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Special issue "The multifaceted activities of nervous and non-nervous neuronal nicotinic acetylcholine receptors in physiology and pathology"

1. Introduction

Langley [1] first reported that nicotine induces the short-term stimulation and subsequent long-term blockade of skeletal muscle, and concluded that it interacted with a *receptive substance* expressed in the muscle itself in 1905; but it was not until thirty years later that Dale *et al.* [2] demonstrated the presence of acetylcholine (ACh) in neuromuscular junctions. Nevertheless, it was these studies that laid the basis for the 1970 discovery of the muscle nicotinic acetylcholine receptor, the first neurotransmitter receptor and ion channel to be isolated and identified [3], and the subsequent advent of the molecular biology revolution of the 1980s that led to the first identification of the neuronal nicotinic acetylcholine receptor (nAChR) family.

Since then, the combined efforts of scientists working in the fields of molecular and cellular biology, medicinal chemistry, pharmacology, electrophysiology, molecular medicine, and experimental psychology have revealed an extended family of homologous pentameric receptors that contribute to multiple brain functions, and whose number and functions are altered in many brain diseases. These native receptor subtypes may be homomeric (consisting of a single type of subunit), or heteromeric receptors (whose very complex subunit composition may consist of up to four different subunits) that have highly diverse functional and pharmacological profiles. Over the years, the continuing development of sophisticated and selective methods and techniques has allowed us to learn increasingly more about the structure, biosynthesis, maturation, targeting mechanisms, molecular interactions, channel properties, regulation, functional roles, and pharmacology of orthosteric and allosteric ligands of abundant and rare neuronal subtypes. However, although various subtype-selective compounds have been developed and tested in human clinical trials, most clinical studies have been interrupted because the beneficial effects were insufficient or side effects were intolerable: the only compound to be put on the market has been varenicline (used for smoking cessation therapy), and that was more than -fifteen years ago.

Studies carried out over the last 25 years have shown that nAChR subunits are also widely expressed outside the nervous system: in the skin, epithelial cells, immune cells, the vascular endothelium, cancer cells and muscle fibres. Their functional significance has been confirmed by means of subtype-specific antagonists and/or by comparing the effects of antagonists on wild-type and nAChR subunit knockout mice. Studies showing the key mediating role of the α7 nAChRs expressed on macrophages and other immune cells in the cholinergic anti-inflammatory pathway are of particular pathophysiological interest as they link the nervous and immune systems. However, the lack of specific means of characterising the biochemical and functional nature of the nAChRs expressed by non-neuronal cells has meant that little is still known about their structure and signalling mechanisms, although there is increasing evidence of unconventional signalling cascades that also involve non-ionic mechanisms.

The breadth and diversification of studies of nAChRs has increased over the last ten years but there has been a decrease in the number of related scientific articles, symposia, and international meetings. We therefore feel that the time has come for a special issue that summarises and critically reviews recent studies of this prototypical receptor with the aim of cross-fertilising different research domains and stimulating a renewed interest in nAChRs. This special issue is divided into six main sections in which leading experts describe the most important research results obtained in various fields over the last five years that have advanced our understanding of nAChRs and may provide a shared basis for future developments.

1) **Specific nAChR subtypes**

The variety of nAChR subtypes in mammals is mainly due to the diversity of the possible combinations of the eleven neuronal subunits that have so far been cloned. nAChR subtypes can be divided into two main classes: 1) αbungarotoxin(αBgtx)-sensitive subtypes, which may be homomeric or heteromeric and are made up of the α7, α9 and α10 subunits; and 2) αBtgx-insensitive receptors, which are heteromeric combinations of α2-α6 and β2-β4 subunits that bind nicotine with high affinity but not αBgtx [4].

nAChRs containing the α4, β2 and α7 subunits are the most widely expressed subtypes in the central nervous system but, although other minor subtypes are only expressed in a limited number of brain regions, they may play crucial functional roles. In their review, Hilsher *et al.* (2023) [5] show that α2-containing receptors are found in a number of discrete populations of inhibitory interneurons where they contribute to the modulation of neurotransmitter release, pain processing, addiction-related behaviours, anxiety, stress responses, and cognitive functions.

There is growing consensus that even a small number of major (e.g. α4-containing, see [6]) or minor (α2-containing, see [5]) nAChRs in just a few neurons of a central circuit may have a considerable functional impact. This and its implications for possible therapeutic interventions are thoroughly discussed by Abbondanza *et al.*(2024) [6], who describe recent studies showing that specific nAChRs in specific neuronal populations of the striatum and prefrontal cortex can control the activity of local circuits and ultimately animal behaviour.

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The α7-containing subtype is peculiar in a number of respects. It forms homomeric receptors and, in addition to its extensive expression in central and peripheral neurons, it is also expressed in multiple non-neuronal cells and tissues. Furthermore, ligand binding is followed not only by channel-mediated ionotropic responses, but also by metabotropic responses due to calcium entry through the channel or its release from intracellular stores, and the receptor-mediated activation of heterotrimeric G proteins and their associated intracellular cascades (see review by Sinclair and Kabbani,2023 [7]). The α7 subunit is coded by the CHRNA7 gene, which is partially duplicated in the human genome and forms a hybrid gene with the FAM7A gene (CHRFAM7A), the transcript of which codes for the α7dup protein that lacks the signal peptide and the ACh ligand-binding domain. Leonard and Benfante (2023 [8]) argue that, although the primary function of dupα7 is to regulate the function of α7 nAChRs negatively as a result of the formation of α7/dupα7 heteropentamers, CHRFAM7A may have different functions depending on the tissue and/or organ involved.

The α9 and α10 nAChR subunits were the last to be identified, and have been characterised in cochlear and vestibular hair cells in which they form functional α9α10 ion channels (reviewed by Elgoyhen, 2023 [9]). More recent studies have shown that α9 and/or α10 subunits are also expressed in other non-neuronal cells such us epithelial cells, immune cells, keratinocytes, the urothelium, placenta cells, and the adrenal medulla, where they play important roles in a number of immune and inflammatory responses, as well as in cancer cells, where they modulate tumoral proliferation and progression. The functions of the α9 and/or α9α10 receptors in immune system and cancer cells do not require ion channel activation, but affect intracellular signal transduction pathways and regulate gene expression. Structural-functional, molecular evolution, pharmacological, and pathophysiological studies define the receptors consisting of α9 and α10 subunits as distinct members of the nAChR family or even a distinct clade of nicotinic subunits [9].

2) **Regulation and modulation of nAChR function**

Nicotinic receptor subtypes consist of five distinct subunits that co-assemble to form the channel. The identity of the five assembled subunits is the main determinant of the receptors' pharmacological and functional properties, but the function of nAChRs is also greatly influenced by surrounding plasma membrane lipids, auxiliary and modulatory proteins, and the activity of other neurotransmitter receptors that co-exist with neuronal nAChRs.

Although there are a potentially large number of possible subunit combinations, the assembly of nAChRs is highly regulated and only certain combinations are favoured in neurons and recombinant systems. Over the last ten years, the use of powerful genome-wide cDNA screening has allowed the identification and characterisation of a number of tissue-specific molecules and mechanisms involved in the assembly and trafficking of receptor subtypes (reviewed in [10]). The latest findings concerning nAChR chaperones and auxiliary proteins, the ways some of them control receptor biogenesis or regulate channel activation and pharmacology, and how changes in them may be involved in nAChR dysfunctions have been reviewed by Gotti *et al.* (2023) [11]. Among the nAChR modulatory proteins, an important role is played by the lymphocyte antigen-6 (Ly6) prototoxin family, which are small proteins capable of interacting with numerous subtypes. These prototoxins, which are secreted or membrane-anchored by means of the glycosylphosphatidyl-inositol (GPI) lipid moiety [12], are endogenous allosteric modulators that associate with nAChRs, alter the ability of ACh to induce their open conformational state [13], and regulate their properties during the different stages of biogenesis. In this special issue, Palumbo and Miwa, (2023) [14] discuss the way in which *Lynx* prototoxins have allosteric modularity effects on nAChR function and number, and their involvement in complex *in vivo* processes such as neuroplasticity, learning, and memory.

In addition to accessory proteins, a number of studies suggest post-translational modifications (PTMs) occurring at multiple levels can act as regulators of the nAChR life cycle. In this special issue, Christia *et al.* (2023) [15] discuss the key role of PTMs in regulating receptor biogenesis, expression, membrane stability, and function. The function of nAChRs is also greatly influenced by their surrounding membrane lipids, and Barrantes, (2023) [16] focuses on nAChR-lipid crosstalk, gives a more comprehensive picture of these lipid-sensitive loci, and provides mechanistic explanations of their ability to modulate the properties of nAChRs.

The effects of nAChRs on brain function also depend on the activity of other neurotransmitter receptors that co-exist with neuronal nAChRs, and interact with them functionally through converging intracellular pathways, or physically at membrane level. Bono *et al.* (2023) [17] review the interactions between nAChRs, ionotropic glutamate receptors and metabotropic dopamine receptors, and underline the relevance of these cross-talks to the modulation of neuronal processes ranging from the classical modulation of neurotransmitter release to neuron plasticity and neuroprotection.

3) **Pathophysiological roles of nAChRs**

Abnormalities in nAChR expression or function have been implicated in the pathophysiology of neurological and psychiatric diseases such as Alzheimer's disease, Parkinson's disease, epilepsy, Tourette's syndrome, schizophrenia, depression, anxiety, and stress disorders, as well as some systemic disorders.

This special issue includes a number of reviews concerning the pathophysiological roles of nAChRs. Terry *et al.* (2023) [18] offer a general review of the involvement of nAChRs in neurological and neuropsychiatric disorders; Becchetti *et al.* (2023) [19] provide an update on the role of heteromeric receptors in epilepsy; and Whiteaker and George (2023) [20] review our evolving understanding of the role of amyloid-β in Alzheimer's disease and highlight the crucial mediatory contribution of nAChRs to its effects. Ables *et al.* (2023) [21] review the vital role of habenula nAChRs in regulating emotional, motivational, and cognitive behaviours, and their involvement in neuropsychiatric disorders such as depression and addiction; and Mineur *et al.* (2023) [22] review the direct role played by the nAChR subtypes present in the limbic regions amygdala, hippocampus and prefrontal cortex in pre-clinical models of stress-relevant behaviours that may be relevant to human affective disorders.

In addition to their well-established role in tobacco smoking and other forms of nicotine dependence, nAChRs have also been implicated in the pathophysiology of other types of addiction and investigated as possible treatment targets. Buzzi *et al.* (2023) [23] review studies showing the important role played by various nAChR subtypes in cannabinoid-dependent reward, dependence and withdrawal, and the promising results of trials of nicotinic drugs for the treatment of cannabinoid use disorder. Kamens *et al.* (2023) [24] summarise the genetic and pharmacological data indicating the involvement of nAChRs in some of the behavioural effects of alcohol, including reward and sedation, and the efficacy of nicotinic drugs in decreasing alcohol consumption.

Finally, many researchers have demonstrated that nicotine can increase blood glucose levels, disrupt glucose homeostasis, and induce insulin resistance in humans and animals. Chen *et al.* [25] provide an overview of data concerning the mechanisms underlying the ways in which central and peripheral nAChRs affect blood glucose homeostasis and the development of diabetes, and suggest that central nAChRs can be used as targets in the treatment of the disease.

4) **nAChR modulation of the immune system and inflammation**

Innate and adaptive immunity are emerging as two of the main functions regulated by nAChRs. Over the last 25 years, a number of studies have revealed the important role of the vagus nerve in the regulation of immunity and inflammation in the physiological

mechanism of the inflammatory reflex. It has been shown that the α7 nAChRs expressed by macrophages and other immune cells are key mediators of the cholinergic anti-inflammatory pathway (CAP) linking the nervous and immune systems. Keever *et al.* (2023) [26] provide an updated review of basic and translational studies of the CAP in inflammatory diseases, and the pharmacology of α7nACh-R-activated drugs. Hone and McIntosh (2023) [27] discuss evidence showing the analgesic and anti-inflammatory properties of α7 nAChR ligands arising from their modulation of immune cell activity by means of the inhibition of pro-inflammatory cytokine and chemokine release.

Richter and Grau (2023) [28] critically overview our current knowledge of the signalling mechanisms induced by the activation of nAChRs in mononuclear phagocytes (a general term indicating monocytes, macrophages, and microglial and dendritic cells). The stimulation of nAChRs in these cells is mainly associated with anti-inflammatory effects, but it is still debated whether nAChRs function as ionotropic receptors and it has been suggested that a multitude of different non-ionic signalling pathways may mediate the down-stream effects of nAChR stimulation.

A number of neurotransmitter receptors are known to be the targets of the pathological autoantibodies that induce various autoimmune diseases. The most frequently studied of these receptors are muscle nicotinic acetylcholine receptors, the main auto-antigen of myasthenia gravis, whereas autoantibodies against nAChRs are extremely rare with the exception of those against ganglionic α3-containing nAChRs. Pechlivanidou *et al.* (2023) [29] review the evidence concerning the detection, presence and function of antibodies against nAChR subtypes, and their involvement in neurological diseases.

5) **Nicotine and nicotine dependence**

Nicotine is a very widely used addictive drug as it is the primary psychoactive component of tobacco and is released by electronic nicotine delivery systems (ENDS). Nicotine is a powerful nicotinic agonist that can switch nAChRs from the closed to the open conformational state that allows ion flux and membrane depolarisation, but it can also stabilise the desensitised state of - the bound agonist and closed channel. The effects of nicotine on the body are complex, multifaceted and interactive because nAChR subtype composition varies in different organs, brain regions and circuits, cell types and subcellular locations, and the effects of nicotine on nAChRs depend on its concentration and how this changes over time. nAChRs appear early in development, are functionally active in foetal brain, and mediate many critical aspects of brain maturation during postnatal development. Castro *et al.* (2023) [30] describe the clinical and preclinical evidence of adverse alterations in the brain and behaviour following nicotine exposure during the two critical developmental periods of gestation and adolescence.

Nicotine exposure can have immediate, short-lasting, and long-lasting effects. There are many potential pathways in the brain that are involved in the long-lasting effects, and one of these involves epigenetic changes. Gould (2023) [31] examines the relationship between nicotine exposure, epigenetic changes, and maladaptive outcomes.

Tobacco smoking is a leading cause of preventable death and disability throughout the world, and smoking cessation is a difficult and complex process because it not only requires overcoming physical nicotine dependence, but also renouncing the satisfaction arising from long-standing rewarding behaviours. Smokers have very recently been offered the possibility of replacing tobacco cigarettes with a less dangerous class of heated (not burned) tobacco products (HTPs) or ENDS. HTPs heat tobacco to generate an aerosol containing nicotine, whereas ENDS heat a liquid that contains nicotine but not tobacco. Sala and Gotti (2023) [32] discuss the principal substances contained in ENDS and the risk of toxicity due to the presence of albeit low concentrations of such a variety of compounds inhaled over a long time. They also review the most widely used pharmacotherapeutic approaches to smoking cessation, and recent epidemiological data showing that ENDS can help some people stop smoking.

6) **Novel nicotinic drugs**

Over the last ten years, nAChR pharmacology has significantly progressed as a result of a number of advances, including the use of cryogenic electron microscopy (cryo-EM) to elucidate the high-resolution structures of the major (α4β2, α3β4 and α7) nAChR subtypes [33,34]. These advances have allowed the identification of ligands that interact at orthosteric or allosteric recognition sites on nAChR proteins and are capable of tuning channel conformational states, identifying chaperone/accessory proteins that allow the better characteri-sation of receptor subtypes and their functional expression, and also make it possible to create novel pharmacological agents that can activate or block nicotinic-mediated cholinergic responses with subtype or stoichiometry selectivity.

In this issue, a series of reviews of the literature published over the last five years cover the small selective ligands of heteromeric receptors (Matera *et al.*, 2023 [35]) and α7- and α9-containing receptors (Giraudo *et al.*, 2023 [36]): i.e. orthosteric agonists and antagonists, non-competitive antagonists and positive allosteric modulators (PAMs). Papke *et al.* (2023) [37] discuss the silent agonists that lead to little or no channel activation in α7 receptors, but stabilise the non-conducting conformations associated with desensitisation. Sanders and Millar (2023) [38] review the α7-selective modulators that bind to receptor sites other than the extracellular orthosteric agonist binding site for ACh: these compounds include ligands and PAMs (allosteric agonists or 'ago-PAMs') that are capable of inducing the direct allosteric activation of α7 nAChRs in the absence of an orthosteric agonist. Finally, Tae *et al.* (2023) [39] exhaustively describe the selective targeting and pharmacology of α-Conotoxins, which are small peptides isolated from the venom of cone snails that are attractive probes for distinguishing nAChR subtypes, and have therapeutic potential as nAChR antagonists.

However, although there are many interesting compounds that are active on nAChRs, their clinical application seems to proceed very slowly. A number of clinical studies have had to be interrupted before their completion because their clinical endpoints were not chosen correctly or the pharmacological characteristics and kinetics of the compounds themselves were not taken into consideration. Furthermore, as the nicotinic system generally seems to act as a fine tuner of very complex and articulated physiological processes rather than an on/off switch, the effects of nicotinic compounds are more difficult to document. All of these difficulties, together with our still insufficient knowledge of the pathophysiology of the target diseases and the enormous costs involved, seem to have dampened the interest of pharmaceutical companies in investing in the development of new nicotinic drugs [40].

Linked articles

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Declaration of Competing Interest

The authors of this editorial wish to acknowledge that they are co-authors of the articles by Gotti et al. (2024) and Sala and Gotti (2023) included in this special issue.

References

[1] J.N. Langley, On the reaction of cells and of nerve-endings to certain poisons, chieflyas regards the reaction of striated muscle to nicotine and curari, J. Physiol. 33 (1905) 374–413.
[2] H.H. Dale, W. Feldberg, M. Vogt, Release of acetylcholine at voluntary muscle motor nerve endings, J. Physiol. 86 (1936) 353–380.
[3] J.P. Changeux, M. Kasai, C.Y. Lee, Use of a snake venom toxin to characterize the cholinergic receptor protein, Proc. Natl. Acad. Sci. USA 67 (3) (1970) 1241–1247.
[4] M. Zoli, F. Pistillo, C. Gotti, Diversity of native nicotinic receptor subtypes in mammalian brain, Neuropharmacology 96 (Pt B) (2015) 302–311.
[5] M.M. Hilscher, S. Mikulovic, S. Perry, S. Lundberg, K. Kullander, The alpha2 nicotinic acetylcholine receptor, a subunit with unique and selective expression in inhibitory interneurons associated with principal cells, Pharm. Res. 196 (2023) 106895 (link issue).
[6] A. Abbondanza, A. Urushadze, A.R.A. Barboza, H. Janickova, Expression and function of nicotinic acetylcholine receptors in specific neuronal populations: focus on striatal and prefrontal circuits, Pharm. Res. (2024) 107190 (link issue).
[7] P. Sinclair, N. Kabbani, Ionotropic and metabotropic responses by alpha 7 nicotinic acetylcholine receptors, Pharm. Res. 197 (2023) 106975 (link issue).
[8] S. Leonard, R. Benfante, Unanswered questions in the regulation and function of the duplicated alpha7 nicotinic receptor gene CHRFAM7A, Pharm. Res. 192 (2023) 106783 (link issue).
[9] A.B. Elgoyhen, The alpha9alpha10 acetylcholine receptor: a non-neuronal nicotinic receptor, Pharm. Res. 190 (2023) 106735 (link issue).
[10] J.A. Matta, S. Gu, W.B. Davini, D.S. Bredt, Nicotinic acetylcholine receptor redux: discovery of accessories opens therapeutic vistas, Science 373 (6556) (2021).
[11] C. Gotti, F. Clementi, M. Zoli, Auxiliary protein and chaperone regulation of neuronal nicotinic receptor subtype expression and function, Pharmacol. Res. (2024) (link issue).
[12] N.A. Vasilyeva, E.V. Loktyushov, M.L. Bychkov, Z.O. Shenkarev, E.N. Lyukmanova, Three-Finger Proteins from the Ly6/uPAR family: functional diversity within one structural Motif, Biochem. (Mosc.) 82 (13) (2017) 1702–1715.
[13] J.M. Miwa, Lynx1 prototoxins: critical accessory proteins of neuronal nicotinic acetylcholine receptors, Curr. Opin. Pharm. 56 (2021) 46–51.
[14] T.B. Palumbo, J.M. Miwa, Lynx1 and the family of endogenous mammalian neurotoxin-like proteins and their roles in modulating nAChR function, Pharm. Res. 194 (2023) 106845 (link issue).
[15] J.F. Chrestia, O. Turani, N.R. Araujo, G. Hernando, M.D.C. Esandi, C. Bouzat, Regulation of nicotinic acetylcholine receptors by post-translational modifications, Pharm. Res. 190 (2023) 106712 (link issue).
[16] F.J. Barrantes, Structure and function meet at the nicotinic acetylcholine receptor-lipid interface, Pharm. Res. 190 (2023) 106729 (link issue).
[17] F. Bono, C. Fiorentini, V. Mutti, Z. Tomasoni, G. Sbrini, H. Trebesova, M. Marchi, M. Grilli, C. Missale, Central nervous system interaction and crosstalk between nAChRs and other ionotropic and metabotropic neurotransmitter receptors, Pharm. Res. 190 (2023) 106711 (link issue).
[18] A.V. Terry Jr., K. Jones, D. Bertrand, Nicotinic acetylcholine receptors in neurological and psychiatric diseases, Pharm. Res. 191 (2023) 106764 (link issue).
[19] A. Becchetti, L.C. Grandi, M. Cerina, A. Amadeo, Nicotinic acetylcholine receptors and epilepsy, Pharm. Res. 189 (2023) 106698 (link issue).
[20] P. Whiteaker, A.A. George, Discoveries and future significance of research into amyloid-beta/alpha7-containing nicotinic acetylcholine receptor (nAChR) interactions, Pharm. Res. 191 (2023) 106743 (link issue).
[21] J.L. Ables, K. Park, I. Ibanez-Tallon, Understanding the habenula: A major node in circuits regulating emotion and motivation, Pharm. Res. 190 (2023) 106734 (link issue).
[22] Y.S. Mineur, A.R. Soares, I.M. Etherington, Z.I. Abdulla, M.R. Picciotto, Pathophysiology of nAChRs: limbic circuits and related disorders, Pharm. Res. 191 (2023) 106745 (link issue).
[23] B. Buzzi, E. Koseli, L. Moncayo, M. Shoaib, M.I. Damaj, Role of neuronal nicotinic acetylcholine receptors in cannabinoid dependence, Pharm. Res. 191 (2023) 106746 (link issue).
[24] H.M. Kamens, G. Flarend, W.J. Horton, The role of nicotinic receptors in alcohol consumption, Pharm. Res. 190 (2023) 106705 (link issue).
[25] Z. Chen, X.A. Liu, P.J. Kenny, Central and peripheral actions of nicotine that influence blood glucose homeostasis and the development of diabetes, Pharm. Res. 194 (2023) 106860 (link issue).
[26] K.R. Keever, V.P. Yakubenko, D.B. Hoover, Neuroimmune nexus in the pathophysiology and therapy of inflammatory disorders: role of alpha7 nicotinic acetylcholine receptors, Pharm. Res. 191 (2023) 106758 (link issue).
[27] A.J. Hone, J.M. McIntosh, Nicotinic acetylcholine receptors: therapeutic targets for novel ligands to treat pain and inflammation, Pharm. Res. 190 (2023) 106715 (link issue).
[28] K. Richter, V. Grau, Signaling of nicotinic acetylcholine receptors in mononuclear phagocytes, Pharm. Res. 191 (2023) 106727 (link issue).
[29] M. Pechlivanidou, E. Ninou, K. Karagiorgou, A. Tsantila, R. Mantegazza, A. Francesca, R. Furlan, L. Dudeck, J. Steiner, J. Tzartos, S. Tzartos, Autoimmunity to neuronal nicotinic acetylcholine receptors, Pharm. Res. 192 (2023) 106790 (link issue).
[30] E.M. Castro, S. Lotfipour, F.M. Leslie, Nicotine on the developing brain, Pharm. Res. 190 (2023) 106716 (link issue).
[31] T.J. Gould, Epigenetic and long-term effects of nicotine on biology, behavior, and health, Pharm. Res. 192 (2023) 106741 (link issue).
[32] M. Sala, C. Gotti, Electronic nicotine delivery systems (ENDS): A convenient means of smoking? Pharm. Res. 195 (2023) 106885 (link issue).
[33] A. Gharpure, C.M. Noviello, R.E. Hibbs, Progress in nicotinic receptor structural biology, Neuropharmacology 171 (2020) 108086.
[34] C.M. Noviello, A. Gharpure, N. Mukhtasimova, R. Cabuco, L. Baxter, D. Borek, S. M. Sine, R.E. Hibbs, Structure and gating mechanism of the alpha7 nicotinic acetylcholine receptor, Cell 184 (8) (2021) 2121–2134, e13.
[35] C. Matera, C. Papotto, C. Dallanoce, M. De Amici, Advances in small molecule selective ligands for heteromeric nicotinic acetylcholine receptors, Pharm. Res. 194 (2023) 106813 (link issue).
[36] A. Giraudo, M. Pallavicini, C. Bolchi, Small molecule ligands for alpha9 * and alpha7 nicotinic receptors: a survey and an update, respectively, Pharm. Res. 193 (2023) 106801 (link issue).
[37] R.L. Papke, M. Quadri, A. Gulsevin, Silent agonists for alpha7 nicotinic acetylcholine receptors, Pharm. Res. 190 (2023) 106736 (link issue).
[38] V.R. Sanders, N.S. Millar, Potentiation and allosteric agonist activation of alpha7 nicotinic acetylcholine receptors: binding sites and hypotheses, Pharm. Res. 191 (2023) 106759 (link issue).
[39] H.S. Tae, D.J. Adams, Nicotinic acetylcholine receptor subtype expression, function, and pharmacology: therapeutic potential of alpha-conotoxins, Pharm. Res. 191 (2023) 106747 (link issue).
[40] A. Crestini, E. Carbone, R. Rivabene, A. Ancidoni, P. Rosa, A.M. Tata, E. Fabrizi, N. Locuratolo, N. Vanacore, E. Lacorte, P. Piscopo, A systematic review on drugs acting as nicotinic acetylcholine receptor agonists in the treatment of dementia, Cells 13 (3) (2024).

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