Review Article

Cellular responses and functions of α7 nicotinic acetylcholine receptor activation in the brain: a narrative review

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Abstract: The α7 nicotinic acetylcholine receptor (α7nAChR) has been studied for many years since its discovery. Although many functions and characteristics of brain α7nAChR are widely understood, much remains to be elucidated. The α7nAChR is widely expressed in the central nervous system, not only in neurons but also in astrocytes, microglia, and endothelial cells. α7nAChR can be activated by endogenous agonist like acetylcholine or exogenous agonists like nicotine and PNU282987. Its agonists can be divided into selective agonists and non-selective agonists. The activation of α7nAChR results in a series of physiological processes which have both short-term and long-term effects on cells, for example, calcium influx, neurotransmitter release, synaptic plasticity, and excitatory transmission. It also induces other downstream events, such as inflammation, autophagy, necrosis, transcription, and apoptosis. The cellular responses to α7nAChR activation vary according to cell types and conditions. For example, α7nAChR activation in pyramidal neurons leads to long-term potentiation, while α7nAChR activation in GABAergic interneurons leads to long-term depression. Studies have also shown some contradictory phenomena, which requires further study for clarification. Herein, the cellular responses of α7nAChR activation are summarized, and the functions of α7nAChR in neurons and non-neuronal cells are discussed. We also summarized contradictory conclusions to show where we stand and where to go for future studies.

Keywords: α7 nicotinic acetylcholine receptor (α7nAChR); signaling pathway; central nervous system diseases (CNS diseases); calcium influx; synaptic plasticity

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Introduction

Nicotinic acetylcholine receptors (nAChRs) are cholinergic receptors which are activated by the endogenous neurotransmitter acetylcholine (1). Distinct from muscarinic acetylcholine receptors, nAChRs can also respond to nicotine, belonging to the cys-loop superfamily of receptors (2,3). The nAChR is a pentameric ligand-gated ion channel containing 5 homometric or heteromeric subunits (4). In total, 9 subunits have been found, and are named as α2-7 and β2-4 (2,5,6). These 9 subunits can form different types of nAChRs, for example $(\alpha4)_3(\beta2)_2$ nAChR,

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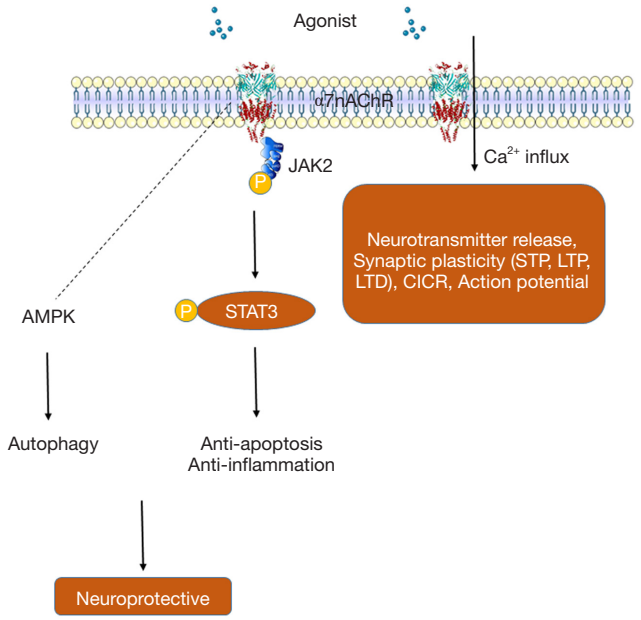

Figure 1 Cellular responses to α7nAChR activation. The activation of α7nAChR can lead to calcium influx directly, which can trigger neurotransmitter release, action potentials, synaptic plasticity, and calcium-induced calcium release. It can also activate the JAK2-STAT3 signaling pathway and further induce anti-apoptotic and anti-inflammatory effects. In addition, it also activates the AMPK-mTOR signaling pathway and induces autophagy. α7nAChR, α7 nicotinic acetylcholine receptor.

$(\alpha4)_2(\beta3)_3$ nAChR, and $(\alpha3)_2(\beta4)_3$ nAChR. The α7 nicotinic acetylcholine receptor (α7nAChR) is a special subtype of nAChR which consists of 5 homometric α7 subunits.

The α7nAChR is widely expressed in the central nervous system (CNS), not only in neurons but also in astrocytes, microglia, and endothelial cells (7-9). It is one of the most well-studied ionotropic receptors. In neurons, it is believed that α7nAChR plays an important role in synaptic plasticity, contributing to dependence, learning, memory, and other cognitive functions (10,11). The activation of α7nAChR can also contribute to neurotransmitter release, calcium influx, neuronal excitability, and other cellular activities (12-15). Studies have also revealed that the activation of α7nAChR in microglia can induce anti-inflammatory effects (16,17). As several benefits have been found, α7nAChR is considered a promising therapeutic target in CNS diseases, such as psychiatric disorders including autism and schizophrenia, neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD), and cerebrovascular diseases including hemorrhage stroke and ischemic stroke (18-21). Although, there were many reviews about α7nAChR in the brain, many of them were focused on certain disease or were out of date. Some even reported contradictory conclusions. In this review, we will summarize recent researches on α7nAChR in the brain and give an update snapshot of where we stand and where to head for in area of α7nAChR. This review will summarize the cellular responses to α7nAChR activation and its different roles in various types of brain cells. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-21-273).

Cellular responses to α7nAChR activation

As a ligand-gated ion channel, the activation of α7nAChR can lead to a series of cellular responses, including but not limited to calcium influx, neurotransmitter release, synaptic plasticity, and excitatory transmission (12-15). It also induces other downstream events, such as inflammation, autophagy, necrosis, transcription, and apoptosis (*Figure 1*).

α7nAChR and calcium influx

When the agonist binds to the ligand-binding domain of α7nAChR, the channel, which is composed of 5 α7 subunits, opens to let cations through. The α7nAChR has a high permeability to calcium (22). To determine this important physiological parameter, early studies used heterologous systems and reported permeability ratios of P_{Ca}/P_{Na} as high as 15 to 20 (3,23). However, Castro and Albuquerque used ion activities and the Goldman-Hodgkin-Katz equation for reversal potentials shifts to calculate the permeability ratios of Ca^{2+} in cultured rat hippocampal neurons. The results showed that the permeability ratio of P_{Ca}/P_{Na} was 6.1±0.5, which was much lower than the results determined by heterologous systems (24). The difference in permeability may be due to the different conditions. Another method to detect the Ca^{2+} permeability of α7nAChR are fluorescent Ca^{2+} indicators (25,26). This method records fluorescence signals and transmembrane currents simultaneously, and maintains good control of cell voltage and excludes any form of Ca^{2+}-induced Ca^{2+} release (CICR) (25). The result is displayed as fractional calcium current (P_f), indicating the percentage of the total current flowing through an ion channel which is carried by Ca^{2+}. A study showed that the P_f value of human neuronal α7nAChR was 11.6%, indicating α7nAChR has a high calcium permeability (27). The

activation of α7nAChR not only raises cytoplasmic Ca^{2+} directly, but also indirectly. For example, the activation of α7nAChR can depolarize neurons, and then induce calcium influx indirectly by voltage-dependent calcium channels (VDCCs) (28). Furthermore, α7nAChR-mediated rising cytoplasmic calcium is partly caused by CICR from the endoplasmic reticulum (29). These are the 3 main ways that α7nAChR can induce increased cytoplasmic Ca^{2+}.

α7nAChR and neurotransmitter release

Neurotransmitter release usually occurs in the presynaptic membrane (30). The main processes of synaptic vesicle exocytosis and neurotransmitter release include: (I) the action potential arrives at the presynaptic terminals and depolarizes the terminal membrane; (II) the depolarized membrane induces calcium influx through VDCCs which dramatically increases the calcium concentration in the cytoplasm near the presynaptic membrane; (III) Ca^{2+} entry contributes to conformational changes in specific proteins in synaptic vesicles, leading to the fusion of synaptic vesicles to the presynaptic membrane. The whole process is an instantaneous response to the action potential, which lasts only a millisecond (31). Although neurotransmitter release is mainly triggered by VDCCs, in certain circumstances, α7nAChR-mediated Ca^{2+} influx is sufficient to induce synaptic vesicles to release neurotransmitters. Gray *et al.* reported that nicotine acts on presynaptic α7nAChR to enhance glutamatergic transmission in the hippocampus (13). It was also shown that activation of α7nAChR in the presynaptic terminals of GABAergic neurons could increase GABA input to 5-HT dorsal raphe nucleus (DRN) neurons and lead to inhibitory postsynaptic spontaneous currents (32). This effect was triggered by α7nAChR-mediated CICR in DRN GABAergic terminals.

However, neurotransmitter release is not only modulated by α7nAChR-mediated calcium changes, but is also regulated by α7nAChR-related signal transduction. Evidence has shown that the release of dopamine could be enhanced by the activation of α7nAChR, which was modulated through protein kinase C (33,34).

α7nAChR and synaptic plasticity

Synaptic plasticity, such as short-term potentiation (STP), long-term potentiation (LTP), or long-term depression (LTD), is a neuronal property characterized by the ability of synapses to strengthen or weaken in response to their increased or decreased activity (35-37). Accumulating evidence suggests that it is one of the most important neurological foundations of learning and memory (38-40). Researchers found that in CA1 pyramidal neurons of the hippocampus, properly timed nicotine-mediated nAChR activation could contribute to the induction of LTP via presynaptic and postsynaptic pathways (41). The results showed that α7nAChR contributed to most of these effects (41). However, different kinds of neurons had different outcomes. For GABAergic interneurons, the excitation caused inhibition of nearby pyramidal neurons, and the activation of α7nAChR-mediated synaptic plasticity led to LTD (41). This synaptic plasticity is associated with α7nAChR-mediated neurotransmitter release at the presynaptic membrane as well as α7nAChR-mediated postsynaptic depolarization and calcium signals (41). Nitta *et al.* reported that infusion of β-amyloid protein into cerebral ventricles for 14 days could lead to impairments in learning and cholinergic neuronal degeneration (42). Furthermore, Chen *et al.* reported a series of impairments in CA1 hippocampal slices, including basal synaptic transmission, LTP, post-tetanic potentiation (PTP), and paired-pulse facilitation (PPF) after continuous intracerebroventricular infusion of β-amyloid protein (43). They also found that activation of α7nAChR was required for LTP induction, highlighting the association between α7nAChR and synaptic plasticity (43). In addition to learning and memory, synaptic plasticity also participates in neuronal connections. Criscuolo *et al.* reported that they found impaired synaptic plasticity in the visual cortex of α7nAChR knockout mice, indicating that α7nAChR contributes to visual cortex function (44).

α7nAChR and anti-inflammatory effects

The relationship between the nervous system and the immune system has been studied for several decades, and it has been consistently demonstrated that these 2 systems interact with each other. Researchers found that stimulation of the vagus nerve could attenuate inflammation by inhibiting macrophage tumor-necrosis factor (TNF) release (45). Further results suggested that this phenomenon was mediated by α7nAChR responding to acetylcholine (45-47). Hence, the anti-inflammatory effect of the vagal nerve is termed the "cholinergic anti-inflammatory pathway (CAP)" (45,46).

The α7nAChR is widely expressed in cells of the immune system, such as macrophages, monocytes, and lymphocytes

(48-50). Pinheiro *et al.* reported that treatment with PNU282987, an α7nAChR agonist, could reduce LPS-induced acute lung injury through reducing neutrophil recruitment and IL-1β, TNF-α, and IL-6 levels via changing the macrophage profile (51). Our lab also found that combination treatment with anisodamine (antagonist of muscarinic acetylcholine receptors) and neostigmine (cholinesterase inhibitor), which promoted the binding of endogenous acetylcholine to α7nAChR, could rescue crush syndrome by reducing inflammation, and this phenomenon was absent in α7nAChR knockout mice (52). Several studies have revealed that the attenuation of inflammatory cytokine release from macrophages by activating α7nAChR was through the JAK2/STAT3 signaling pathway (16,52-54).

In addition to the roles of α7nAChR in the peripheral CAP, many studies have investigated whether such roles exist in the CNS. In the brain, microglia are the resident immune cells, and the activation of these cells accounts for neuroinflammation (55,56). Shytle *et al.* reported for the first time that the brain CAP regulated microglial activation through α7nAChR, and pretreatment with nicotine could reduce LPS-induced TNF-α release (47). Furthermore, De Simone *et al.* also demonstrated the existence of the CAP in the brain and the expression of α7nAChR in microglia, and found that nicotine enhanced the expression of cyclooxygenase-2 and the synthesis of one of its major products, prostaglandin E2 (12). Our lab also demonstrated *in vivo* that activation of microglial α7nAChR by PNU282987 reduced the production of IL-6, IL-1β, IL-18, and TNF-α, thereby alleviating experimental autoimmune encephalomyelitis (57,58).

α7nAChR and autophagy

Autophagy or "self-eating" is, as its name suggests, a basic cellular process that degrades and recycles misfolded or long-lived proteins and damaged organelles (59). Evidence has shown that autophagy is involved in the pathophysiological changes in many CNS diseases (60-65). Hung *et al.* found that α7nAChR could bind with amyloid β (Aβ) and internalize into the cytoplasm to further inhibit Aβ-induced neurotoxicity through autophagy (66). They further demonstrated *in vivo* and *in vitro* that overexpression of LC3 led to neuroprotective effects by increasing α7nAChR expression, which increased binding to Aβ and enhanced autophagy activity (67). Jeong *et al.* also found that α7nAChR could be modulated and upregulated by melatonin, which enhanced autophagy and exerted neuroprotective effects on prion diseases (68). Our lab has focused on α7nAChR for many years and found that activation of α7nAChR by PNU282987 enhanced microglia autophagy and suppressed neuroinflammation in experimental autoimmune encephalomyelitis mice (57). Enhanced autophagy induced by α7nAChR activation was mediated by AMPK-mTOR-P70S6K signaling pathway activation (57). Interestingly, Hou *et al.* reported that autophagy was inhibited by α7nAChR activation using PNU282987 and induced protection against myocardial ischemia/reperfusion injury *in vivo* and hypoxia/reoxygenation injury in primary cardiomyocytes *in vitro* (69). They demonstrated that these effects were mediated by JAK2 and PI3K activation in cardiomyocytes (69). These different phenomena in microglia and cardiomyocytes indicate that the relationship between autophagy and α7nAChR activation varies in different organs or cells (70).

α7nAChR and anti-apoptotic effects

It has been demonstrated that activation of α7nAChR can affect cellular apoptosis (71-73). De Rosa *et al.* reported that nicotine upregulated α7nAChR in human lymphocytes, which then decreased cortisol-induced apoptosis (71). However, the authors did not address the underlying mechanisms of this finding. Furthermore, Hejmadi *et al.* found that the presence of nicotine could protect primary cortical neurons against apoptosis induced by oxygen deprivation, which was mediated by 2 subtypes of nAChR, including α7nAChR and β2nAChR (74). Further studies have revealed the mechanisms of nicotine-mediated anti-apoptotic effects. Toborek *et al.* reported that the anti-apoptotic effect of α7nAChR activation in spinal cord neurons was dependent on increased phosphorylated ERK1/2 and total ERK1/2 activity, indicating that the ERK1/2 signaling pathway was involved in the anti-apoptotic effects of nicotine (75). It is interesting that different signaling pathways involved in α7nAChR-mediated anti-apoptotic effects have been found by researchers. Parada *et al.* found that PNU282987 could rescue rotenone and oligomycin A-induced apoptosis via the JAK2/PI3K/Akt cascade in SH-SY5Y cells (72). In addition, Marrero and Bencherif reported that nicotine induced anti-apoptotic effects targeting α7nAChR mainly through JAK2 activation, increased NF-κB, and the production of Bcl-2 in PC12 cells (73). It is interesting that different signaling pathways have been found to be involved in the same phenomenon. This may be due to the different cells and different stimuli

used in studies.

Functions of α7nAChR in neurons and non-neuronal cells

α7nAChR in neurons

The α7nAChR is widely expressed in neurons. It is also found in different locations in neurons, including the presynaptic membrane, postsynaptic membrane, and perisynaptic sites (76,77). The activation of α7nAChR in neurons mainly leads to calcium-dependent events and a variety of other downstream signaling events which depend on receptor location. In general, activation of α7nAChR leads to calcium influx which increases Ca^{2+} levels in neurons, triggering downstream responses (13,78,79). The basic neuronal physiological functions cannot be achieved without α7nAChR. Activation of α7nAChR in the presynaptic membrane leads to transmitter release, which contributes to synaptic transmission. Also, the effect of transmitter release induced by α7nAChR does not need other forms of calcium influx like VDCCs or CICR (13). Postsynaptic α7nAChR activation participates in intracellular signaling cascades and downstream processes. The most important function is to influence synaptic plasticity related to learning, memory, and addiction (80-82). As discussed above, properly-timed activation of α7nAChR produces LTP or LTD, which remodels and strengthens connections within neuronal networks.

Furthermore, many studies have reported that α7nAChR activation can have anti-apoptotic effects on neurons (83-85). A series of signaling pathways involved in the anti-apoptotic effects mediated by α7nAChR have been uncovered. Huang *et al.* reported that neuroprotection by nicotine against colchicine-induced neuronal apoptosis was mediated by the PI3K/Akt signaling pathway (85). Also, Yu *et al.* demonstrated that α7nAChR activation reduced β-amyloid-induced neuronal apoptosis through the PI3K signaling pathway (86). However, Chen *et al.* reported that the α7nAChR agonist PHA568487 inhibited neuronal apoptosis through the TLR/Myd88/NF-κB signaling pathway (83).

Moreover, as mentioned above, Hung *et al.* reported that α7nAChR could induce Aβ transport into the cytoplasm and promote degradation through autophagy in SH-SY5Y cells (66). Jeong and Park also indicated that α7nAChR upregulated autophagy in SH-SY5Y cells and protected against prion-mediated mitochondrial neurotoxicity (68). In summary, α7nAChR activation not only contributes to instantaneous processes such as calcium influx and neurotransmitter release, which comprise basic neuronal functions, it also participates in long-term effects like synaptic plasticity, and influences intracellular signaling pathways to produce anti-apoptotic effects and increased autophagy.

α7nAChR in astrocytes

Astrocytes are star-shaped glial cells in the CNS. According to the research, astrocytes in the brain account for 20% to 40% of all glial cells. For a long time, scientists regarded astrocytes as merely support cells for neurons. However, many important functions have been recently uncovered, including but not limited to the regulation of neurotransmitters, the maintenance of the blood-brain barrier (BBB), the formation of the tripartite synapse, metabolic support, glucose sensing, the regulation of ion concentration in the extracellular space, and the repair of CNS injury through glial scar formation (87-95).

The α7nAChR is also distributed in astrocytes and its activation can influence cellular functions (96). Teaktong *et al.* reported that the expression of α7nAChR in astrocytes was increased in AD compared to that in dementia with Lewy bodies, which might contribute to alterations in calcium homeostasis and nitric oxide production in response to Aβ-mediated inflammation in AD (97). Yu *et al.* also found a significant increase of α7nAChR expression in astrocytes in patients with AD or in patients carrying the Swedish APP 670/671 mutation, however, it was more pronounced in patients carrying the Swedish APP 670/671 mutation (98). They further indicated that the increased expression of α7nAChR in astrocytes was positively correlated with the extent of pathological changes, especially the number of neuritic plaques in AD patients, which indicates its important role in the pathogenesis of AD (98). Although these studies demonstrated the relationship between α7nAChR in astrocytes and CNS diseases, they did not describe the exact roles of α7nAChR in these diseases. Later, Liu *et al.* reported the protective effect of α7nAChR against dopaminergic neuron loss in a PD model via inhibition of astrocyte activation (99). In contrast to this finding, Talantova *et al.* reported that Aβ induced astrocytic glutamate release through α7nAChR, which activated extrasynaptic NMDA receptors on neurons and damaged synapses in AD (100). Taken together, α7nAChR activation in astrocytes can lead to different

effects under different conditions, which may be dependent on various ligands or brain regions.

α7nAChR in microglia

Microglia are the brain's resident immune cells, which contribute to CNS inflammation. Decades ago, Wang *et al.* demonstrated that α7nAChR was essential for acetylcholine inhibition of macrophage TNF-α release, which was named CAP (45). Whether its counterpart microglia also had this effect was a mystery until Shytle and colleagues uncovered it in their study (47). For the first time, Shytle *et al.* indicated that α7nAChR was expressed in primary cultured microglial cells and brain slices (47). In addition, pretreatment with acetylcholine and nicotine inhibited LPS-induced TNF-α release in microglial cells, and this effect could be attenuated by α-bungarotoxin, a α7nAChR antagonist (47). Many other studies have also demonstrated this effect (101-107). However, Thomsen *et al.* found that blockade of α7nAChR by the antagonists methyllycaconitine (MLA) and NS6740 reduced LPS-induced microglia TNF-α release, which indicated that the α7nAChR-induced anti-inflammatory effects of microglia were not due to calcium influx through ion channels (108).

Furthermore, Suzuki *et al.* also reported that the nicotine-induced increase in microglia intracellular Ca^{2+} levels was independent of extracellular Ca^{2+}, and this effect could be blocked by the phospholipase C (PLC) inhibitor U73122 and the inositol trisphosphate (IP_3) receptor blocker xestospongin C (101). In addition, nicotine-modulated LPS-mediated TNF-α release was also blocked by U73122 and xestospongin C (101). They suggested that nicotine triggered intracellular Ca^{2+} increases in microglia and their anti-inflammatory effects, which were mediated through the activation of PLC and Ca^{2+} release from the endoplasmic reticulum (101). Other signaling pathways involved in α7nAChR-mediated microglial anti-inflammatory effects have also been uncovered. Parada *et al.* discovered a new signaling pathway involved in α7nAChR-mediated neuronal protection in ischemic stroke (104). They suggested that activation of α7nAChR in microglia contributed to the CAP through nuclear factor erythroid-2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) activation, leading to neuroprotective effects in ischemic stroke (104). Morioka *et al.* also suggested a novel mechanism of microglial α7nAChR-mediated neuroprotection beyond anti-inflammatory effects (109). They reported that treatment of microglia with nicotine significantly increased the expression of the glutamate/aspartate transporter (GLAST), which is the main transporter in microglia, and increased glutamate uptake (109). The upregulation of GLAST was mainly through the IP_3 and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) signaling pathway (109).

α7nAChR in cerebrovascular endothelial cells

It was first reported in 2001 by Wang *et al.* that α7nAChR was expressed in human bronchial epithelial and endothelial cells (110). They used both western blot and immunohistochemistry with an anti-α7nAChR antibody and demonstrated that α7nAChR was expressed in human aortic endothelial cells (110). They also used patch-clamp and found that the presence of fast desensitization currents activated by acetylcholine and nicotine could be blocked by MLA and α-bungarotoxin, thus further demonstrating the presence of α7nAChR in endothelial cells (110). In spite of this discovery, they still did not know the exact role of α7nAChR. In 2006, Li and Wang reported that the α7nAChR agonist choline increased α7nAChR expression, proliferation, and tube formation in human umbilical vein endothelial cells (HUVECs), and this phenomenon could be reversed by applying the antagonist α-bungarotoxin *in vitro* (111). They also investigated capillary density in a myocardial infarction (MI) rat model and reported that an α7nAChR agonist increased capillary density in infarct tissues while the antagonists reversed this effect (111). This study indicated that activation of α7nAChR could contribute to angiogenesis.

Ng *et al.* investigated the relationship between α7nAChR and angiogenesis (112). They found that nicotine could dose-dependently enhance human microvascular endothelial cell (HMVEC) migration, which is a key process in angiogenesis (112). Furthermore, the induction of angiogenesis by other growth factors, including fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), also relied on the activation of α7nAChR, as their effect was abolished or attenuated after treatment with the α7nAChR antagonist α-bungarotoxin (112). Wu *et al.* also detected the mRNA expression of α7nAChR by RT-PCR in a series of human endothelial cell types: human pulmonary arterial endothelial cells (HPAEC), HMVECs, HUVECs, and human retinal endothelial cells (HREC) (113). Consistent with previous studies, they found that α7nAChR was expressed in these cell types, however, there were differences in the levels of expression (113). Higher

Table 1 Studies show contradictory findings

Related functions	Author/year	Cell type/region	Primary findings	Species
α7nAChR and synaptic plasticity	Ji D *et al.* (2001)	GABAergic interneuron	Activation of α7nAChR by Ach can mediate synaptic plasticity leads to LTD, which can be blocked by methyllycaconitine (MLA)	Mouse
	Chen L *et al.* (2006)	Brain hippocampal slice	Activation of α7nAChR by [3-(2,4-dimethoxybenzylidene)-anabaseine] (DMXB) can induce LTP which can be blocked by MLA or alpha-bungarotoxin (alpha-BTX)	Rat
α7nAChR and autophagy	Hou Z *et al.* (2018)	Cardiomyocyte	Activation of α7nAChR by PNU282987 inhibits Beclin-1 associated autophagy and reduces cardiomyocyte injury induced by hypoxia/reoxygenation	Rat
	Shao BZ *et al.* (2017)	Microglia	Activation of α7nAChR by PNU282987 enhanced microglia autophagy and suppressed neuroinflammation	Mouse
α7nAChR and anti-apoptosis effect	Parada E *et al.* (2017)	SH-SY5Y	PNU282987 can rescue rotenone and oligomycin A induced apoptosis via JAK2/PI3K/Akt cascade	Human
	Marrero and Bencherif (2009)	PC12	Activation of α7nAChR induces anti-apoptosis effect through JAK2 activation and increasing NF-κB and Bcl-2	Mouse
α7nAChR in astrocytes	Liu Y *et al.* (2012)	Astrocyte and dopaminergic neuron	Activation of α7nAChR has protective effect against dopaminergic neuron loss in PD model via inhibition of astrocyte activation	Mouse
	Talantova M *et al.* (2013)	Astrocyte and neuron	Amyloid-β binds to α7nAChR to induce release of astrocytic glutamate, which activates NMDA receptors and damages synapse in AD	Rat, mouse, and human
α7nAChR in cerebrovascular endothelial cells	Abbruscato TJ *et al.* (2002)	Brain microvessel endothelial cells	Nicotine and cotinine can increase permeability of blood-brain barrier under hypoxia condition and reduce expression of ZO-1, which canbu reversed by α7nAChR antagonist PHA543613 can decrease permeability of blood-brain barrier and increase expression of claudin-5 by activating α7nAChR	Bovine
	Kimura I *et al.* (2018)	Brain endothelial cells		Rat

α7nAChR, α7 nicotinic acetylcholine receptor; LTD, long-term depression; LTP, long-term potentiation; AD, Alzheimer's disease.

α7nAChR expression was detected in HUVECs (113). They also reported that α7nAChR plays a dominant role in nicotine-induced cell signaling and endothelial cell migration, proliferation, and tube formation (113).

In spite of the positive effects of α7nAChR activation in these endothelial cells, studies in cerebrovascular endothelial cells showed contrasting results. Abbruscato and colleagues reported in 2002 that nicotine and its metabolite, cotinine, could increase the permeability of the BBB in a bovine brain microvessel endothelial cell model under hypoxic condition (114). Furthermore, nicotine and cotinine reduced the expression of ZO-1 (tight junction protein) which could be reversed by the α7nAChR antagonist α-bungarotoxin, indicating that both the nicotine and cotinine-induced effects were mediated by the α7nAChR (114). However, Kimura *et al.* reported different results in 2018. They demonstrated that the selective α7nAChR agonist PHA543613 decreased the permeability of the BBB and increased the expression of claudin-5 and occludin, which are key tight junction components (115). Additionally, they did not show a positive effect of nicotine. The different results may be due to the different agonists and different *in vitro* models used in studies.

Conclusions

Based on the discussion above, evidence from *in vivo* and *in vitro* studies has shown significant cellular responses to α7nAChR activation. However, some results are contradictory and require further study (*Table 1*). For example, although α7nAChR is a ligand-gated ion channel, it can also increase intracellular cAMP levels through adenylate cyclase 1 (AC1), which is a common signaling pathway of G protein coupled receptors (116). Does

α7nAChR activate AC1 directly or indirectly? The cellular responses and functions of α7nAChR in the brain show promising therapeutic effects in CNS diseases. The many benefits of α7nAChR activation in the CNS may be the reason why smokers are at a lower risk of developing PD compared with non-smokers (117). As α7nAChR has various effects on cells, agonists, antagonists, and other allosteric modulators are widely used in many animal models to study CNS diseases. Many agonists or allosteric modulators are involved in clinical trials to treat CNS diseases. However, whether these α7nAChR targeting drugs have adverse effects or not should be studied in-depth.

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