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Review Article

Molecular mechanisms of α7-nAchR-mediated anti-inflammatory effects

Mahmoud Elsaid Youssef[1], Yasser Moustafa[2], Heba Abdelrazek[3]

[1]Department of Pharmacology and Biochemistry, Delta University for Science and Technology, Mansoura, Dakahlia, [2]Department of Pharmacology and Toxicology, Suez Canal University, [3]Department of Physiology, Suez Canal University, Ismailia, Egypt.

***Corresponding author:**
Mahmoud Elsaid Youssef, Department of Pharmacology and Biochemistry, Delta University for Science and Technology, International Coastal road, Mansoura 35511, Dakahlia, Egypt.

mahmoodelsaid@hotmail.com

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ABSTRACT

The cholinergic anti-inflammatory pathway is described as an interaction between the nervous system and the immune system. This interaction is regulated by the α7 subtype of cholinergic nicotinic Ach receptors (α7-nAchR), which leads to a marked decrease in the inflammatory cytokines, such as interleukin (IL)-1β, IL-6 and tumour necrosis factor α. Several ligands that interact with α7-nAchR have been recently discovered. These ligands vary in their source, chemical structure, selectivity, potency and efficacy. Activation of α7-nAchR either selectively or non-selectively showed an anti-inflammatory effect that could be due to the inhibition of inflammatory signalling pathways such as Toll-like receptor 4/nuclear factor kappa B inflammasome and mammalian target of rapamycin-mediated autophagy pathways. In addition, it was proved that continuous activation of α7-nAchR could stimulate several anti-inflammatory signalling mechanisms, including Janus activated kinase-2/signal transducer and activator of transcription 3, nuclear factor erythroid 2-related factor 2/HO-1 and adenosine monophosphate-activated protein kinase signalling. In this review, we focused on the recent discoveries of α7-nAchR agonists and antagonists and their anti-inflammatory mechanisms.

Keywords: α7-nAchR, Inflammation, Cholinergic anti-inflammatory pathway, Toll-like receptor 4, Nuclear factor kappa B, Janus activated kinase-2, Signal transducer and activator of transcription 3, Mammalian target of rapamycin, Nuclear factor erythroid 2-related factor 2, HO-1, Adenosine monophosphate-activated protein kinase

INTRODUCTION

The cholinergic anti-inflammatory pathway was subjected to many studies since its discovery. Catabolite activator protein (CAP) is described as an interaction that occurs among the nervous and the immune systems. CAP is believed to be involved in the regulation of controls the inflammatory process.[1] This pathway is initiated by the stimulation of the afferent vagus nerve either by lipopolysaccharides (LPS) or pro-inflammatory cytokines.[2] The vagal signal is processed centrally through a muscarinic-receptors dependent pathway.[3] The initiated anti-inflammatory signal reaches the celiac-superior mesenteric plexus through the efferent vagus nerve.[4] The anti-inflammatory signal is transmitted to the spleen with the aid of the splenic nerve that is connected to efferent vagus nerve fibres.[5] Norepinephrine is released at the terminal of the splenic nerve, leading to the activation of β_2 receptors and an increase in the expression of choline acetyltransferase enzyme that synthesises acetylcholine (Ach) in specialised T-lymphocytes.[6] Activated T-lymphocytes release Ach in the spleen, which stimulates α7 nicotinic Ach receptors (α7-nAchR) in macrophages, which leads to a downregulation in the pro-inflammatory cytokines expression[7] without affecting the anti-inflammatory cytokines levels. CAP was previously studied in human monocytes after exposure to LPS. Treatment with nicotine led to a marked

decrease in the plasma levels of inflammatory cytokines such as interleukin 1β (IL-1β), IL-6 and tumour necrosis factor α (TNF-α) in previously challenged human monocytes by LPS through activation of α7-nAchR,[8] whereas, the plasma levels of anti-inflammatory cytokines such as IL-10 were not affected.[9] In addition, the role of α7-nAchR was confirmed by subjecting monocytes with the knockout α7-nAchR gene to LPS.[10] These experiments have revealed the crucial role of α7-nAchR in regulating CAP. It is believed that the anti-inflammatory effect that mediated by α7-nAchR could be due the attenuation of several inflammatory pathways. This review article describes the different agonists and antagonists of α7-nAchR. In addition, we reviewed the recent studies of these drugs in different animal models, including neuronal and non-neuronal effects, which are based on the activation of α7-nAchR. Finally, this review illustrates the molecular mechanisms that mediate the anti-inflammatory effect of α7-nAchR. We have reviewed research articles that focus on studying the mechanisms by which α7-nAchR prevent inflammation in various animal models of inflammatory diseases.

α7-nAchR

nAchR are member of the Cys-loop ligand-gated ion channel superfamily, which also includes serotonin subtype 3 (5-HT_3) receptors and γ-aminobutyric acid receptors (GABA).[11] nAchR participates in several physiological functions, as they control the contraction of skeletal muscles in the neuromuscular junction and regulate the ganglionic functions in the autonomic nervous system. In addition, nAchR are found in non-neuronal cells, such as endothelial cells, glial cells and immune cell where in these sites, α7-nAchR regulate anti-inflammatory and angiogenic responses. nAchR are formed by the assembly of five subunits that are arranged symmetrically in the form of a ring with a concentric channel through which selective cations pass.[12,13] Each subunit is composed of hydrophobic transmembrane domains specified as M1 through M4, an intracellular loop between M3 and M4 and extracellular N-terminal.[14] nAchR are widely distributed in the central nervous system, peripheral nervous system, muscles and many other tissues. They are the primary receptors in the neuromuscular junction for controlling skeletal muscle contraction. In the autonomic ganglia, they transmit signals from presynaptic neurons to post-synaptic neurons in both sympathetic and parasympathetic systems. Angiogenesis, in addition to the inflammatory response, is regulated by nAchR in blood vessels and immune cells by intracellular mechanisms.[15] nAchR subunits have been recognised and classified into muscle-type and neuronal-type subunits.[16] These subunits are subdivided into four subfamilies (I-IV) that are specified according to similarities in the protein sequence.[17] Besides, the subfamily III has been further divided into three subtypes [Table 1].

α7-nAchR are formed by the assemblage of five subunits of the α7 subtype. For this reason, α7-nAchR are considered homomeric receptors.[18] The α7-nAchR are expressed mainly in the hippocampus and prefrontal cortex, where they influence glutamatergic and GABAergic synapses.[19] There is substantial evidence for the contribution of α7-nAchR to synaptic potentiation of the hippocampus due to increased Ca^{++} permeability.[20] α7-nAchR participate in memory and learning. In addition, they have implications in some neurological disorders such as Parkinson's disease, schizophrenia[21] and Alzheimer's disease.[22] α7-nAchR are also expressed in immune cells such as lymphocytes, monocytes and macrophages their stimulation mediates CAP. In endothelial cells, furthermore, α7-nAchR are believed to regulate the angiogenesis process.

CLASSICAL AGONISTS

There is a high diversity of molecules that interact selectively and non-selectively with α7-nAchR [Table 2]. Therefore, a high number of α7-nAchR agonists and antagonists have been developed. α7-nAchR agonists are presented with structural diversity, whether they are separated naturally from animals or plants or they are completely synthesised. These well-known agonists are non-selective and differ in their potency and efficacy.[23] Ach is a non-selective endogenous agonist of all cholinergic receptors. However, its usage is confined due to the lack of selectivity between nicotinic and muscarinic receptors in addition to its short duration of action due to rapid hydrolysis. Atropine, a non-selective muscarinic antagonist, is usually given with Ach to improve its selectivity toward nAchR. However, choline, the metabolite of Ach hydrolysis, is a selective α7-nAchR agonist.[24] Anatoxin is a potent non-selective agonist that resembles Ach with 8 times more potency.[25] Carbachol, the carbamate analogue of Ach, is a weak nicotinic Ach agonist with more selectivity toward muscarinic receptors. It has a lower activity on α7-nAchR.[26]

Table 1: nAchR subunits.

Type	Neuronal-type					Muscle-type
Subfamily	I	II	III			IV
			i	ii	iii	
Subunit	α9	α7	α2	β2	β3	α1
	α10	α8	α3	β4	α5	β1
			α4			δ
						γ
						ε

The nAchR subunits are composed by the assembly of five subunits. This table shows the different 17 subunits, which comprise the different nAchR subfamilies

Table 2: α7-nAchR agonists and antagonists.

Drug	Selectivity	Activity	Key findings	Maximum *in vivo* dose
Classical agonists and antagonists				
Ach	All muscarinic and nAchR	Agonist		
Atropine	All muscarinic receptors	Antagonist		0.04 mg/kg
Choline	α7-nAchR	Agonist		60 mg/kg
Anatoxin	All nAchR	Agonist		0.4 mg/kg
Carbachol	nAchR	Weak agonist		1 mg/kg
	Muscarinic receptors	Strong agonist		
Epibatidine	All nAchR	Strong agonist		
Nicotine	All nAchR except α9-nAchR	Strong agonist		400 μg/kg
Cotinine	All nAchR	Weak agonist		
Synthetic α7-nAchR agonists				
A-582941	α7-nAchR	Partial agonist	• Improved negative symptoms of schizophrenia.[32] • Enhanced memory.[33] • Improved cognitive defects in schizophrenia.[31]	10 mg/kg
A-844606	α7-nAchR	Partial agonist	• Needs further investigations.[35]	
AR-R 17779	α7-nAchR	Strong agonist	• Cognitive enhancing activity[38,39] • Anti-inflammatory activity.[40] • Treatment of neurodegenerative diseases.[41]	2 mg/kg
	α4β2-nAchR	Weak agonist		
	α3β2-nAchR	Weak agonist		
	α3β4-nAchR	Weak agonist		
GTS-21	α7-nAchR	Partial agonist	• Treatment of dementia.[44] • Improved attention in schizophrenia.[45] • Cognitive enhancement.[46] • Management of neurodegenerative diseases.[47] • Treating nicotine addiction.[50] • Improvement of Alzheimer's disease.[51] • Anti-inflammatory.[53] • Attenuation of body wight loss.[56] • Reduces vascular permeability.[57]	10 mg/kg
	α4β2-nAchR	Weak antagonist		
PHA-543613	α7-nAchR	Strong agonist	• Neuroprotective activity.[59] • Treatment of Parkinson's disease.[60] • Cognitive enhancement.[58,61] • Treatment of dementia.[62,63] • Angiogenic.[64] • Reducing neuropathic pain.[66]	1 mg/kg
PNU-282987	α7-nAchR	Strong agonist	• Cognition enhancement.[68] • Treatment of Parkinson's disease.[72] • Reduced dopaminergic neurons loss.[73] • Anti-inflammatory effect.[75] • Prevented prolonged febrile seizures.[74] • Prevented the damage of retinal ganglion.[82]	30 mg/kg
	5-HT_3	Weak agonist		
Tropisetron	α7-nAchR	Partial agonist	• Improved P50 auditory suppression in schizophrenia.[84] • Improved cognitive dysfunction.[86] • Ameliorated the disruption of dopaminergic neurons.[88] • Attenuated morphine withdrawal symptoms.[90] • Anti-inflammatory effect.[92]	3 mg/kg
	α9α10	Strong antagonist		
	5-HT_3	Strong antagonist		
Antagonists of α7-nAchR				
α-bungarotoxin	α1β1γεδ-nAchR	Strong antagonist		
	α7-nAchR	Strong antagonist		
	α9 nAchR	Strong antagonist		
Methyllycaconitine	α7-nAchR	Strong antagonist		10 mg/kg
	α9-nAchR	Strong antagonist		
	α9α10-nAchR	Strong antagonist		
	α1β1γεδ-nAchR	Weak antagonist		

Another well-established, very potent, non-selective agonist is epibatidine. It showed α7-nAchR activity in the micromolar range.[27] Nicotine is the most common non-selective nAchR agonist. It activates all nAchR, except α9 receptors, at micromolar concentrations.[28] Nicotine is an alkaloid separated from tobacco and has been historically used to differentiate between different nAchR**.** The lipid solubility of nicotine is high, which accounts for its ability to cross the blood-brain barrier. It is metabolised to cotinine, which shows weak activity toward some nAchR.[29] The maximum response of nicotine is achieved by the administration of a subcutaneous dose of 400 μg/kg.[30]

SYNTHETIC α7-nAchR AGONISTS

A-582941

It is a partial selective α7-nAchR agonist with a high affinity. Its activity toward other nAchR is neglected. It was applied in different studies with variable doses ranging from 0.04 to 10 mg/kg.[31] A-582941 improved negative symptoms and cognition in the ketamine-induced model of schizophrenia in rats.[32] In another study, A-582941 enhanced memory and exhibited sustained pro-cognitive effects after repeated administration.[33] In addition, the administration of A-582941 in combination with other antipsychotic agents was not only useful for improving schizophrenia-associated cognitive defects but it also enhanced the efficacy against positive symptoms and minimised the motor adverse effects associated with these drugs.[31]

A-844606

This drug is derived from tilorone, a known interferon inducer that has a strong selectivity towards α7-nAchR.[34] In a study carried on monkeys and mice, A-844606 showed a high distribution capability in the mouse brain, whereas in monkeys, it was found in higher concentrations in the hippocampus and thalamus than in other brain areas such as the cerebellum. For this reason, it was believed that A-844606 could be a potential ligand for α7-nAchR in the human brain.[35]

AR-R 17779

It is one of the earliest developed selective α7-nAchR agonists.[36] It has a greater affinity for α7-nAchR than other nAchR, including α4β2, α3β2 and α3β4 subtypes.[37] AR-R 17779 is believed to possess cognitive enhancing activity besides its activity in improving social recognition memory in rats.[38,39] Activation of α7-nAchR by AR-R 17779 showed notable anti-inflammatory activity in microglial cells due to the upregulation of α7-nAchR.[40] In addition, AR-R 17779 could be used in the treatment of neurodegenerative diseases such as glaucoma by studying its neuroprotective effect using a purified retinal ganglion cell culture.[41] Moreover, AR-R 17779 activated CAP and ameliorated the post-operative ileus in mice through activation of α7-nAchR.[42]

GTS-21

GTS-21 was initially reported to have cognitive-enhancing activity due to activation of α7-nAchR,[43] then, it was considered a partial selective agonist to α7-nAchR. GTS-21 showed a promising findings in treating dementia when given to healthy male volunteers.[44] In addition, administration of GTS-21 to schizophrenic patients has improved attention and memorisation, which could be related to its ability to modulate the glutamate receptors.[45] The anti-amnesic effect of GTS-21 was investigated in different animal models where it ameliorated cognitive defects in mice injected with β-amyloid by enhancing glutamate activity through an α7-nAchR-mediated mechanism.[46] GTS-21 attenuated cognitive abnormalities and neurodegeneration induced by permanent occlusion of the main carotid arteries, suggesting its beneficial role in the management of neurodegenerative diseases.[47] Moreover, it mitigated the memory impairment induced by isoflurane in aged rats due to its neuroprotective effect.[48] In cerebral ischemia, GTS-21 not only improved memory and learning but also prevented delayed-neuronal death.[49] Furthermore, GTS-21 was investigated in treating nicotine addiction[50] and Alzheimer's disease.[51] Activation of CAP by GTS-21 attenuated many inflammatory conditions with variant anti-inflammatory mechanisms such as acute renal injury,[52] LPS-induced myocardial injury,[53] burn-induced inflammation[54] and hepatic injury induced by polymicrobial sepsis.[55] In addition, GTS-21 reduced the loss in the body and muscular mass, which may be associated with systemic inflammation[56] in addition to its effect in reducing vascular permeability during endotoxemia.[57]

PHA-543613

It is a novel selective α7-nAchR agonist with negligible or very weak effects on other nAchR.[58] PHA-543613 readily crosses the blood-brain barrier.[59] It was proved that PHA-543613 has neuroprotective activity in neurodegenerative diseases.[59] In Parkinson's disease model, PHA-543613 protected the damage of dopaminergic neurons through the activation of α7-nAchR.[60] In addition, it improved cognitive impairment and memory deficits associated with schizophrenia.[58,61] PHA-543613 could be useful in treating dementia associated with Alzheimer's disease, which was proven in β-amyloid-induced amnesic effect in mice.[62,63] Low doses of PHA-543613, at microgram scale, could stimulate the angiogenic process. Its administration in the isoprenaline-induced myocardial infarction model in rats increased capillaries density and restored normal

cardiac function and architecture.[64] Moreover, PHA-543613 could attenuate chronic pain related to post-traumatic stress disorder due to the suppression of glial cells.[65] In addition, it reduced neuropathic pain by suppressing dynorphin A activity in microglia.[66]

PNU-282987

It is a potent selective α7-nAchR agonist; however, it showed weak activity on 5-HT_3 receptors.[67] Its activity on α7-nAchR has been widely investigated. Centrally, the action of PNU-282987 on spatial learning and cognitive functions is controversial. It showed no effect on the acquisition of spatial learning in the Alzheimer's disease model.[68] In contrast, another study stated that the administration of PNU-282987 improved cognitive function in mice subjected to β-amyloid, where it reduced apoptosis and increased the level of synaptic associated proteins.[69] Furthermore, it reversed the amnesic effect induced by chlorpheniramine, a histamine receptor antagonist.[70] In phencyclidine-induced cognitive impairments, PNU-282987 daily administration could reverse the learning deficits associated with schizophrenia without causing tolerance.[71] The administration of PNU-282987 could be a promising treatment for Parkinson's disease. Its daily administration protected astroglia cells, which play a crucial role in maintaining normal brain function. It reduced the apoptosis rate by suppressing anti-apoptotic proteins.[72] In addition, it reduced dopaminergic neurons loss and attenuated neuroinflammation induced by MPTP neurotoxin in mice.[73] PNU-282987 could prevent prolonged febrile seizures by maintaining normal levels of GABA neurotransmitter in the hippocampus.[74] The study of the anti-inflammatory effect of PNU-282987 is promising. The activation of α7-nAchR by PNU-282987 improved the inflammatory profile by modulating macrophages function in acute lung injury.[75] In addition, similar results were obtained in acute pulmonary injury that induced by cardiopulmonary bypass models in rats,[76] sepsis-induced acute lung injury,[77] LPS-induced acute lung injury[78] and acid-induced acute lung injury in rats.[79] In ischemic disorders, PNU-282987 ameliorated cardiac injury due to myocardial reperfusion by modulating beclin-1-mediated autophagy.[80] Furthermore, it showed a protective profile against hepatic injury in the hepatic-reperfusion model by repressing the nuclear factor kappa B (NF-κB) pathway and high-mobility group box 1 protein (HMGB-1) expression.[81] It is thought that PNU-282987 could prevent damage to retinal ganglion cells in glaucoma, which is eventually responsible for blindness that could be due to its ability to stimulate neurogenesis.[82]

Tropisetron

Tropisetron is a potent α7-nAchR agonist with an antagonistic effect on 5-HT_3 receptors and α9α10 nAchR subtypes.[83] *In ivo* administration of tropisetron improved the P50 auditory suppression deficits associated with schizophrenia, suggesting its role as a possible therapeutic target for neurodegenerative diseases.[84] Similar data were obtained by another study in which tropisetron improved the deficient auditory processing in DBA/2 mice due to the activation of α7-nAchR.[85] In addition, the subchronic administration of tropisetron improved cognitive dysfunction raised by the administration of phencyclidine in mice[86] or risperidone-induced schizophrenia.[87] In the ventral tegmental area, tropisetron ameliorated the disruption of dopaminergic neurons of prepulse inhibition and sensorimotor gating deficits.[88] In addition, low doses of tropisetron enhanced memory-related tasks in young or aged rats.[89] Moreover, it could attenuate withdrawal symptoms that occur due to the acute administration of naloxone in rats previously treated with a single dose of morphine, which was explained by its potent effect on α7-nAchR.[90] Tropisetron showed neuroprotective activity by diminishing the excitatory effect of glutamate by stimulating the internalisation of the NMDA glutamate receptor.[91] Tropisetron exerted an α7-nAchR-mediated anti-inflammatory effect in different animal models. In the acetic acid model of ulcerative colitis, it significantly decreased the infiltration of neutrophils and exhibited a notable anti-inflammatory effect, which could be mediated by activation of peroxisome proliferator activated receptor gamma.[92] In addition, tropisetron blocked TNFα-mediated expression of IL-6 and IL-8 in a mechanism independent on p65/NF-κB signaling.[93] Tropisetron attenuated inflammation and acute pancreatitis induced by cerulein, an oligopeptide that stimulates digestive secretions.[94]

ANTAGONISTS OF α7-nAchR

α7-nAchR were developed to discover the mechanism and activity of different nAchR in addition to the generation of impaired nAchR animal models.[95] Some nAchR antagonists were separated from a natural source and many other drugs were chemically synthesised.

α-bungarotoxin

It is a protein toxin that separated from the venom of the Taiwanese banded krait (*Bungarus multicinctus*).[96] It is a non-selective nAchR antagonist that blocks the muscular nAchR (α1β1γεδ), α7 and α9 nAchR with a great affinity.[96] For this reason, its practical applications are limited to the experimental studies of nAchR activity. A complete blockade is obtained after its preincubation for 1 h at nanomolar concentrations (10 nm), however, the increase in α-bungarotoxin concentration reduces the needed preincubation time.[97] The blockade of nAchR, especially muscular type, is not reversed by washing out due to sow dissociation rate.[98]

Methyllycaconitine (MLA)

It is a reversible nAchR antagonist. It is a norditerpenoid alkaloid separated from the Delphinium species.[99] Its blockade activity is rapid and reversible, making it a suitable alternative to α-bungarotoxin. It has a great binding affinity to α7-nAchR with additional blocking activity to α9 and α9α10 nAchR. However, its binding ability to muscular nAchR is lower.[100] Therefore, MLA is considered a selective α-nAchR antagonist over other nAchR.[101]

Mecamylamine

It is a widely used nAchR antagonist. It was first developed for the treatment of hypertension through blocking the ganglionic receptors.[102] It is highly distributed and crosses the blood-brain barrier, producing a variety of peripheral and central effects.[103] Mecamylamine blocks most neuronal nAchR with more sensitivity toward α3β4 nAchR.[104] The antagonism of α7-nAchR by mecamylamine is reversible.[105] It is used in studying the role of nAchR in behaviour.[95] In addition, the administration of mecamylamine could be efficacious in the treatment of depression.[106]

MOLECULAR MECHANISMS OF CAP

Toll-like receptor 4 (TLR4)/NF-κB

NF-κB plays an important role in regulating the release of TNFα and IL-6 as pro-inflammatory cytokines, which are involved in the inflammatory process. The inflammatory response, which is mediated by NF-κB, is quick as it is previously stored in the cytoplasm in an inactivated form. TLR4 is a pattern recognition receptor, which is activated by different pathogen-associated molecular patterns (PAMPs). This will enhance the innate immune response and initiate inflammatory response.[107] The extracellular part of TLR4 is bound to an intracellular toll-interleukin receptor (TIR) domain that regulates the intracellular signalling cascade of TLR4/MyD88/NF-κB axis, which is ended with formation of pro-inflammatory cytokines.

Many adaptor proteins are essential for the downstream signalling, including myeloid differentiation primary response gene 88 (MyD88), TIR domain-containing adaptor protein (TIRAP) and TIR-domain-containing adaptor-inducing interferon-β. The activation of TLR4/MyD88/NF-κB begins after extracellular activation of TLR4 by PAMPs**.** The TIRAP is recruited to two TIR domains of two TLR4 where they form a binding site for MyD88.[108] MyD88 forms a complex with two interlein-1 receptor-associated kinases (IRAK2 and IRAK4).[109] After the formation of MyD88/IRAK complex, TNF receptor-associated factor 6 (TRAF6) is activated forming a trimer [Figure 1]. The IKKγ complex recognises the polyubiquitin chains of TRAF6 leading to its recruitment.[110] This will activate TAK1 and promote the phosphorylation reaction of IκB, which promotes the release and the activation of NF-κB. In addition, TAK1 recruits mitogen-activated protein kinases (MAPKs).[111] Both NF-κB and MAPKs induce the formation and activation of various inflammatory cytokines such as IL-1β, TNF-α and IL-6.[112]

It was previously reported that the translocation of NF-κB and the consequent release of inflammatory cytokines could be prevented by the activation of α7-nAchR [Table 3]. The anti-inflammatory mechanism of α7-nAchR-meditaed blockade of TLR4/NF-κB is not clear and need further investigations.[10] However, it was proven that the α7-nAchR activation suppresses the phosphorylation of Iκ-B by IKK, leading to a consequent suppression of NF-κB production.[8] Furthermore, nicotine was proposed to induce the anti-inflammatory effect of IRAK-M through enhancing its upregulation. The IRAK family consists of two different kinases, active kinases (IRAK-1 and IRAK4) and inactive kinases (IRAK-2 and IRAK-M). IRAK-M serves as a negative regulator of the TLR-4/MyD88 dependent pathway thus, its activation will result in an anti-inflammatory effect.[113] Furthermore, the activation of α7-nAchR by PHA568487 reduced the expression of TLR4, MyD88 and NF-κB in the hippocampus and prevented neurological damage during cardiopulmonary bypass.[114] The same mechanism was obtained by nicotine in airways epithelial cells subjected to LPS.[115] The administration of GTS-21 as a partial selective agonist of α7-nAchR attenuated the Akt/NF-κB pathway in response to LPS challenge.[53,116] In addition, nicotine modulated LPS-induced inflammation and nitric oxide synthesis through suppressing the MAPK pathway.[117] The activation of α7-nAchR alleviated the neurotoxicity and cognitive function induced by β-amyloid protein in the schizophrenic model in mice by inhibiting the MAPK pathway[118] or by blocking PI3K signalling.[119]

Janus activated kinase-2 (JAK2)/signal transducer and activator of transcription 3 (STAT3)

JAK2 is a non-receptor tyrosine kinase, while STAT3 is a member of the STAT family that plays a role as a transcription factor, which is encoded as a STAT3 gene in humans.[120] The JAK2/STAT3 pathway could regulate the CAP.[121] The activation of α7-nAchR results in the recruitment of JAK2 to the α7 subunit, which, in turn, results in autophosphorylation of JAK2 [Table 3].[10] This triggers the phosphorylation process of STAT3 to form phosphorylated STAT3 (pSTAT3). pSTAT3 molecules form dimers that translocate to the nucleus, as shown in [Figure 1]. pSTAT3 dimers act as negative regulators of the inflammatory response.[122,123] Moreover, the activation of α7-nAchR upregulates the expression of JAK2/STAT3 signalling and causes a further suppression in the levels of inflammatory cytokines such as IL-1β.[124]

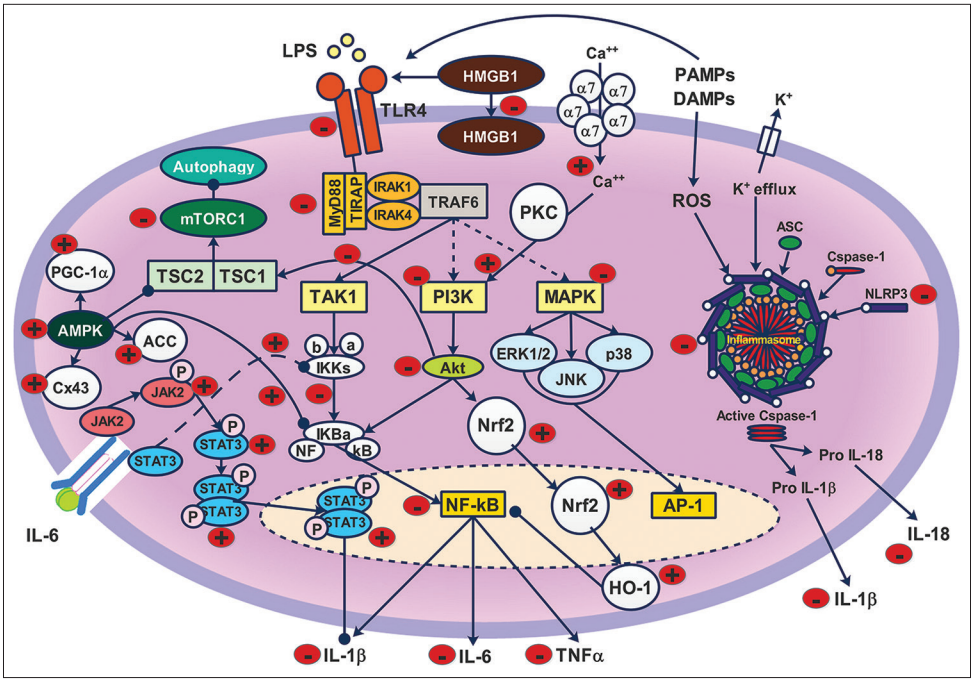

Figure 1: Schematic diagram of the possible anti-inflammatory mechanism of α7-nAchR. Activation of α7-nAchR inhibits TLR4/NF-κB, where it decreases the expression of TLR4, MyD88, IKKs and NF-κB. In addition, CAP reduced the activity of PI3K and Akt. However, some studies showed that the α7-nAchR could increase PI3K activity, which leads to a consequent increase in Nrf2/HO-1 anti-inflammatory activity. Moreover, activation of α7-nAchR reduces the expression of NLRP3 and reduces the assembly of inflammasome. CAP decreased autophagy and exerted an anti-inflammatory effect by decreasing the activity of mTORC1. It was observed that α7-nAchR stimulation decreased the expression and internalisation of HMGB1. Finally, CAP showed an anti-inflammatory effect through stimulation of anti-inflammatory pathways such as JAK2/STAT3 and AMPK/Cx43/PGC-1α.

In intracerebral haemorrhage model performed in murine models, the administration of PHA-543613 as a selective α7-nAchR agonist attenuated neuroinflammation by activating the JAK2/STAT3 pathway.[125] The mechanism by which the JAK2/STAT3 pathway is regulated by CAP is not completely understood. However, some studies suggested that it is linked to the enhancement of the formation of tristetraprolin (TTP). The enhanced formation of TTP will stimulate the CAP by binding to adenylate-uridylate-rich elements (AU-rich element, AREs).[126] AREs are located in the 3' untranslated region (3'UTR) of various messenger ribonucleotide (mRNA) molecules that code the transcription of nuclear transcription factors and cytokines[127] In addition, AREs target the rapid degradation of mRNA molecules. Therefore, TTP destabilises the transcripts of pro-inflammatory containing AREs in the 3'UTR. In contrast, another study suggested that unphosphorylated STAT (uSTAT), not pSTAT, plays an essential role in the cholinergic anti-inflammatory effect. uSTAT interferes with the inflammatory response by binding to NF-κB, leading to the displacement of Iκ-B. The formed uSTAT/NF-κB complex could prevent NF-κB activation, giving rise to the α7-nAchR-mediated cholinergic anti-inflammatory effect.[128]

Nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) induction

CAP is regulated alternatively by activating HO-1 [Figure 1]. Many studies proved that the activation of α7-nAchR could increase the expression of HO-1 and this effect was obliterated when α7-nAchR was blocked selectively by MLA [Table 3]. The possible mechanism of HO-1 activation by α7-nAchR could be due to the enhancement of Ca^{++} influx. Ca^{++} ions activate protein kinase C, which, in turn, causes an increase in reactive oxygen species (ROS) through NADPH oxidase-mediated mechanism.[129] This leads to the activation of the PI3K/Akt pathway, which ends with stimulation of Nrf2, leading to the upregulation of HO-1 and the accompanying anti-inflammatory effect. This mechanism was confirmed by studying the effects of PNU-282987 as a selective α7-nAchR agonist in rescuing SH-SY5Y cells from apoptosis.[130] In addition, the activation of α7-nAchR protected the kidneys in the acute ischemic renal injury model[131] and endotoxic rats[132] by activating the PI3K/Akt/Nrf2 pathway. In the cerebral ischemia model, the administration of PNU-282987 afforded neuroprotection and anti-inflammatory effects by modulating Nrf2 and HO-1 activity.[133] Moreover, the cholinergic-mediated increase in

Table 3: Summary of the molecular mechanisms of α7-nAchR-mediated anti-inflammatory effect.

Pathway	Target proteins	Effect of α7-nAchR
TLR4/NF-κB	Iκ-B	Decreases its phosphorylation by IKK[8]
	IRAK-M	Induces protein upregulation[113]
	TLR4	Reduces its expression[114]
	Myd88	Reduces its expression[114]
	NF-κB	Reduces its expression[114]
	Akt	Reduces its activation[53,116]
JAK2/STAT3	JAK2	Stimulates its recruitment and autophosphorylation[10]
		Upregulates its expression[124]
	STAT3	Stimulates its phosphorylation int pSTAT3[122,123]
	pSTAT3	Stimulates the dimerisation of two molecules of pSTAT3
	TTP	Increases TTP formation, which stimulate CAP[126]
	uSTAT	Stimulates its binding to NF-κB forming inactive complex[128]
Nrf2/HO-1	HO-1	Increases its activation
		Increases its expression
	PKC	Enhances its activation by increasing Ca^{++} influx[129]
PI3K/Akt	PI3K	Activation of PI3K, which ends with the activation of Nrf2[133]
mTOR	Beclin-1	Increases its level[141]
	LCII/I ratio	Increases the ration of ICII/I[141]
NLRP3	NLRP3	Decreases its expression[146]
		Prevents mitochondrial DNA release, which prevent NLRP3 signalling[15]
	β-arrestin-1	Regulation of its activity where it is essential in the assembly of NLRP3[147]
	C-reactive protein	It stimulates α7-nAchR leading to subsequent inhibition of NLRP3.[149,150]
AMPK	p-AMPKα	Increases its expression[152]
	Cx43	Enhances the expression of Cx43 by enhancing p-AMPKα[153]
	PGC-1α	Enhances mitochondrial biogenesis by stimulating AMPK phosphorylation[155]
	NF-κB	Prevents its translocation[156]
AMPK-mTOR	mTOR	Stimulates the autophagy and reduces inflammation
HMGB1	HMGB1	Restricts its internalisation[162]
		Prevents its formation[164]
COX-2	COX-2	Increases its expression and suppresses the release of inflammatory cytokines[174,175]
	PGE2	Enhances its expression

HO-1 ameliorated inflammatory reactions associated with hepatic ischemia.[134]

Mammalian target of rapamycin (mTOR) signalling

The mTOR participates in internal and external mechanisms that regulate cellular metabolism [Figure 1], growth, proliferation, survival and many other metabolic activities.[135] The mTOR protein belongs to the PI3K family and is differentiated into two distinct multiprotein complexes, mTOR complex 1 and mTOR complex 2 (mTORC1 and mTORC2, respectively).[136] The tuberous sclerosis complex (TSC) is composed of hamartin (TSC1) and tuberin (TSC2) and it is believed to be one of the most important proteins that are involved in the regulation of mTORC1.[137] Inflammation has been shown to regulate mTORC1 signalling, where inflammatory mediators signal mTORC1 through the TSC1/2 complex.[136] The IκB kinase-β is activated by many pro-inflammatory cytokines, such as TNF-α, which plays a role in activating TCS1, leading to activation of mTORC1.[136] It is thought that the positive relationship between mTORC1 and inflammation is important in the development of tumour angiogenesis.[138] Autophagy is defined as an essential metabolic process for the decay of long-lived proteins, damaged tissues and misfolded proteins. It was demonstrated that the autophagy process is very important in the suppression of inflammation in many pathological processes, including myocardial infarction[139] and atherosclerosis.[140] mTOR signalling has an inhibitory effect on autophagy. Many studies showed that the α7-nAchR-mediated anti-inflammatory effect could inhibit the mTOR-related signalling [Table 3]. It was proved that knocking of α7-nAchR aggravated myocardial infarction and the accompanying inflammatory reaction through mTOR-related signalling autophagy. In this study, α7-nAchR deficiency lead to a marked decrease in the autophagy-related proteins such as Beclin-1 and LC3II/I ratio.[141] In addition, the activation of α-nAchR selectively by PNU-282987 significantly alleviated myocardial ischemia through inhibition of the PI3K/mTOR pathway.[80]

Inflammasome

The inflammasome is an intracellular protein complex formed from the nucleotide-binding oligomerisation domain and leucine-rich repeat-containing NOD-like receptors (NLRs) as cytosolic sensors in addition to other proteins, including absent in melanoma 2-like receptors, adapter proteins termed apoptotic speck-containing protein (ASC) or NLR family CARD domain-containing protein 4 and the effector protein pro-caspase-1.[142] The inflammasome assembly [Figure 1] is initiated by recognising molecular patterns such as damage-associated molecular patterns and PAMPs, which are followed by the interaction with ASC. Activated ASC is aggregated into specks, which, in turn, activates procaspase 1 and auto-proteolysis.[143,144] This leads to subsequent cleavage of gasdermin D and elevation of IL-1β and IL-18,[143,144] which will stimulate pyroptosis, which is considered as pro-inflammatory programed cell death.[145] The inflammasome is recognised as a key player in innate immunity. The NLR family, pyrin domain containing 3 (NLRP3) inflammasome connects the innate immunity and the inflammation where it represents one of the most popular inflammatory reactions.[142] It was previously reported that the activation of α7-nAchR could decrease the NLRP3 activity. In the middle cerebral artery occlusion model in rats, the administration of PHA-543613 as a selective α7-nAchR agonist showed a marked inhibitory effect on the NLRP3 activity. This effect was blocked by the administration of α-bungarotoxin, the α7-nAchR antagonist.[146] In another study, it was suggested that activation of α7-nAch mitochondrial receptors could inhibit NLRP3 signalling by preventing mitochondrial DNA release in macrophages.[15] In addition, targeting β-arrestin-1 in monocytes could affect the NLRP3 activation where β-arrestin-1 is essential for its assembly. Therefore, the activation of α7-nAchR could regulates the β-arrestin-1, which leads to a subsequent inhibition of NLRP3 activation.[147] In the animal model of pulmonary hypertension, PNU-282987 administration reduced NLRP3 inflammasome activity and successfully exerted an anti-inflammatory effect and treated pulmonary hypertension.[148] Furthermore, CAP is believed to be modulated endogenously by C-reactive protein, which is formed in the liver and reaches high plasma levels in response to the excessive release of IL-1β in plasma. This could inhibit ATP-induced inflammasome activation due to the stimulatory effect of C-reactive protein on α7-nAchR.[149,150]

Adenosine monophosphate-activated protein kinase (AMPK)

AMPK consists of three subunits, α, β and γ forming a functional enzyme that gives metabolic adaptation by acting as an energy sensor.[151] The adaptation of metabolic energy and the regulation of the immune system exerted by AMPK activation was proven to be protective against many diseases. Activation of CAP could increase the expression of phosphorylated AMPKα, which exerts anti-inflammatory and antifibrotic effects [Figure 1 and Table 3]. In addition, activation of AMPK signalling could suppress the inflammatory response and enhance the expression of gap junction protein connexin 43 (Cx43), which leads to the suppression of IL-1β.[152] Therefore, the preservation of Cx43 could play a critical protective role during inflammatory conditions. AMPK signalling is an important participator in regulating energy balance by several biochemical reactions through the AMPKα/acetyl-CoA carboxylase (ACC) pathway.[153] It is believed that phosphorylation of AMPKα affects the transcriptional cofactor, peroxisome proliferator-activated receptor-γ coactivator (PGC-1α), leading to an enhancement in mitochondrial biogenesis.[154] Activation of CAP by PNU-282987 increases PGC-1α levels through activation of AMPK/ACC signalling.[155] These effects could improve energy metabolism and provide sufficient energy for eukaryotic cells. Moreover, the stimulation of α7-nAchR caused a marked decrease in the nuclear translocation of NF-κB by AMPK-signalling.[156] Furthermore, it was reported that the activation of α7-nAchR in inflammatory bowel disease model in mice stimulate the autophagy and reduce inflammation by the induction of AMPK-mTOR-p70 ribosomal protein S6 kinase pathway. In this study, α7-nAchR-deficient mice showed an injurious effect on bowel inflammation that insulted with dextran sodium sulphate.[157]

HMGB1

HMGB1 is one of the most important chromatin proteins. It interacts with nucleosomes and transcription factors in the nucleus, which regulate DNA transcription.[158] Several immune cells, such as monocytes and macrophages, secrete HMGB1 as an inflammatory mediator cytokine. The mechanism of HMGB1-mediated inflammation is regulated by TLR2 and TLR4 [Figure 1]. The interaction between HMGB1 and TLR4 leads to an elevated expression of NF-κB and MAPK, which leads to a further increase in cytokine levels.[159] In addition, the HMGB1-TLR4 interaction stimulates the formation of ROS by NADPH oxidase.[160] Moreover, the anti-inflammatory effect of HMGB1 could be due to its ability to bind with other-immune activating molecules and facilitate their endocytosis by the aid of the receptor for advanced glycation end-products (RAGE). These pro-inflammatory complexes are targeted to the endolysosomal compartment where HMGB1 permeabilises the lysosomes.[161] It was proved that selective activation of α7-nAchR restricted the internalisation of HMGB1; [Table 3] however, direct inhibition of HMGB1/TLR4 mediated pathway did not suppress the internalisation of HMGB1.[162] The molecular mechanisms of CAP-mediated inhibition of HMGB1 internalisation are still unclear and

need further investigation. PNU-282987 prevented the production of HMGB1 and migration in macrophages after LPS administration.[163] Similarly, PNU-282987 gave the same results as it showed a protective effect against hepatic ischemia-reperfusion injury.[81] The lung injury produced by cardiopulmonary bypass was attenuated by electroacupuncture by reducing HMGB1 formation and accompanying inflammatory cytokines by a mechanism that is mediated by α7-nAchR activation.[164] Furthermore, GTS-21 attenuated the production of TNFα, HMGB1 and RAGE in human patients with severe sepsis.[165] In addition, GTS-21 reduced HMGB1 cytoplasmic translocation from macrophages in mice subjected to pulmonary *Pseudomonas aeruginosa* infection,[166] in addition to its effect on inhibiting the HMGB1/TLR4/NF-κB pathway in radiation-induced lung injury.[167]

Cyclo-oxygenase 2 (COX-2)

COX-2 is the inducible isoform of COX enzymes, which is responsible for the first step in the formation of prostaglandin E_2 (PGE_2), one of the most important inflammatory mediators that are responsible for several functions of macrophages and lymphocytes.[168] It was shown that PGE2 is associated with many harmful and protective effects, depending on its level. At nanomolar concentrations, PGE2 was proved to exhibit an anti-inflammatory effect in and neuroprotective effect in addition to maintaining cerebral immune hemostasis in a mechanism independent of the PGE2 EP receptors[169] or dependent on EP2 receptors activation.[170] Contrarily, at micromolar concentrations, PGE2 participates in cell death and triggering of apoptosis.[171] It is also involved in the downregulation of microglial cells and the expression of some inflammatory mediators such as TNF-α.[172] Moreover, it was suggested that PGE2 released from macrophages contributes to engulfing apoptotic cell death.[173] It was demonstrated that the selective activation of α7-nAchR enhances the formation of PGE2 by inhibiting the p38/MAPK/NF-κB pathway [Table 3], which could be involved in the alteration of the COX2/PGE2 pathway. This leads to an enhancement in the expression of COX2 enzyme and suppression in the release of pro-inflammatory cytokines.[174,175]

CONCLUSION

The link between the nervous system and the immune system is encouraging to be translated into an effective therapeutic strategy for the treatment of different inflammatory conditions in different body sites. The experimental, pre-clinical and clinical studies showed positive observations. Despite the presence of several α7-nAchR-mediated anti-inflammatory molecular mechanisms, there remain several inflammatory pathways and signalling mechanisms that need further investigation. In addition, more comparative studies are needed to differentiate the anti-inflammatory effects of different α7-nAchR agonists. As these drugs are supposed to be used in the treatment of chronic inflammation, the effect of these drugs on the nervous system should be investigated. In addition, the adverse effects and α7-nAchR independent anti-inflammatory effect should be studied. Finally, the future of using these drugs in the treatment of chronic inflammation is promising and needs more attention.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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