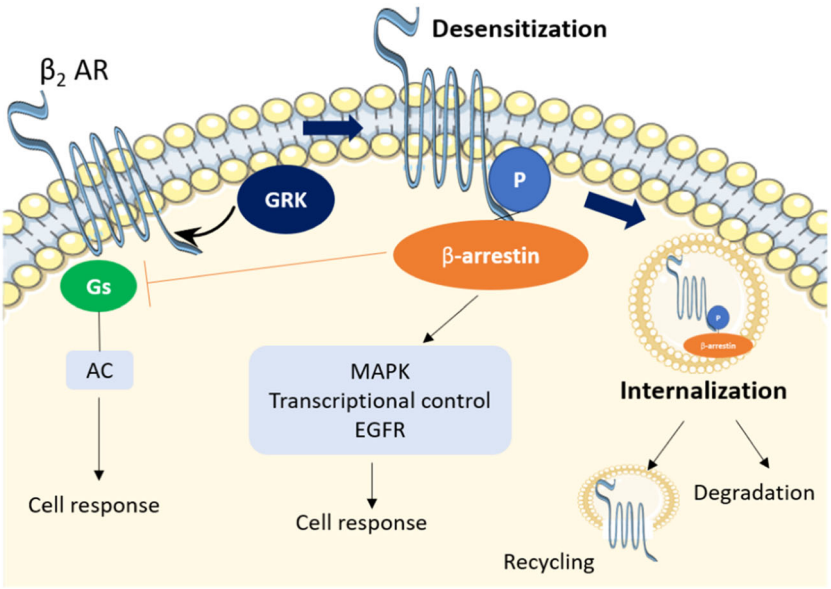
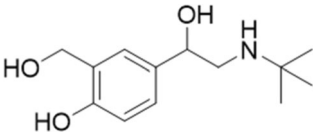
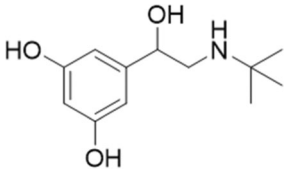
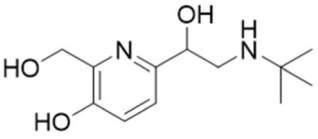
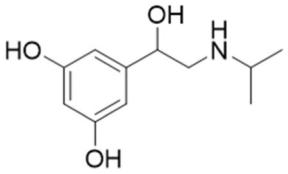
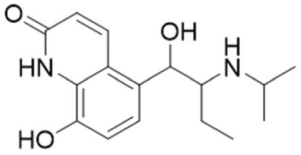
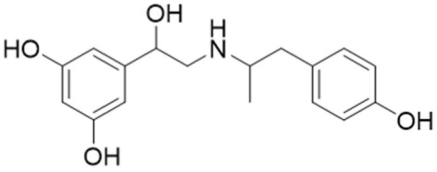
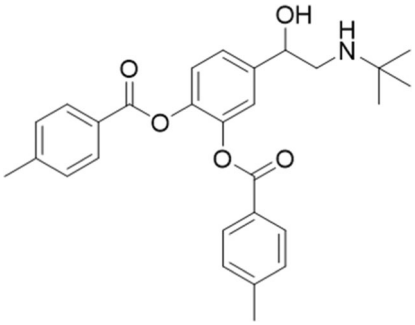


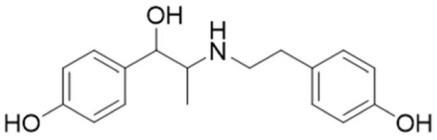
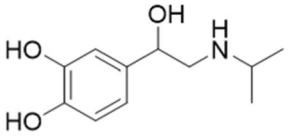
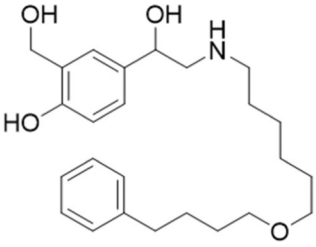
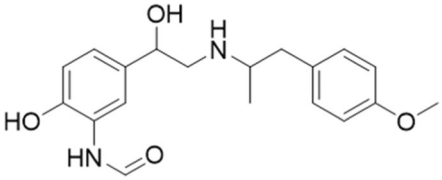
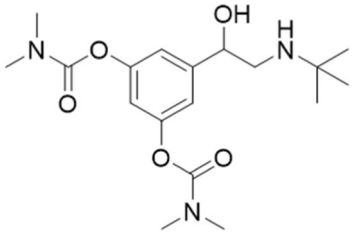
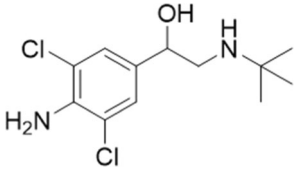
FIGURE 2 | Membrane mechanisms of β_2AR desensitization.

TABLE 1 | Classification and selectivity of clinical used β_2AR ligands.

Duration of action	Name and structure	Selectivity ratio β_1 vs β_2 [15]	logP consensus/BBB permeability (SwissADME)[a]
Short-acting agonist	Salbutamol 	21.4	1.22 No
	Terbutaline 	40.7	1.23 No
	Pirbuterol 	ND	0.45 No
	Metaproterenol 	3.9	0.97 No
	Procaterol 	199.5	2.04 No
	Fenoterol 	97.7	1.82 No
	Bitolterol mesylate (colterol's prodrug) [16] 	ND	4.81 No

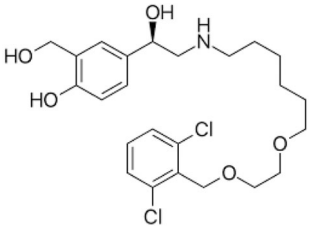
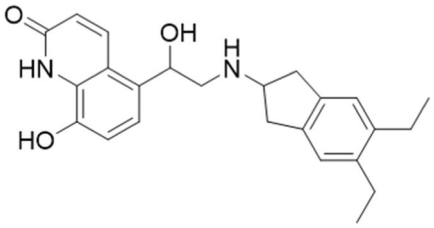
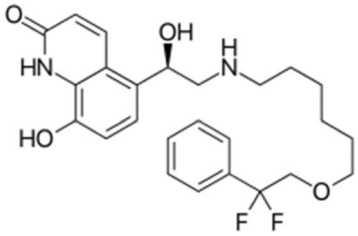
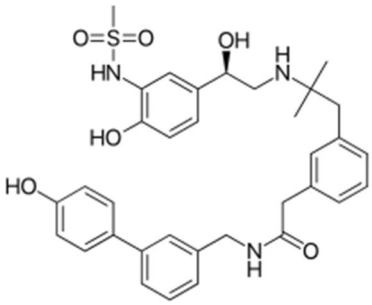
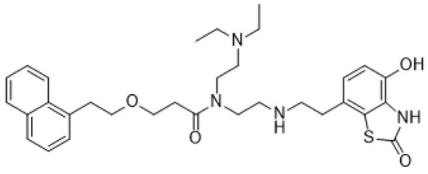
(Continues)

TABLE 1 | (Continued)

Duration of action	Name and structure	Selectivity ratio β_1 vs β_2 [15]	logP consensus/BBB permeability (SwissADME)[a]
	Ritodrine 	21.4	2.21 Yes
	Isoprenaline 	3.8	0.18 No
Long-acting agonist	Salmeterol 	3388.4	4.02 No
	Formoterol 	331.1	2.06 No
	Bambuterol (terbutaline's prodrug) 	ND	1.84 No
	Clenbuterol 	19.5	2.63 Yes

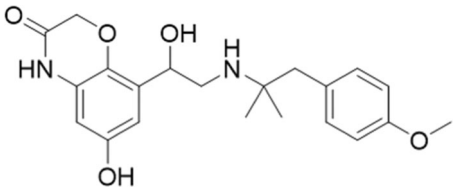
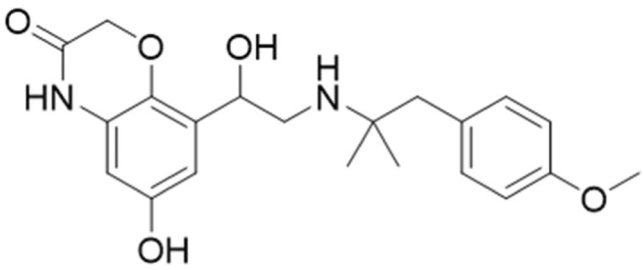
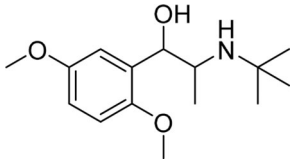
(Continues)

TABLE 1 | (Continued)

Duration of action	Name and structure	Selectivity ratio β_1 vs β_2 [15]	logP consensus/BBB permeability (SwissADME)[a]
	Vilanterol 	2400 [17]	4.23 No
Ultra-long acting agonist	Indacaterol 	16 [17]	3.53 No
	Abetiterol 	116 [18]	3.94 No In clinical trial [19]
	PF-610355 	220 [20]	3.93 No In clinical trial [21]
	AZD3199 	> 1000	4.61 No In clinical trial [22]

(Continues)

TABLE 1 | (Continued)

Duration of action	Name and structure	Selectivity ratio β_1 vs β_2 [15]	logP consensus/BBB permeability (SwissADME)[a]
	Olodaterol 	241 [23]	2.01 No
Antagonists	ICI-118551 	549.5 [24]	3.11 Yes
	Butaxamine or butoxamine 	ND	2.37 Yes

Abbreviation: ND, not determined.
[a]*Source:* http://www.swissadme.ch/.

Thus, the interest of β_2AR modulation as a new target against AD has been detailed according to epidemiological data and different effects on pathophysiological markers.

3.1 | Epidemiological Data

In the review by Yu et al., [44] clinical observations of nursing home patients with probable dementia were reported. People treated with beta-blockers (e.g., propranolol), had better scores for aggressive behavior. Longitudinal studies to assess the effect of beta-blockers on the incidence of AD have noted that the use of beta-blockers appears to have a protective effect on the development of AD.

However, in a retrospective cohort study conducted between 1994 and 2019 showed that the risk of developing AD was higher in patients exposed to nonselective adrenergic antagonists (beta-blockers: propranolol, sotalol, pindolol, oxprenolol). This risk decreases in patients exposed to selective β_2AR agonists (salbutamol, terbutaline, salmeterol, formoterol) [45].

These conflicting observations may be related to the use of selective or nonselective β_2AR ligands. Beta-blockers are not β_2AR selective, and their effect on the incidence of developing dementia is not exclusively related to their effect on β_2AR. To validate the hypothesis of the effect of β_2AR antagonists on the incidence of AD, further studies using selective β_2AR antagonists are required.

Based on these data, it appears that exposure to selective β_2AR agonists may reduce the incidence of developing AD.

3.2 | Neurodegeneration

β_2AR signaling is involved in the regulation of glucose metabolism in astrocytes. Activation of β_2AR by an agonist leads to the transport of blood glucose to astrocytes by acting on the type 1 glucose transporter (GLUT1). This process allows glycogenolysis in astrocytes to provide the ATP energy supply for axon function. Thus, deregulation of glucose metabolism can lead to neurodegeneration, as observed in multiple sclerosis patients [46]. However, in AD patients, β_2AR hyperactivity and reduced glucose metabolism have been observed. These effects are associated with β_2AR desensitization.

Clenbuterol administration attenuated memory deficits in APP/PS1 (amyloid precursor protein/presenilin (1) mutant transgenic mice. Neurogenesis, as well as an increase in the hippocampal dendritic network and synaptogenesis, were observed [47]. These results were also observed after treatment

TABLE 2 | The effects of modulation of peripheral β_2AR.

β_2AR ligands	Targeted organs	Pharmacologic effects	Therapeutic effects (models)	References
Agonists (short or long acting)	Heart	Coronaries arteries dilatation	Increase cardiac perfusion (human)	Woo et al. [25]
	Bronchi, lungs	– Bronchodilatation – Fluids clearance	– Asthma, COPD (human) – Pulmonary edema (rat and human)	Barisione et al. [26] Yang et al. [27] Xing et al. [28] Ippolito et al. [12] Tokmakova et al. [29] Factor et al. [30] Mutlu et al. [31]
	Adipose tissue	Glycogenolysis, lipolysis	Thermogenesis (human)	Blondin et al. [32] Ying et al. [33]
	Liver and muscles	– Short-acting: increase catabolism-long-acting: increase anabolism	– Glycogenolysis, obesity treatment (animal) – Gluconeogenesis, muscular weakness treatment (rat and mice)	Ziegler et al. [34] Sato et al. [35]
	Smooth muscles (digestif tract, bladder, and uterus wall)	Relaxation	Decrease bowel motility Uterine relaxation (human)	Johnson [3]
	Kidney	Natrium resorption increased	Recovery of renal function (mice)	Arif et al. [36]
	Immune system	Lymphocytes B and T stimulated	Stimulates immune response (human)	Sanders et al. [37] Kolmus et al. [38]
Beta-blocker (in general)	Heart	Decrease contraction	Arterial hypertension (human)	Do Vale et al. [39]
ICI-118-551 (selective β_2AR antagonist) or beta-blocker	Liver	Apoptosis induced	Hepatocarcinoma (human HCC cells)	Dang et al. [40]
Biased agonists	– Lung – Heart	– Bronchodilatation and decrease inflammation – Contractile response	– Asthma, COPD (human) – Heart failure (canine)	Woo et al. [25]

with formoterol in Ts65Dn mice, a model of Down's syndrome [48]. A study on healthy mice showed that chronic administration of salmeterol resulted in hippocampal neurogenesis [49]. Locus cœreleus adrenergic signaling protects against Aβ peptide-induced neurotoxicity in hippocampal neurons [50].

This neuroprotective effect can be explained by the activation of endogenous nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) following cAMP production via β_2AR activation. Indeed, in a clinical trial using salmeterol as monotherapy, an increase in BDNF concentration was observed in the serum and platelets of asthmatic patients [51].

In the review by Peterson et al. [52] β_2AR activation by long-acting agonists activates astrocytes and has a neuroprotective effect on brain-injured or poststroke in vivo models [53–55]. Neuroprotective effects have also been observed in rat models of Parkinson's disease (PD) where formoterol administration slowed the loss of dopaminergic neurons and reduced neuroinflammation [56].

3.3 | Neuroinflammation

β_2AR are expressed on the surface of microglia cells and regulate neuroinflammation. Activation of these receptors via β-arrestin and MAPK pathways leads to inhibition of the transcription factor NF-κB. This prevents the production of proinflammatory cytokines and reduces microglial activity [52]. This observation was established by low-dose administration of salmeterol in mouse models of PD, where dopaminergic neurotoxicity was induced by LPS [57]. Similar results were found with formoterol in streptozocin-intoxicated mice to develop cognitive decline and oxidative stress as in AD. A reduction in oxidative stress, neuroinflammation and improved neuronal survival have been observed [58]. The use of isoproterenol also protects microglia against inflammation induced by soluble oligomers of Aβ peptide in mice [59]. Moreover, chronic treatment with a beta-blocker has been shown to lead to a loss of adrenergic neurotransmission and thus exacerbate neuroinflammation in AD models' mice intoxicated with amyloid precursor protein (APP) [60].

Conflicting studies have shown decreased expression of the transcription factor NF-κB and reduced neuroinflammation in the injured brain of mice that do not express β_2AR [61]. A neuroprotective effect has been observed, associated with a decrease in proapoptotic signaling pathways in the brain [62]. In contrast, high-dose administration of salmeterol leads to an inflammatory response and toxicity on dopaminergic neurons associated with ROS production. This proinflammatory effect is caused by activation of the ERK signaling pathway in microglial cell models [63].

Conflicting results have been discussed regarding the effect of β_2AR on neuroinflammation and neuroprotection. This may be related to the concentration administered, the different conformations of β_2AR present in different cells, and to the cellular environment. The cellular mechanism of the anti-inflammatory effect of β_2AR is not fully understood [43]. However, it seems that in a large majority of studies, β_2AR agonists showed protection against neuronal damage in different neurodegenerative models.

3.4 | Amyloid Peptide (Aβ) Accumulation

Amyloid plaques have been found mainly in certain olfactory structures, the cerebral cortex, hippocampus, amygdala and cerebellum of AD model transgenic mice brain [64]. These regions also display extensions of adrenergic neurons [42, 43]. Activation of β_2AR by clenbuterol decreases Aβ peptide production by reducing APP phosphorylation and increasing α-secretase activity. This promotes the non-neurotoxic metabolism of APP peptide. Enhanced synaptogenesis and dendritic network were observed in hippocampal neurons of AD APP/PS1 gene mutant mice models [47, 65]. In another study, stimulation of β_2AR by isoproterenol resulted in degradation of Aβ peptide in microglia at the locus cœreleus. These results suggest that adrenergic signaling is required for the clearance of Aβ peptide by microglia [66]. These findings are consistent with the administration of a selective antagonist, ICI-118551, which led to Aβ peptide production and exacerbated cognitive decline in 3xTg mice [10]. One study also showed that the use of β_2AR agonists reduces the formation of Aβ peptide oligomers by decreasing histone deacetylase (HDAC) levels. This restores synaptic plasticity in the hippocampus of Aβ peptide-intoxicated mice [67].

In the review by Wang et al., [68] the use of β_2AR agonists decreases Aβ peptide formation and tau protein hyperphosphorylation. Furthermore, the ratio between $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ peptides tends to become unbalanced with an increase in $A\beta_{1\text{-}40}$ in patients with dementia. The use of β_2AR agonists could restore the balance of them.

Other studies show the negative effects of activating these receptors in different models.

Activation of β_2AR has also been shown to increase Aβ peptide production and amyloid plaques formation in other mouse models of AD. This has been linked to β_2AR internalization activating signaling pathways increasing presenilin 1 and γ-secretase activity [69]. Another study suggests that β_2AR activation via β-arrestin 2 pathway results in hyperactivity of γ-secretase catalytic subunit, increasing Aβ peptide production [70].

In addition, β_2AR activation increases intracellular calcium concentration and phosphorylation of the ryanodine receptor. An increase of APP metabolism and Aβ peptide production were noted [71]. Another study showed β_2AR activation by clenbuterol in acutely stressed mice led to Aβ peptide production, whereas administration of the selective antagonist ICI-118551 reduced Aβ peptide levels [72].

Aβ peptide binds to β_2AR, inducing PKA hyperactivity. This promotes AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor hyperactivity and increased calcium flux, resulting in neuronal death in AD APP mutant mice [73].

However, studies have shown that inactivation of the β_2AR leads to improved learning and memory capacity in AD

presenilin 1 and APP gene mutated mice [74]. In addition, it has also been shown that Aβ peptide binds to the β_2AR and causes internalization and degradation of the receptor. These phenomena lead to a decrease in synaptic transduction of adrenergic and glutamatergic neurons in the prefrontal cortex, which is generally observed in neurodegenerative diseases [75]. Furthermore, β_2AR internalization caused by Aβ peptide can activate β-arrestin signaling pathway. According to the review by Jiang et al. [76] activation of the β-arrestin pathway appears to increase Aβ peptide production and thus progress AD. However, this pathway is involved in many signaling pathways and more studies will be needed to find out whether β-arrestin participate in the pathogenesis of AD.

All these results show that there is a link between β_2AR and amyloid plaque formation but the cellular mechanism remains to be determined.

3.5 | Tau Protein Hyperphosphorylation

A study has shown that suppression of β_2AR expression results in a decrease in tau protein phosphorylation in the PS1/APP genes mutated mice. Indeed, in prefrontal cortex neurons, Aβ peptide binds to β_2AR and activates the PKA-JNK signaling pathway, which is responsible for tau protein phosphorylation at residues of Ser-214, Ser-262, and Thr-181 [77, 78]. Another study on transgenic mice overexpressing tau protein and lacking β_2AR showed a decrease in tauopathy. These β_2AR-induced changes in tau protein are thought to be linked to a reduction in the activity of GSK3β et CDK5, which are the two main kinases involved in tau protein phosphorylation [79]. An in vitro study using circular dichroism showed that salbutamol decreases tau protein filament aggregation, thereby reducing the formation of neurofibrillary tangles. Salbutamol intercalates between tau monomers, preventing tau filament aggregation [80].

Biochemical and cellular studies show that β_2AR coupled to β-arrestins 1 and 2 lead to microtubule destabilization and reduced autophagy flux. This leads to hyperphosphorylation of tau protein and promote pathogenic tau accumulation in PS19 mice. It has also been demonstrated that β-arrestin levels are increased in the brains of patients with frontal and temporal lobe neurodegeneration [81].

However, it has been shown that administration of a selective antagonist, ICI-118551, increases tau protein phosphorylation and improves its accumulation forming neurofibrillary tangles in 3xTg-AD mice. This is associated with an increase in APP metabolism, which increases Aβ peptide production. This increase in Aβ peptide levels causes an increase in tauopathy. ICI-118551 exacerbated spatial learning and memory deficits in 3xTg-AD mice [10].

These studies show that the link between β_2AR and AD is a very complex issue and suggest that the use of agonist or antagonist to treat AD should be approached with caution. Further studies are needed to better understand the involvement of β_2AR in the pathogenesis of AD, to better modulate these receptors for beneficial effects. Indeed, modulation of this receptor could have an impact on AD progression by targeting different cellular mechanisms (Figure 3).

The involvement of β_2AR in the various pathophysiological mechanisms of AD has been summarized. For each mechanism, the number of publications, the effect of the ligand, the level of evidence and an opinion have been studied (Table 3).

A screening of FDA-approved drugs was carried out in zebrafish to identify drugs active in neurodegeneration [82]. In this study, β_2AR agonists turn out to be active molecule for the treatment of AD. Although conflicting data on the use of antagonists are also described in the literature, agonists appear to be more convincing for their beneficial effects shown in animal models of AD [83].

As far as we know, only three clinical trials have been conducted with βAR ligands in AD. Two studies evaluated the development of AD following the use of a β_2AR agonist: salbutamol (study in progress) [84] or formoterol (study withdrawn) [85].

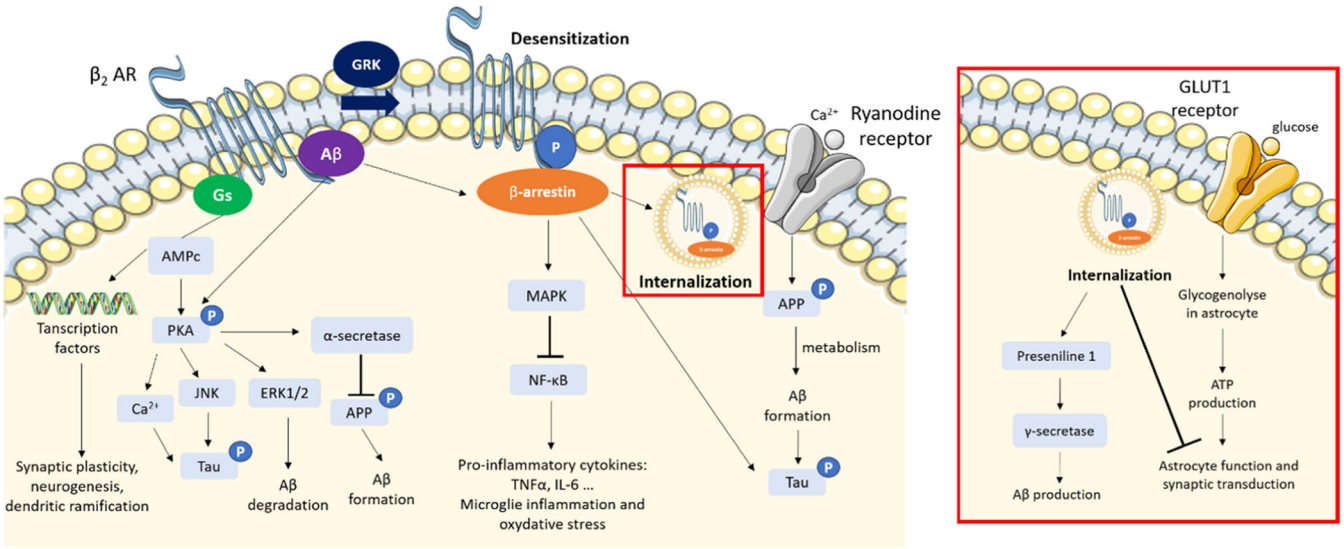


FIGURE 3 | Implication of β_2AR in the pathogenesis of AD.

TABLE 3 | Level of proof for β_2AR ligands in the pathophysiological mechanisms of AD.

Pathophysiological pathway	# publication	Ligand profile	Proof level	References	Opinion
Neurodegeneration	10	Agonist	Mice and human	[46–56]	Consistent results with the same compounds (e.g., salmeterol)
Neuroinflammation	4	Agonist	Mice	[52, 57–59]	Contradictory results may be related to dose difference
	2	No express β_2AR or high concentration of agonist	In cellulo and mice	[62–63]	
Aβ accumulation	6	Agonist	Mice	[10, 47, 65–68]	Contradictory results may be due to β-arrestin activation or receptor internalization
	7	Inactivation of receptor or antagonist	Mice	[69–75]	
Tau hyperphosphorylation	3	No express β_2AR	Mice	[77–79]	Requires more in vivo studies with comparable doses
	1	Agonist	In vitro	[80]	

A study of a beta-blocker, carvedilol [86], has shown results in AD. In this randomized, double-blind study, the association between carvedilol treatment and the development of AD was assessed on the basis of HVLT (Hopkins Verbal Learning Test) memory scores and cerebrospinal fluid concentrations of tau protein and $A\beta_{42}$ peptide. Memory scores differed little between the placebo and carvedilol groups. However, concentrations of both biomarkers were higher in the carvedilol-treated group than in the placebo group. No more results have been published, but on the basis of this observation, inhibition of the adrenergic system doesn't seem of interest for the treatment of AD.

These numerous studies show the involvement of β_2AR on AD pathogenesis. However, these studies were carried out using different doses (e.g. salmeterol from 1 to 1000 nM), administration schedules and models (Table 4). At high concentrations of agonist, activation of the β-arrrestin pathway may occur, which could explain the contradictory results. It is therefore necessary to harmonize studies with similar concentrations for each type of ligand to validate the therapeutic effect of β_2AR ligands against AD.

4 | Discussion and Conclusion

Overall selective β_2AR agonists appear to have interesting potential as new agents against AD. Since a number of β_2AR agonist ligands are already used in therapy, repurposing these active compounds could appear as the simplest method to develop a new anti-Alzheimer drug [90]. Due to the large number of selective ligands available, the first step would be to select the agonist with the best development potential: highest selectivity (salmeterol), adequate lipophilicity for central distribution, permeability across the BBB (clenbuterol, salmeterol, indacaterol), optimal duration of action, and lowest toxicity. Considering these factors, the best candidates would be: salmeterol, clenbuterol, and indacaterol.

However, several obstacles may slow down future developments. (i) The existing formulations are unsuitable for administration through the general circulation or for targeted delivery to the brain. Most commercial forms are powders or suspensions intended for airway administration, often combined with a corticosteroid. (ii) Due to the peripheral localization and functions of the receptors, the use of full agonists may lead to numerous off-target side effects on vital processes [91]. It is worth noting that, in an Alzheimer's murine model study, it was necessary to administer a peripheral beta-blocker to mitigate these side effects [48]. (iii) Finally, determining the appropriate dose, or at least the effective intracerebral concentration, and the dosing regimen could be problematic. Indeed, in evaluations using murine models, the doses explored cover a range of 1 in 1000 (Table 4).

To address these challenges, it seems necessary to develop the best compromise between the mode of administration, the formulation, and the targeted brain concentration. Several strategies can be considered and combined. To enhance ease of use, an oral form could be envisaged. To minimize significant peripheral effects, the dose of such a form should be limited. Advanced pharmacokinetic studies will be required to monitor CNS absorption, that is, by calculating the unbound brain-to-plasma partition ratio ($K_{p,uu}$), using methods such as Brain Exposure Assessment [92].

Vectorization strategies could be considered to facilitate the passage across the BBB. For oral administration, several solutions can be proposed, and a number of review studies list these possibilities [93–96]. Given the peripheral biological effects representing off-target actions, it may be considered to target the delivery of the active compound directly into the brain [93–96].

Considering that intrathecal administration is not feasible, an alternative route could be intranasal delivery, as it bypasses the BBB. Numerous studies [97] have explored this type of administration, and a recent review compiles the data obtained [98].

Although the repurposing strategy is likely the most effective, the development of new β_2AR agonists is also a possibility. According to our bibliographic research, there is very little

TABLE 4 | β_2AR ligands involved in the pathogenesis of AD.

Molecules	Models	Administration	Pharmacological effects	References
Clenbuterol (agonist)	Mice APP/PS1	Chronic, 2 mg/kg, once a day for 2 months, intraperitoneal (i.p.) route	Decrease Aβ peptide level, neurogenesis, synaptogenesis, and dendritic network enhanced	Chai et al. [47]
	Acutely stressed C57 mice	Acute, 2 mg/kg, i.p. route	Aβ peptide production	Yu et al. [72]
	Intranigral LPS rat model of PD	Chronic, 100 μg/kg/day for 7 days, i.p. route	Attenuated the LPS-induced deficits in forelimb kinesis, lower neuroprotective effect than formoterol	O'Neill et al. [56]
Formoterol (agonist)	Ts65Dn mice	Acute, 2 mg/kg 4 h before behavioral tests, i.p. route, pretreatment of mice with nadolol (antagonist) to limit peripheric effects of formoterol	Neurogenesis, synaptogenesis, and dendritic network enhanced	Dang et al. [48]
	Swiss albino mice treated by streptozotocin	Chronic, 25/50/100 μg/kg/day for 21 days, i.p. route	Improvement in spatial memory; reduction of oxidative stress, neuro-inflammation, apoptosis (diminution of caspase 3); positive effect of neurotransmitters levels (acetylcholine and glutamate); decreased of nuclear pyknosis and degeneration in neuron in cerebral cortex and hippocampus with a 100 μg/kg/day dose	Abdel Rasheed et al. [58]
	Intranigral LPS rat model of PD (wistar rats)	Chronic, 100 μg/kg/day for 7 days, i.p. route	Reduction of: oxidative stress, loss of dopaminergic neurons and neuro-inflammation	O'Neill et al. [56]
Salmeterol (agonist)	C57BL/6 J mice	Chronic, 10 μg/kg/day for 21 days, subcutaneous route (s.c.)	Promote neurogenesis and increase dendritic arborizations in hippocampus	Bortolotto et al. [49]
	Cell culture from C57BL/6 J mice and congenic BALB/c β_2AR-deficient mice	Continuous infusion of extremely low doses (1 ~ 10 μg/kg/day), 2 weeks	At low dose: neuroprotective effect and anti-inflammatory effect by reducing of LPS-mediated ROS, TNF-α and NO production	Qian et al. [57]
Isoproterenol (agonist)	BL6/129 mice intoxicated by Aβ peptide	Chronic, 0.1 g/L for 4–6 weeks, daily drinking water	Decrease microglia inflammation, improve Aβ peptide degradation	Xu et al. [59]
	Ischemic rats	Acute 50 μg/kg	Reduction of blood glutamate levels, neurological improvement after traumatic brain injury	Zlotnik et al. [55]
Isoproterenol, salmeterol	Human primary hippocampal neuron culture intoxicated by Aβ peptide	Isoproterenol (dissolved in water, 1–100 μM), salmeterol (dissolved in DMSO, 100 nM–10 μM)	Neurotrophic effect, inhibition of Aβ-induced oxidative stress, neuroprotection against Aβ peptide	Counts and Mufson [50]

(Continues)

TABLE 4 | (Continued)

Molecules	Models	Administration	Pharmacological effects	References
Clenbuterol, salmeterol vs. ICI-118551, butaxamine	Primary cultures of hippocampal neurons and glial cells	Clenbuterol (1–100 μM), salmeterol (0.001–1 μM), ICI-118551 (10 μM), butaxamine (10 μM)	Clenbuterol and salmeterol induce astrocyte activation by β_1AR and β_2AR and cerebroprotective effects by β_2AR stimulation	Junker et al. [87]
ICI-118551 (antagonist)	mice 3xTg	Chronic, 1 mg/kg, daily i.p. injections for 6 weeks	Aβ peptide production, exacerbate cognitive decline, tau protein hyperphosphorylation and accumulation to form NF tangles	Branca et al. [10]
	Acutely stressed C57 mice	Acute, 1 mg/kg, i.p. route	Decrease $A\beta_{1\text{-}40/1\text{-}42}$ peptide production	Yu et al. [72]
	Mice APPswe/PS1ΔE9	Chronic, 1 mg/kg, oral route, daily for 30 days	Decrease Aβ peptide level	Patent US20120004254 [88]
	SH-SY5Y neuroblastoma cells	10–100 μM	Protect SH-SY5Y cells against staurosporine-induced apoptosis through a dual action on the mitochondria and on caspase 9	Mikami et al. [89]
Butaxamine or butoxamine (antagonist)	Mice APPswe/PS1		Behavioral test (escape latency): improvement of cognitive ability	Patent US20120004254 [88]
Deletion of the β_2AR gene	Mice PS1/APP (β_2-KO) mice overexpressed tau		Decrease tau protein phosphorylation. β_2AR-signaling regulates Aβ-induced tau phosphorylation. Alleviate tauopathy	Wang et al. [78] Wisely et al. [79]

research on new orthosteric agonists. A review of patents from 2015 to 2020 highlights this decline [28]. This may be explained by the existence of compounds that are already very effective, selective, and well-tolerated. Now, research on β_2AR ligands seems to be focused more on the development of allosteric modulators aimed at achieving biased pharmacological activity. Although numerous studies exist on negative modulators [99, 100], to our knowledge, only one team has been able to develop a positive allosteric modulator (PAM) [101, 102]. The advantage of this highly selective modulator is the ability to reduce the effective doses of the agonists used in parallel.

One pathway that remains underexplored is the design of β_2AR agonists with chemical targeting, such as the development of prodrugs of existing compounds: BRL-47672 for clenbuterol and bambuterol for terbutaline [103, 104]. It is also possible to consider the design of prodrugs targeting the CNS: such as "bio-oxidizable" prodrug strategy [105], and light activation strategies (optopharmacology) [106, 107].

Finally, given the complexity of the β_2AR signaling pathway, targeting these receptors alone could appear to be limited in the treatment of AD [108]. The development of ligands targeting both β_2AR and other pathological pathways involved in AD may be envisaged, notably through the pleiotropic ligand or multi-target directed ligands (MTDLs) approach. This concept involves combining two or more pharmacophores or structures active on known targets. This makes it possible to treat several molecular causes by administering a single molecule, to achieve synergistic action and reduce the adverse effects associated with drug interactions [109, 110].

In vitro studies with bambuterol analogs have shown inhibition of butyrylcholinesterase (BChE), an enzyme that metabolizes acetylcholine involved in the functioning of cholinergic transmission [111, 112]. In AD patients, BChE activity tends to increase, which decreases presynaptic acetylcholine levels. This explains the decline in cholinergic neurotransmission found in AD patients. A patent (WO2019202400) on the use of bambuterol in the treatment of AD has shown a neuroprotective effect, reduced tau protein hyperphosphorylation and synaptic preservation in rat hippocampal neuronal cultures intoxicated with Aβ peptide [113, 114]. Furthermore, intranasal administration of bambuterol in AD mice model was beneficial for long-term spatial memory impairment and neuronal survival, while reducing peripheral adverse effects. Based on the therapeutic benefits of pleiotropic ligands, new MTDLs ligands can be developed using other selective β_2AR agonists to find an effective treatment for AD.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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