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INVITED REVIEW

# Therapeutic potential of α7 nicotinic receptor agonists to regulate neuroinflammation in neurodegenerative diseases

**Laura Foucault-Fruchard**[1, 2, *], **Daniel Antier**[1, 2]
1 UMR INSERM U930, Université François Rabelais, Tours, France
2 CHRU de Tours, Hôpital Bretonneau, Tours, France

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## Abstract
Neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's diseases, are all characterized by a component of innate immunity called neuroinflammation. Neuronal loss and neuroinflammation are two phenomena closely linked. Hence, the neuroinflammation is a relevant target for the management of the neurodegenerative diseases given that, to date, there is no treatment to stop neuronal loss. Several studies have investigated the potential effects of activators of alpha 7 nicotinic acetylcholine receptors in animal models of neurodegenerative diseases. These receptors are widely distributed in the central nervous system. After activation, they seem to mediate the cholinergic anti-inflammatory pathway in the brain. This anti-inflammatory pathway, first described in periphery, regulates activation of microglial cells considered as the resident macrophage population of the central nervous system. In this article, we shortly review the agonists of the alpha 7 nicotinic acetylcholine receptors that have been evaluated *in vivo* and we focused on the selective positive allosteric modulators of these receptors. These compounds represent a key element to enhance receptor activity only in the presence of the endogenous agonist.

***Key Words:*** *α7 nicotinic receptors; cholinergic anti-inflammatory pathway; Alzheimer's disease; Huntington's disease; Parkinson's disease; neuroinflammation; neurodegeneration; positive allosteric modulators*

***Correspondence to:**
*Laura Foucault-Fruchard, laura.foucault@univ-tours.fr.*

***orcid:***
*0000-0002-8037-9457 (Laura Foucault-Fruchard)*

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## The Role of Neuroinflammation in Neurodegenerative Diseases
Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases represent a heterogeneous group of pathologies all characterized by a progressive loss of cognitive and functional skills. The common element of these pathologies is a physiological component of innate immunity called neuroinflammation, a non-specific reaction initiated against a pathogen or tissue damage that aims to promote tissue repair. Neuroinflammation involves cells from the microglia and astroglia. In the central nervous system, microglia is abundant and constantly surveys the cerebral environment. Although microglial cells are located within all cerebral structures, they are predominant in the white matter and myelinated zones. During neuroinflammation, microglia's response can be either neurotoxic or neuroprotective depending on the nature of the activating signal. This disturbance of brain homeostasis is associated with rapid proliferation and profound changes in the microglial cell shape, gene expression and functional behavior. Phenotypically, the complexity of the cellular processes is reduced and microglia reverts to an amoeboid appearance. These activated cells have the capacity to migrate, proliferate and phagocytose. When acute neuroinflammation is regulated, microglial function rapidly returns to normal contrary to chronic neuroinflammation in neurodegenerative diseases. During chronic neuroinflammation, brain tissue homeostasis is disturbed over an extended period of time and fully activated microglial cells become neurotoxic. Chronic microglia activation leads to the release of pro-inflammatory cytokines (*e.g.*, interleukelin (IL)-1β, IL-6), reactive oxygen species (ROS), and derivatives of nitric oxide, which induce neuronal death mainly by apoptosis (Block et al., 2007; Hanisch and Kettenmann, 2007). Neuronal death, in turn, stimulates microglial cells to produce pro-inflammatory cytokines and nitric oxide. Thus, chronic neuroinflammation, which is characterized by massive microglial activation, and neuronal death are closely linked phenomena that promote each other, leading to the establishment of a detrimental vicious cycle that is characteristic of neurodegenerative diseases. Consequently, targeting neuroinflammation represents a major therapeutic interest to modulate neuronal loss and is currently the subject of several studies.

## Alpha 7 Nicotinic Receptors and the Cholinergic Anti-inflammatory Pathway
So far, no pharmacological treatment to prevent or heal neuroinflammation has received market authorization.

Epidemiological studies have shown that smokers have a lower risk of neurodegenerative diseases compared to non-smokers, and the risk seems to be inversely correlated with the intensity and duration of nicotine intake (tobacco smoking) (O'Reilly et al., 2005; Thacker et al., 2007). Therefore, several research teams have investigated the effects of nicotine and more specifically the potential effects of alpha 7 nicotinic acetylcholine receptor (α7nAChR) agonists in neurodegenerative diseases models. α7nAChRs are ligand-gated ion channels comprising five alpha subunits forming an ionic pore highly permeable to $Ca^{2+}$ and widely distributed in the nervous system, peripheral tissues, and immune system (Zoli et al., 2015). α7nAChRs desensitize very rapidly in the presence of high concentration of agonist, reducing the damages that may occur in the event of massive cytosolic calcium releases (Couturier et al., 1990; Séguéla et al., 1993; Quick and Lester, 2002). In the central nervous system, α7nAChRs are found in both non-neuronal cells (microglia, astroglia, oligodendrocytes, and endothelial cells) and neurons of the cortex and the hippocampus, two structures related to cognition, attention, and memory tasks (Dominguez del Toro et al., 1994; Gotti et al., 1997; Quik et al., 2015).

Wang et al. (2003) reported in 2003 that α7nAChR expressed in blood-borne macrophages are required for the inhibition of macrophage tumor necrosis factor (TNF) release. Four years later, Shytle et al. (2004) described the existence of cholinergic anti-inflammatory pathway in the brain by showing that preventive nicotine treatment of murine microglial cells expressing α7nAChRs decreased TNF-α release induced by lipopolysaccharide. These findings suggest the existence of a cerebral cholinergic pathway mediated by α7nAChR activation (analogous to the peripheral pathway) that regulates proinflammatory cytokines production (TNF, IL1β, IL-6, IL-18) and consequently microglial activation. In recent years, published studies have shown that this pathway is responsible for the activation of the PI3K/AKT antioxidant pathway, which promotes the translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) to the electrophile response element in the nucleus, and consequently the expression of numerous anti-oxidative proteins such as heme oxygenase-1 (HO-1). The end products of HO-1 activity (carbon monoxide and biliverdin, which is quickly converted to bilirubin) are known for their ability to reduce the inflammatory response. On the other hand, studies have shown that α7nAChR activation negatively regulates the nuclear translocation of nuclear factor kappaB (NFκB) and Toll-like receptor-4 resulting in an important decrease in the synthesis of proinflammatory cytokines and ROS. Hence, an essential nicotinic link in the central nervous system has been identified between the cholinergic anti-inflammatory pathway and the activation of α7nAChRs (Egea et al., 2015). Consistent with these observations, activation of α7nAChRs results in decrease neuroinflammation, supporting the concept that α7nAChRs activators may represent a hope for the management of neuroinflammation in neurodegenerative diseases.

## α7nAChR Agonists: A Hope in the Management of Neurodegenerative Diseases

Several α7nAChR agonists, including partial agonists, have been evaluated in preclinical studies in the treatment of neurodegenerative diseases. In animal models of Parkinson's disease, the daily administration of nicotine one week before and six weeks after the injection of a neurotoxin to induce neurodegeneration in the substantia nigra showed a beneficial effect on motor coordination as well as on neuronal survival, and microglial and astrocytic activation (Liu et al., 2012). α7nAChR agonists such as DMXBA (GTS-21) and ABT-107 have also had beneficial effects in 6-hydroxydopamine (6-OHDA)-induced damage to nigrostriatal neurons in rats (More and Choi, 2016). In another study, repeated administrations of an α7nAChR agonist (PHA 543613) in a rat model mimicking the early stages of Huntington's disease (striatal quinolinic acid lesion) resulted in a significant protective effects on neurons and a dose-related decrease in microglial activation (Foucault-Fruchard et al., 2017). In an Alzheimer's disease animal model, treatment with the α7nAChR agonist A-582941 showed neuronal protective effects characterized by an improvement of learning and memory ability (Medeiros et al., 2014). In transgenic mice with susceptibility to Alzheimer's disease, the α7nAChR agonist PNU-282987 resulted in a reversal of stress effects on retention in the Morris water maze (Vicens et al., 2017). AR-R17779 and ABBF, two other agonists of α7nAChRs, showed an improvement of the learning and memory abilities in rodents (Van Kampen et al., 2004; Boess et al., 2007). Taken together, these studies support the hypothesis that α7nAChR agonists can provide beneficial effects in the treatment of neurodegenerative diseases through potential modulation of microglial activation in clinical research.

Several clinical trials have been performed to evaluate the neuroprotective and anti-inflammatory potential of transdermal nicotine administration in non-smoking patients with Parkinson's disease. Although some of these studies have shown an improvement of cognitive and motor functions, others did not report improvements in symptomatology. The disparity of the results observed could be due to differences in nicotine treatment duration between studies. Some authors reported an aggravation of motor functions and the occurrence of digestive side effects or high blood pressure related to the lack of specificity of nicotine, which stimulates the autonomic

nervous system (Lemay et al., 2004; Trenkwalder et al., 2016). The α7nAChR agonist AQW051 was evaluated in patients with Parkinson's disease and levodopa-induced dyskinesia but this drug did not significantly reduce dyskinesia or Parkinson's disease severity (Trenkwalder et al., 2016). Clinical trials also investigated the effects of varenicline and ABT-126 administered to patients with Alzheimer's disease (Kim et al., 2014; Florian et al., 2016; Lewis et al., 2017). The results showed that these α7nAChR agonists were not a robust treatment for cognitive dysfunction: Varenicline did not improve cognition, behavior, or global change in mild-to-moderate Alzheimer's disease, and ABT-126 did not improve cognition in subjects with mild-to-moderate Alzheimer's disease treated with stable doses of acetylcholinesterase inhibitors (Lewis et al., 2017). The absence of α7nAChR selectivity and the inadequate pharmacokinetic profile of these drugs may explain the unsatisfactory results observed.

A promising strategy for the treatment of neurodegenerative diseases that has been the focus of several recent research studies consists of using positive allosteric modulators (PAMs). The therapeutic success of PAMs of γ-aminobutyric acid (GABA)A receptors for their sedative and anxiolytics properties strengthens the will to further research on PAMs of α7nAChRs. These compounds may offer several advantages compared to the direct agonist approach such as a higher selectivity related to the orthosteric site, which is more conserved than allosteric sites (Williams et al., 2011). Nikiforuk et al. (2015) suggest that the PAMs of α7nAChRs may be beneficial in smoking patients because the nicotine could interfere with a direct agonist. The PAMs, which are capable of increasing α7nAChRs' amplitude of response and duration of activity, are classified as type I and type II based on the type of modulation produced. N-(4-chlorophenyl)-alpha-[[(4-chloro-phenyl)amino]methylene]-3-methyl-5-isoxazoleacet-amide, a type I PAM selective of α7nAChRs capable of penetrating the blood-brain barrier, has been evaluated in rodents. This molecule, also known as compound 6, CCMI, AVL-3288 or XY4083, significantly improved their cognitive performance in the presence of the endogenous agonist (Nikiforuk et al., 2015). NS-1738, another type I PAM of α7nAChRs has also demonstrated a cognitive enhancement *in vivo* (Timmermann et al., 2007). However, type II allosteric modulators seem to have the greatest potential for therapeutic management of neurodegenerative diseases because they have a higher selectivity than type I and they can sometimes reverse desensitized receptors (Gronlien et al., 2007; Williams et al., 2011, 2012). One of the most powerful type II PAM of α7nAChRs is PNU-120596 (Hurst et al., 2005). This high selective compound enhances and prolongs α7nAChRs activation by endogenous choline. Systemic administration of PNU-120596 in rodents with post-traumatic brain injury significantly reduced brain cell damage and reactive gliosis in the hippocampal regions (Gatson et al., 2015). However, to date, none type II PAMs of α7nAChRs has been evaluated *in vivo* in a model of Alzheimer's, Parkinson's, and Huntington's diseases. Hence, although PAMs are considered viable therapeutic agents to increase cholinergic transmission, their impact should be better characterized in preclinical studies, particularly in neuroinflammation, before assessing their potential efficacy for the management of neurodegenerative diseases in clinical trials.

## Future Directions

Despite promising and converging results obtained in animal models and in early clinical trials, the therapeutic value of α7nAChR agonists still needs to be proven in larger controlled clinical trials of neurodegenerative diseases. Because α7nAChRs are rapidly and deeply desensitized by repeated administrations of agonists, the effects on chronic inflammation in rodents' brains after a short-term treatment period may not accurately predict the effects in humans treated over several months or years. An alternative approach to increase the effectiveness of α7nAChR stimulation will be to target elements of the cholinergic anti-inflammatory pathway. Hence, a possible approach would be to combine lower doses of an α7nAChR agonist with a PAM (above the dose to activate α7nAChRs and below the dose to inactivate α7nAChRs) and/or to induce the Nfr2/HO-1 axis. This alternative strategy should be investigated by the scientific community.

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***Comments to authors:*** *The invited paper reviewed that the alpha7 nicotinic receptor agonists regulate neuroinflammation in neurodegenerative diseases. The paper described the role of inflammation, alpha7 nicotinic receptor system and application of the receptor agonists. Finally, the authors suggest the future directions.*

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