**American Journal of Bioscience and Clinical Integrity**
https://biojournals.us/index.php/AJBCI
**ISSN: 2997-7347**

# Analysis of the Significance and Applications of Drugs Affecting Nicotine-Sensitive Cholinergic Receptors in Medical Practice

**Sokhib Rashidov Zamon o‘g‘li, Khilola Musaeva Usmonqul qizi, Barchinoy Abdulmurodova Dilshod qizi**
Department of Pharmacology of Tashkent State Medical University
rashidovsohib9295@gmail.com

**Received:** 2025, 15, Aug
**Accepted:** 2025, 21, Sep
**Published:** 2025, 27, Oct



**Annotation:** In terms of brain development, physiology, and pathology, the cholinergic system is crucial. Here, we go over how some changes in this system, such as genetic mutations or aberrant receptor function, might result in defective brain circuitry that causes illness. The nicotinic acetylcholine receptor (nAChR) and its involvement in addiction, neuropsychiatric and neurodegenerative disorders, and epilepsy are the main topics of the review. Cholinergic dysfunction is linked to inflammatory processes primarily through the interaction of peripheral immune cells and brain-expressed α7 nAChRs. Research indicates that diseased conditions are triggered and exacerbated by these neuroinflammatory processes. We go over the preclinical data showing that nAChR ligands have therapeutic potential in treating autosomal dominant sleep-related hypermotor epilepsy, Parkinson's disease, Alzheimer's disease, and schizophrenia spectrum disorders. In both human and animal models, nicotinic acetylcholine receptor (nAChR) activation improves sensory-cognitive performance; however, the underlying brain mechanisms are still unclear. Recent research on the nicotinic modulation of neuronal processing in the cerebral cortex that suggests possible pathways underpinning improved

cognitive function is compiled in this article. Studies from our laboratory focus on nicotinic modulation of auditory cortex and consequences for auditory–cognitive processing, although relevant emerging discoveries from multiple brain locations are highlighted. Recent findings suggest additional, possibly significant contributions from α2 subunits that are relatively rare in cortex, despite the well-established important contributions of the prevalent nAChRs with α7 (homomeric receptors) or α4 and β2 (heteromeric) subunits. The goal of ongoing research is to clarify the distinct roles that various nAChRs play in cognitive and cortical function.

**Keywords:** Alzheimer's disease, Parkinson's disease, schizophrenia spectrum diseases, epilepsy, addiction, AChRs.

**Introduction.** Nicotinic acetylcholine receptors (nAChRs) belong to the superfamily of pentameric ligand-gated ion (cation) channels (pLGIC), which also comprises other ion channels in prokaryotes and neurotransmitter receptors in metazoa. 17 vertebrate genes encode the different nAChR subunits (α1–α10, β1–β4, γ, ε, and δ). nAChRs usually form a hetero-pentameric structure by combining two pairs of αβ subunits with an auxiliary subunit. A large combinatorial diversity of neuronal and muscle-type nAChRs (fetal and adult) with unique pharmacological and biophysical properties is made possible by the possibility of homonuclear structures with only α subunits. A variety of dynamic conformational states are present in nAChRs. The receptor rests with its ion channel closed when there is no ligand present. The receptor protein quickly changes to an open state when an agonist is present, allowing tiny cations to enter. The open channel conformer has the option of transiting to a desensitized (and closed) state or returning to the closed state [1,2,3]. The nAChR cannot be triggered by ligand binding when it is desensitized. According to available information, nicotine activates two mechanisms at nicotinic acetylcholine (ACh) receptors (nAChRs) in neurons. Activation of nAChRs on the plasma membrane (PM) has historically been the most well-characterized pathway. The activation of nAChRs at the PM may be referred to as the "outside-in" pathway if events are taken into account at the neuronal scale. Similar to activation by the endogenous neurotransmitter ACh, exogenous nicotine activation through the outside-in activation pathway entails depolarization, an increase in the frequency of neuronal action potentials, and an influx of Na+ and Ca2+ ions. When nicotine enters the airways by tobacco combustion (smoking) or an electronic nicotine delivery system (ENDS; "vaping"), the outside-in pathway and maybe the ensuing desensitization of nAChRs cause the acute effects. As the name suggests, acetylcholine is composed of two components: choline, a vitamin found in foods like egg yolks, soy, and legumes, and an acetyl group, which is generated from glucose. The liver also synthesizes choline [4-10]. Choline acetyltransferase (ChAT) catalyzes the synthesis of ACh, and its presence in a neuron indicates that the neuron uses ACh as a neurotransmitter. A distinguished feature of ACh in comparison with other neurotransmitters is that its action in the synapse is readily terminated by the enzyme acetylcholinesterase (AChE), in contrast to the reuptake mechanism prevalent with other neurotransmitters. Upon the action of AChE, ACh is broken down into acetate and choline, where the latter is taken up for re-use by the nerve. ACh can

accumulate when AChE is inhibited by pesticides or nerve gases. Depolarization of the post-synaptic cell and paralysis would result from too much ACh at the neuromuscular junction. The main causes of nerve gas death are respiratory paralysis and excessive secretion. However, in conditions when ACh transmission is insufficient, certain AChE inhibitors (AChEIs) can be employed as therapeutic drugs [11-15]. This includes neurological conditions like Alzheimer's disease (AD) and myasthenia gravis, where AChEIs increase the amount of ACh in the neuromuscular junction and enhance muscle activation, contraction, and strength. Muscarinic (mAChRs) and nicotinic (nAChRs) are two different kinds of receptors that mediate the activity of ACh. This chapter focuses on how these two different receptor classes interact and how that affects both health and sickness. Therefore, an update on mAChRs and nAChRs and how their interplay may affect neuropsychiatric/neurodegenerative illnesses will be given after a brief explanation of ACh activities and its central circuitry. Additionally, a possible new therapeutic approach based on these interactions will be discussed [16-20].

**The main purpose** of this presented manuscript is a brief analysis of the significance and applications in medical practice of drugs acting on nicotine-sensitive cholinergic receptors.

**Acetylcholine receptors that are nicotinic.** Acetylcholine is bound by nAChRs, the quintessential ionotropic receptor. The receptor is made up of five subunits that are grouped around an ion channel-like pore. Neural subtypes of nAChRs can be either heteromeric, containing a combination of α and β subunits from two subfamilies, β2 through α10 and β2 through β4, or homomeric, containing five α subunits. The effects of various α and β subunit combinations on receptor function, including ion permeability, particularly to Ca2+, and channel kinetics, have been demonstrated via the expression of nAChRs in Xenopus oocytes. The two most common subtypes in the brain are heteromeric α4β2* nAChRs, which bind nicotine with high affinity, and homomeric α7 nAChRs, which have low affinity (the asterisk indicates potential extra, accessory subunits that can affect function) [4-9]. Other subunits, such α2 (see below) or α5, are present in the cortex at low levels but may play a crucial role in some processes. For instance, the presence of an α5 subunit in the prefrontal cortex is necessary for attentional function in difficult situations and decreases receptor desensitization. These findings demonstrate that the variety of nAChR subtypes multiplies the variety of nAChR function provided by receptor site (pre- and postsynaptic; excitatory and inhibitory neurons). shows the locations and subunit makeup of nAChRs in the prefrontal cortex, illuminating this intricacy. Additional properties of nAChRs that impact synaptic transmission and modulation include receptor upregulation (increased number of receptors during chronic exposure to agonist) and receptor desensitization (decreased sensitivity in the continuous presence of agonist). Therefore, it will be necessary to integrate the contributions of several nAChRs with different subunit composition, location, and responses to long-term agonist administration in order to fully comprehend therapeutic nicotinic control [10-14].

**The roles of nAChRs in the auditory cortex and their spectral integration.** The spectrum integration of afferent inputs to the primary auditory cortex (A1) provides a good foundation for thinking about the nicotinic modulation of auditory–cognitive function. In order to process spectrally complex stimuli, spectral integration entails connecting frequency representations. Other studies demonstrate that single neurons within A1 receive subthreshold inputs across a much wider range of frequencies, despite extracellular recordings showing a relatively constant breadth of suprathreshold frequency receptive fields (i.e., those based on action potential recordings) throughout the main (lemniscal) ascending auditory pathways [5-11]. It is postulated that behavioral status (such as sleep, waking, and attention) and experience regulate the integration of spectral inputs via intracortical processing, leading to dynamic changes in receptive fields. A thorough understanding of nicotinic modulation, including the location and function of pertinent nAChR subtypes, may enable targeted therapies for particular sensory–cognitive deficits, since these mechanisms mediate sensitivity to both complex stimuli and top-down regulation from higher cortical regions. Since nicotine improves performance on auditory

tasks while nicotinic antagonists, genetic deletion of nAChRs, or disease-induced loss of nAChRs impair performance, activation of nAChRs is known to promote sensory–cognitive function in auditory (and other sensory) systems. A common theory is that nicotine enhances "attentional narrowing," which focuses attention on pertinent acoustic cues, such as speech, even though the exact processes controlled by nAChRs are not entirely understood [1,3,4,9]. Systemic nicotine improves neuronal processing in the auditory cortex, resulting in narrower receptive fields and higher gain. This effect resembles auditory selective attention and probably plays a role in the auditory-cognitive boost brought on by nicotine. Local injection of the antagonist dihydro-β-erythroidine blocks the excitatory effects of systemic nicotine, while local injection of an agonist or a positive allosteric modulator mimics them. This indicates that even though nicotine is administered systemically, the locus of excitatory action is within A1 and the auditory thalamocortical pathway. Systemic nicotine also has inhibitory effects on the auditory midbrain, thalamus, and A1. Despite the fact that the action of dihydro-β-erythroidine has been interpreted as implicating α4β2* nAChRs, dihydro-β-erythroidine also binds to α2β2 nAChRs, and their contributions cannot be excluded due to their prevalence in the cortex. Next, we'll talk about the possible functional effects of nAChRs with α2 subunits [9,11,12].

**ACh routes in the brain and their importance.** ACh is used as a neurotransmitter by a vast local interneuron network in brain regions such the striatum, nucleus accumbens, and neocortex that are involved in motor, cognitive, and reward functions. Additionally, the regulation of cognition, motivation, hedonic mood, and reinforcement depends on the cholinergic pathways that connect the basal forebrain, a network of four cholinergic nuclei that project to the cerebral cortex, hippocampus, amygdala, and olfactory bulb. The pedunculopontine nucleus (PPN) and laterodorsal tegmental nucleus (LDTN) supply cholinergic input to the substantia nigra pars compacta (SNpc), ventral tegmental area (VTA), thalamus, and hypothalamus, regions essential for controlling the motor, reward, and endocrine systems. Furthermore, because of its possible involvement in cognition and the etiology of a number of mental illnesses, the lateral habenula (LatH), a component of a complex nucleus that employs ACh to connect the limbic forebrain to the midbrain, has drawn a lot of interest. More research has recently been done on the medial habenula (MedH), which is further differentiated into a ventral region with dense cholinergic neurons and a dorsal portion with non-cholinergic excitatory neurons such substance P and tachykinin [7-11]. Cholinergic projections of MedH are currently thought to have a role in both drug addiction and mood control, and their modification may have therapeutic benefits. ACh is therefore used as a neurotransmitter in many different parts of the brain, including cortical connections that mediate decision making and planning; projections to the hippocampus and amygdala that influence attention, memory, fear, and stress responses; mesolimbic pathways that affect response to reward; and the hypothalamic system that regulates homeostatic responses like thermoregulation, food intake, and sleep. Additionally, the cholinergic system is crucial for supporting neuronal growth and synaptic plasticity. These factors have led to a great deal of research on the cholinergic systems, specifically the basal forebrain complex, PPN, and LDTN, in connection with age-related progressive neurodegenerative illnesses like AD and PD [11-15].

**Both inflammation and AChRs.** Nicotinic receptor function. It is now known that nicotinic acetylcholine receptors are the primary, though not the only, mechanism via which a cholinergic anti-inflammatory pathway functions. This particular route has been thoroughly studied in peripheral organs like the spleen, where stimulation of the splenic nerve results in the release of norepinephrine, which in turn triggers the release of ACh, which has an anti-inflammatory impact. This is due to the fact that many immune cells, such as B cells, T cells, and macrophages, express nicotinic (α7 nAChR). Without influencing the synthesis of anti-inflammatory cytokines like IL-10, activation of these receptors can inhibit the production of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 [1,7,8,10]. In fact, vagal stimulation improves a number of animal models, including sepsis, ischemia-reperfusion, and pancreatitis, which are linked to increased levels of pro-inflammatory cytokines. This improvement is thought

to be achieved through macrophage α7 nAChR activation. The observation that animals lacking α7 nAChRs exhibit elevated endotoxin-induced TNF-α production, which is insensitive to electrical vagal activation, lends more credence to this claim. Nicotine was postulated as a possible therapeutic to decrease the cytokine storm associated with COVID-19 because it is a strong activator of nAChRs, particularly the α7 subtype [12,14,15,16].

**Discussion.** A review of the literature suggests that a major problem for both PVS and LC/ME/CFS may be a major impairment of cholinergic neurotransmission. Highly encouraging outcomes in the widespread use of this technique on many patients have supported the theory of a viral blockade of nAChRs and the potential for a competitive reversal of this blockade by LDTN. To find out if these initial findings can be supported by data, randomized controlled studies are required. Nonetheless, the use of LDTN offers a lot of patients a treatment that has a high chance of relieving their symptoms with few adverse effects, and it is a reasonably priced therapeutic option for the vast majority of those impacted globally. Additionally, in order to create individually tailored treatment plans for dosage and duration, dose-finding studies are necessary. In conclusion, ACh continues to play a significant role in the development and course of a number of neurodegenerative illnesses [1,3,5,9]. The discovery of nicotinic receptors and their significant role in many critical central nervous system functions, including cognitive behaviors like learning and memory, has opened up new therapeutic possibilities, despite the fact that the use of mAChRs and their exploitation was the predominant mode of cholinergic intervention in a variety of disorders, including neurodegenerative diseases. This holds true for neuropsychiatric conditions like depression and schizophrenia as well as neurodegenerative diseases like AD and PD. Furthermore, there is a substantial interaction between these two different receptor groups. Aβ, a culprit protein in AD, for instance, interacts with both receptors, albeit at different places and distinct cells (e.g., neuronal vs. glial) [12,13,14]. The intricacy of the cholinergic system in general and the nicotinic system in particular necessitates more research on the distinct roles of receptor subtypes in health and sickness, despite significant advances in our understanding of these receptors. Notably, it is maintained that in any neurodegenerative or neuropsychiatric condition, pulsatile delivery of nicotine or nicotinic agonists-modulators should be taken into account. This is because of the intricate pharmacokinetic and pharmacodynamic interactions that nicotine has with its receptors. While pulsatile administration permits functional recovery of the receptor and, consequently, additional stimulation, continuous exposure to nicotine (for example, through a patch) may cause receptor desensitization. More treatment targets for neurodegenerative and/or neuropsychiatric disorders are expected as our knowledge of the cholinergic system advances [15,16,17,18].

**Conclusion.** Skeletal muscle contraction and preganglionic sympathetic or parasympathetic activation are impossible without acetylcholine (ACh). In addition to disrupting the flow of fluids from different glands, including tears, saliva, digestive juices, perspiration, and milk, this can lead to dysregulation of cardiac, pulmonary, gastrointestinal, and renal systems. Crucially, a lack of ACh in the brain can have serious effects on cognition.

Muscarinic (mAChRs), which are G-protein coupled (metabotropic) receptors, and nicotinic (nAChRs), which are ligand-gated ion channels (ionotropic receptors), are two different kinds of receptors that mediate the activity of ACh. This chapter focuses on how these two different receptor classes interact and how that affects both health and sickness. Therefore, an update on mAChRs and nAChRs and how their interplay may affect neuropsychiatric/neurodegenerative illnesses will be given after a brief explanation of ACh activities and its central circuitry. Additionally, possible new therapeutic approaches based on these interactions will be discussed, especially as they relate to Parkinson's and Alzheimer's illnesses.

**References.**


1. Vallés AS, Barrantes FJ. Nicotinic Acetylcholine Receptor Dysfunction in Addiction and in Some Neurodegenerative and Neuropsychiatric Diseases. Cells. 2023; 12(16):2051. https://doi.org/10.3390/cells12162051
2. Leitzke, M., Roach, D.T., Hesse, S. et al. Long COVID – a critical disruption of cholinergic neurotransmission?. Bioelectron Med 11, 5 (2025). https://doi.org/10.1186/s42234-025-00167-8
3. Miyazaki, Y., Sakushima, K., Niino, M., Takahashi, E., Oiwa, K., Naganuma, R., … Kikuchi, S. (2022). Smoking and younger age at onset in anti-acetylcholine receptor antibody-positive myasthenia gravis. Immunological Medicine, 46(2), 77–83. https://doi.org/10.1080/25785826.2022.2143077
4. Anitha P GovindYolanda F VallejoJacob R StolzJing-Zhi YanGeoffrey T SwansonWilliam N Green (2017) Selective and regulated trapping of nicotinic receptor weak base ligands and relevance to smoking cessation eLife 6:e25651.https://doi.org/10.7554/eLife.25651
5. Susan M Gil, Raju Metherate, Enhanced Sensory–Cognitive Processing by Activation of Nicotinic Acetylcholine Receptors, Nicotine & Tobacco Research, Volume 21, Issue 3, March 2019, Pages 377–382, https://doi.org/10.1093/ntr/nty134
6. Askew C, Intskirveli I, Metherate R. Systemic nicotine increases gain and narrows receptive fields in A1 via integrated cortical and subcortical actions. eNeuro. 2017;4(3):e0192-17.2017 1–18.
7. Takesian AE, Bogart LJ, Lichtman JW, Hensch TK. Inhibitory circuit gating of auditory critical-period plasticity. Nat Neurosci. 2018;21(2):218–227.
8. Mazzaferro S, Bermudez I, Sine SM. α4β2 Nicotinic acetylcholine receptors: relationships between subunit stoichiometry and function at the single channel level. J Biol Chem. 2017;292(7):2729–2740.
9. Kleeman E, Nakauchi S, Su H, Dang R, Wood MA, Sumikawa K. Impaired function of α2-containing nicotinic acetylcholine receptors on oriens-lacunosum moleculare cells causes hippocampus-dependent memory impairments. Neurobiol Learn Mem. 2016;136:13–20.
10. Lotfipour S, Mojica C, Nakauchi S, et al. α2* Nicotinic acetylcholine receptors influence hippocampus-dependent learning and memory in adolescent mice. Learn Mem. 2017;24(6):231–244.
11. Tizabi, Y., Getachew, B., Tsytsarev, V., B. Csoka, A., L. Copeland, R., & Heinbockel, T. (2023). Central Nicotinic and Muscarinic Receptors in Health and Disease. IntechOpen. doi: 10.5772/intechopen.112447
12. Pasquini J, Brooks DJ, Pavese N. The cholinergic brain in Parkinson's disease. Movement Disorders in Clinical Practice. 2021;8(7):1012-1026. DOI: 10.1002/mdc3.13319
13. Lee HW, Yang SH, Kim JY, Kim H. The role of the medial Habenula cholinergic system in addiction and emotion-associated Behaviors. Frontiers in Psychiatry. 2019;10:100. DOI: 10.3389/fpsyt.2019.00100
14. Tizabi Y, Getachew B, Aschner M. Novel pharmacotherapies in Parkinson's disease. Neurotoxicity Research. 2021;39(4):1381-1390. DOI: 10.1007/s12640-021-00375-5
15. Tizabi Y., Getachew B., Copeland RL., Moratalla R., Patricio F., Ilhuicamina Daniel Limón ID., Del Bel E., Aschner M. Novel pharmacotherapies for L-DOPA-induced dyskinesia. In: Kostrzewa R.M. (eds) Handbook of Neurotoxicity. Springer, Cham. 2021. p 1-19. doi.org/10.1007/978-3-030-71519-9_218-1

16. Simon T, Kirk J, Dolezalova N, Guyot M, Panzolini C, Bondue A, et al. The cholinergic anti-inflammatory pathway inhibits inflammation without lymphocyte relay. Frontiers in Neuroscience. 2023;17:1125492. DOI: 10.3389/fnins.2023.1125492

17. Hu S, Wang Y, Li H. The regulation effect of α7nAChRs and M1AChRs on inflammation and immunity in Sepsis. Mediators of Inflammation. 2021;2021:9059601. DOI: 10.1155/2021/9059601

18. Uwada J, Nakazawa H, Muramatsu I, Masuoka T, Yazawa T. Role of muscarinic acetylcholine receptors in intestinal epithelial homeostasis: Insights for the treatment of inflammatory bowel disease. International Journal of Molecular Sciences. 2023;24(7):6508. DOI: 10.3390/ijms24076508