

Journal of Medicinal Chemistry

© Copyright 2008 by the American Chemical Society

Volume 51, Number 4

February 28, 2008

Perspective

Allosteric Modulators of the $\alpha 7$ Nicotinic Acetylcholine Receptor

Ramin Faghih,* Murali Gopalakrishnan, and Clark A. Briggs

Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, Illinois 60064

Received March 7, 2007

Introduction

Ion channels expressed in the plasma membrane are broadly classified as voltage-gated ion channels (VGIC^a) or ligand-gated ion channels (LGIC) where the ligand usually is considered to be an extracellular messenger such as a neurotransmitter. Often, the same transmitter acts upon an array of G-protein-coupled receptors (GPCR) as well as LGIC, for example, acetylcholine acting via the muscarinic GPCR and nicotinic acetylcholine receptor (nAChR) LGIC. A few notable exceptions include glycine which, to date, is known to act on LGIC only, and neuropeptides and histamine which appear to act exclusively via GPCRs. Known LGIC comprise three to five transmembrane subunits assembled to host a central ion channel and an extracellular ligand-binding domain. Opening of the ion channel and associated ion flux evokes an electrical signal with amplitude and polarity depending upon ion distribution across the membrane, channel conductance, and selectivity for cations or anions. Additionally, some LGIC can trigger Ca^{2+} -dependent events not only through depolarization and activation of voltage-gated Ca^{2+} channels but also by Ca^{2+} flux through the LGIC itself. The $\alpha 7$ nAChR, as well as the NMDA-sensitive glutamate receptor, is highly permeant to Ca^{2+} such that part of its signal, perhaps the more important signal, may be metabotropic in nature, triggered by Ca^{2+} influx.

nAChRs, members of the Cys-loop superfamily of LGIC, are widely characterized transmembrane proteins involved in the

physiological responses to the neurotransmitter ACh¹ and are distributed throughout the central nervous system (CNS) and the peripheral nervous system (PNS).^{2,3} These receptors are pentameric assemblies of subunits surrounding a central pore that gate the flux of Na^+ , K^+ , and Ca^{2+} ions.⁴ In addition to their localization in neurons, nAChRs are found in endocrine cells (adrenal chromaffin cells) and in classically nonexcitable cells such as endothelial, epithelial, and immune system cells.^{5,6} Thus, ligands acting upon nAChR may have a diversity of actions, depending upon the nature of the nAChR subunit(s) and the profile of the ligand. The extensive therapeutic potential for various nAChR targets has been summarized in a recent review.⁷

By definition, the receptor site occupied by the endogenous ligand is called the orthosteric site. The prototypical agonist nicotine, other natural and synthetic agonists, and competitive antagonists interact with this site. Several excellent reviews describing properties of agonists and antagonists are available.^{8,9} nAChRs also host multiple allosteric sites. Binding of an allosteric modulator alone generally has little or no discernible effect on channel gating but alters the ability of orthosteric ligand to effect channel gating. Molecules that increase the response to agonist are known as positive allosteric modulators (PAMs), whereas those that reduce the response to agonist (excluding orthosteric competitive antagonists, simple channel blockers, and structural alterations such as proteolysis) are known as negative allosteric modulators (NAMs). Such modulators are thought to alter the relative energy levels of specific receptor states and/or the energy barriers for state transitions.^{10,11} Thus, not only channel opening/closing but also receptor deactivation, desensitization, or resensitization kinetics may be modified.

Allosteric modulators are distinct from and offer, in principle, a number of advantages over orthosteric ligands. Allosteric modulators often exhibit little or no intrinsic activity because their mode of action is to augment or hinder the action of the endogenous agonist. This mode of action provides greater

* To whom correspondence should be addressed. Phone: 847-937-2972. Fax: 847-937-4143. E-mail: ramin.faghih@abbott.com.

^a Abbreviations: nAChR, nicotinic acetylcholine receptor; ACh, acetylcholine; PAM, positive allosteric modulator; NAM, negative allosteric modulator; VGIC, voltage-gated ion channels; LGIC, ligand-gated ion channels; TM, transmembrane; GPCR, G-protein-coupled receptors; CNS, central nervous system; PNS, peripheral nervous system; MLA, methyllycaconitine; MCI, mild cognitive impairment; AD, Alzheimer's disease; TNF- α , tumor necrosis factor; CSF, cerebrospinal fluid; NMDA, *N*-methyl-D-aspartate; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA_A, γ -aminobutyric acid; 5-HT₃, 5-hydroxytryptamine-3.

physiological selectivity compared to agonists or antagonists that act upon receptors selectively but indiscriminately with regard to ongoing physiological activity. Since allosteric binding sites are typically located at sites distinct from the orthosteric site, the potential exists for identifying molecules with superior subunit selectivity, especially between related family members. This has been well illustrated with benzodiazepines acting at the GABA_A receptor.¹² The mechanisms and modeling of nAChR allosteric transitions and modulator effects have been reviewed.^{10,11} Further, exhaustive reviews of nAChRs have recently appeared.^{9,13,14} This review will focus on medicinal chemistry developments in the area of $\alpha 7$ nAChR PAMs. First, however, a brief overview of the physiology and pharmacology of $\alpha 7$ nAChRs is presented.

Nicotinic Acetylcholine Receptors

Seventeen distinct nAChR subunits have been reported.¹⁵ nAChR subunits containing the Cys-loop signature vicinal cysteines in the appropriate position are designated " α ". ACh and other agonists bind in the interface between subunits. An α subunit is required for channel gating, and mature pentameric nAChRs generally are thought to contain at least two α subunits of identical or different types. Recent studies have taken advantage of a homologous snail protein (acetylcholine binding protein), which assembles as a pentamer similar to the nAChR extracellular domain, to determine the structural underpinnings of agonist binding and channel gating.^{16,17} Moreover, structure–function studies have revealed that the short amino acid segment between the second and third transmembrane domain is an important determinant in the gating process that takes place during receptor activation.¹⁸

Subunits other than α were named β , δ , γ (embryonic), and ϵ (adult substitute for γ) in skeletal muscle and fish electroplaque. Since the cloning of neuronal nAChR, muscle α has become $\alpha 1$ and neuronal α subunits are numbered in sequence of discovery. Neuronal nAChR subunits that did not contain the signature vicinal cysteines were designated "non- α " in the earlier literature. Today, all neuronal non- α are designated " β " and numbered in order of discovery with the muscle subunit designated $\beta 1$. Functional neuronal nAChR assemblies, defined in expression systems, can be homomeric, comprising $\alpha 7$ or $\alpha 8$ or $\alpha 9$ subunits. Other subunits require heteromeric assembly, with at least one subunit (usually two or three) from the α group ($\alpha 2$, $\alpha 3$, $\alpha 4$, or $\alpha 6$) and the remainder from the β group ($\beta 2$ or $\beta 4$). Additionally, $\alpha 7$ may combine with $\alpha 8$ in chick^{19,20} or with $\beta 2$ in mammal,^{21–23} and $\alpha 9$ expression is dramatically enhanced by $\alpha 10$ suggesting that the preferred assembly is $\alpha 9\alpha 10$.²⁴ The roles of $\alpha 5$ and $\beta 3$ are less clear; they may function to modify other assemblies or may combine with subunits not yet identified.

Native nAChR complexes are not yet fully elucidated. However, five major categories are generally recognized: (1) $\alpha 3\beta 4^*$ and $\alpha 3\beta 2^*$, which mediate peripheral ganglionic nicotinic transmission and some CNS functions; (2) $\alpha 4\beta 2^*$, which appears to be CNS-specific and comprises 90% of the high-affinity nicotine binding sites in rodent brain; (3) $\alpha 7^*$, which is widespread in brain and shows sensitivity to the antagonists α -bungarotoxin and methyllycaconitine (MLA); (4) $\alpha 6\beta 2^*$, also apparently CNS-specific but less abundant than $\alpha 4\beta 2^*$; and (5) $\alpha 9^*$. The asterisk wild card indicates the possibility that other subunits might contribute to the native receptor. An additional level of complexity may be envisaged even with just two subunits, as with $\alpha 4$ or $\alpha 3$ and $\beta 2$, where at least two pharmacologically distinct nAChRs with high and low sensitivities to agonist^{25–27} and differing Ca²⁺ permeabilities²⁸ can be expressed in recombinant systems.

It is apparent that nAChRs are involved in a range of synaptic and extra-synaptic functions. The muscle-type nAChR is a key mediator of transmission at the neuromuscular junction and fish electroplaque. In the PNS, $\alpha 3\beta 4^*$ and $\alpha 3\beta 2^*$ nAChRs mediate ganglionic neurotransmission, whereas in the CNS a variety of nAChR subtypes, with $\alpha 4\beta 2^*$ and $\alpha 7^*$ being the most widespread, mediate synaptic and possibly paracrine functions. Accordingly, nAChRs are implicated in a range of physiological and pathophysiological functions related to cognitive function, learning and memory, reward, motor control, arousal, and analgesia.¹³ Both $\alpha 7^*$ and $\alpha 4\beta 2^*$ nAChRs are expressed at high levels in areas involved with learning and memory and play key roles in modulating neurotransmission in these regions. Reduced cholinergic activity and dysregulation of nAChRs have been correlated with cognitive deficits and progressive dementia.^{29–31}

$\alpha 7$ Nicotinic Acetylcholine Receptors

$\alpha 7$ nAChRs in the CNS have received much attention since their discovery in the early 1990s.^{13,32–34} These subunits are found within the brain, autonomic ganglia, adrenal chromaffin cells, non-neuronal cells, and even skeletal muscle during development or following denervation. The $\alpha 7$ – $\alpha 9$ subtypes are distinguished from other nAChRs by their relatively high permeability to Ca²⁺^{35–38} rapid desensitization and sensitivity to antagonists such as α -bungarotoxin and MLA. However, $\alpha 8^*$ is known only in chick,³⁹ and $\alpha 9^*$, although found in mammals, has a highly restricted distribution in CNS.^{40–43} By virtue of the high Ca²⁺ permeability, these LGIC may participate not only in electrical signaling but also directly in the activation of Ca²⁺-dependent processes. At the cellular level, the activation of $\alpha 7$ nAChRs can regulate interneuron excitability,^{44–47} modulate the release of excitatory and inhibitory neurotransmitters,^{48–54} and play a neuroprotective role.^{55–58} Additionally, roles for this nAChR subtype in endothelial cells, epithelial cells, immunocompetent cells, and sperm have been implicated.^{59–68} While $\alpha 7$ expression is widespread, knockout mice showed surprisingly subtle deficits.⁶⁹ However, recent studies with the knockout mice and with antisense in rats have demonstrated roles for $\alpha 7$ nAChRs in cognitive and attentive tasks.^{70–72} For example, $\alpha 7$ nAChR gene knockout mice have shown impaired performance in ethanol-induced contextual fear conditioning,⁷² and when crossed with Tg2576 mice expressing human amyloid β ($A\beta$), they showed further deterioration in hippocampus-selective associative learning and memory.⁷³

Given their pivotal roles in CNS function, targeting $\alpha 7$ nAChRs may be considered a viable strategy for treating a variety of disorders, particularly those involving cognitive and attention deficits, such as mild cognitive impairment (MCI), attention deficit disorders, cognitive deficits associated with schizophrenia, Alzheimer's disease (AD), and various other dementias.^{74–77} Further, $\alpha 7$ nAChRs may have role in slowing disease progression in AD.³³ Thus, modulating, or modifying, the activity of $\alpha 7$ nAChRs has the potential to treat a variety of cognitive and neurodegenerative disorders.⁷⁸ Studies with subtype selective ligands, particularly agonists, have supported this concept in preclinical models for memory, attention, and schizophrenia.^{76,79–81} Additionally, there is growing evidence that nAChRs, particularly $\alpha 7$, can modulate cellular functions beyond synaptic transmission. Reported examples include anti-inflammatory effects via inhibition of the release of macrophage tumor necrosis factor (TNF- α) and high mobility group box 1 (HMGB1),^{65–67,82–84} roles in cutaneous homeostasis,⁶⁴ and promotion of angiogenesis.^{62,85,86} Thus, compounds targeting

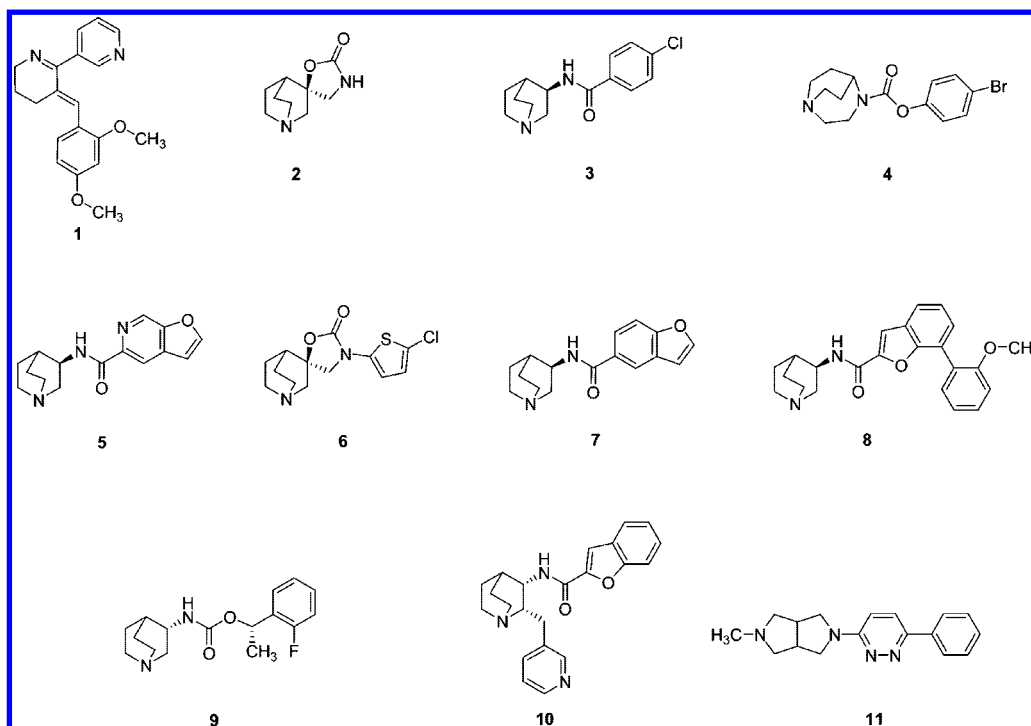


Figure 1. Examples of agonists selective for $\alpha 7$ nAChR.

$\alpha 7$ nAChRs have also been considered to have potential for treating various inflammatory diseases, septic shock, wound healing, angiogenesis, and skin disorders.^{67,84}

$\alpha 7$ nAChR Agonists

The prototypical nAChR agonist, nicotine, has itself been shown to improve attention and cognitive performance, reduce anxiety, normalize sensory gating, and effect neuroprotection.^{87,88} However, nicotine is not sufficiently selective among nAChRs and its utility is limited by side effects including seizures, irregular heartbeat, hypertension, and gastrointestinal effects.^{89–92} Accordingly, identification of subtype-selective compounds that embrace the beneficial effects of nicotine while eliminating or decreasing its adverse effects continues to be an active area of research.

One of the first compounds reported to be an $\alpha 7$ nAChR selective agonist is compound **1** (GTS-21), including its hydroxy metabolite.^{93–97} However, compound **1** also binds $\alpha 4\beta 2$ nAChR, and the $\alpha 7$ selectivity relates primarily to function. Compound **1** shows partial agonist activity at $\alpha 7$ and essentially no agonist activity at $\alpha 4\beta 2$ nAChR. To what extent the $\alpha 4\beta 2$ binding contributes to or detracts from activity of the compound such as in sensory gating⁹⁸ is not clear. Subsequently, substantially more potent, selective, and efficacious compounds have appeared with which to test the $\alpha 7$ nAChR hypothesis specifically. Several reviews have appeared on this subject.^{9,34,99,100}

Compound **2** (AR-R 17779) is an early example of an efficacious $\alpha 7$ nAChR agonist (Figure 1). This compound has been reported to facilitate the induction of hippocampal long-term potentiation (LTP) and to improve cognitive performance in social recognition, water maze, inhibitory avoidance, and scopolamine-induced memory impairment models.¹⁰¹ However, compound **2** also activates the homologous 5-HT₃ LGIC in addition to $\alpha 7$ nAChR,¹⁰² confounding mechanistic interpretation. Additionally, CNS penetration is low with brain levels being only about 10% of the plasma concentration.^{103,104} Further improvements in $\alpha 7$ nAChR selective compounds are exemplified by compounds **3–5** (Figure 1). Other quinuclidine analogues (Figure 1) also are known.^{105–109} Compound

3 (PNU-282987) was shown to enhance GABAergic synaptic activity in brain slices and to restore sensory gating deficits in rats.^{110,111} The partial agonist **4** (SSR 180711A) was shown to be efficacious in cognitive domains thought to be deficient in schizophrenia.¹¹² Compound **5** (PHA-543613), characterized by rapid brain penetration and high oral bioavailability in rat, has been shown to improve sensory gating and cognitive performance.¹¹³ Compound **8** (ABBF) improved cognitive performance in social recognition, object recognition, and water maze tasks.¹⁰⁵ Compound **11** (A-582941), another selective $\alpha 7$ nAChR agonist, was shown to activate MAP kinase signaling pathways and exhibit broad spectrum efficacy in models that capture domains of working memory, sensory gating short-term recognition memory, and long-term memory consolidation, cognitive domains implicated in deficits observed in Alzheimer's disease and schizophrenia.^{114–116} Collectively, these findings support a procognitive role for $\alpha 7$ nAChR agonists.

Allosteric Modulation of Nicotinic Acetylcholine Receptors

Modulation of transmission is widely considered to be a favorable path for neuronal therapeutics. Positive modulators can increase the gain of the physiological signal without causing an inappropriate tonic signal, whereas negative modulators could reduce the gain without completely blocking transmission. Such effects take advantage of physiological spatial and temporal selectivity, a considerable advantage in the CNS where the same receptor may be distributed among a variety of neurons with different physiological roles. In a broad sense, therapeutic examples of transmission modulators include biogenic amine reuptake inhibitors (antidepressants), acetylcholinesterase inhibitors (AD), and L-dopa (Parkinson's disease), all of which, by reduced catabolism or increased synthesis, boost synaptic levels of transmitters contingent upon physiological release of the transmitter. Benzodiazepines and related "benzodiazepine receptor agonists", barbiturates, and neurosteroids are examples of LGIC (GABA_A) modulator therapeutics.^{88,117–122} In the case

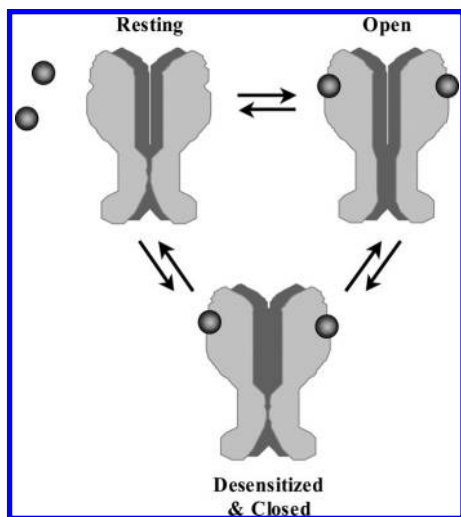


Figure 2. Model of allosteric transitions among resting, activated, and desensitized states consequent to binding of two molecules of conventional agonist.

of nAChRs, despite the beneficial effects of subtype selective agonists, uncertainty exists whether chronic treatment with agonists might provide suboptimal benefit due to sustained activation and desensitization of the nAChR.¹²³ An alternate approach to modulate $\alpha 7$ nAChR function is by enhancing effects of the endogenous neurotransmitter acetylcholine via positive allosteric modulation, reinforcing endogenous cholinergic neurotransmission without directly and indiscriminately activating the receptor. This provides another level of selectivity in that the modulator would be expected to produce little effect except upon the physiologically determined synaptic release of neurotransmitter ACh. A potential disadvantage in the PAM approach is that by relying on endogenous neurotransmitter, efficacy may diminish under certain conditions, such as in advanced stages of neurodegeneration.

General Principles and Considerations for nAChR Modulation

As noted above, nAChRs, like other receptors and ion channels, function by allosteric transitions and could be affected by modulators as well as conventional agonists and antagonists.¹²⁴ Agonist, once bound, is able to induce conformational transition of the LGIC from a resting state (channel closed) to an activated state (channel open, Figure 2). Activation may be followed by return to the resting state with agonist dissociation or by transition to a desensitized state (channel closed) if agonist remains bound. For $\alpha 7$ nAChR, high concentrations of agonist can produce desensitization in <1 s. Return to a reactivatable state is generally thought to require agonist dissociation and transition back to the resting conformation. However, some modulators are able to reactivate $\alpha 7$ nAChR currents¹²⁵ and it is not clear that this requires agonist dissociation. Transition between resting and desensitized state is thought to be bidirectional such that some ligands could induce transition from resting to desensitized state without transitioning through the activated channel open state.^{126,127}

The kinetics of these allosteric transitions are governed by rate constants related to the energy barriers between allosteric states, determining the probability that any individual LGIC will be found in a given conformation at any instant in time.^{10,128,129} In a simple model (Figure 2), channel activation is governed by on and off rate constants for agonist binding, a rate constant for transition from resting to activated (open) state, and rate

constants for transition out of the activated state to desensitized and to resting states. The LGIC undergoes spontaneous transitions between resting and activated states, and perhaps between other states, but with low probability. Binding of orthosteric agonist markedly increases the probability of resting to activated transition. Subsequently, the LGIC may enter desensitized state with bound ligand, a low-energy state. Additionally, there is evidence that some orthosteric ligands, e.g., one type of partial agonist, may induce transition to desensitized state directly, bypassing the open channel state. Modulators should interact with the LGIC in some way but should not directly compete for the same site as conventional agonist/antagonist ligands. Positive allosteric modulators (PAMs) increase the agonist response and may do so by stabilizing the activated, open channel state. Additionally, because rapid desensitization limits the peak response to agonist, especially for $\alpha 7$ nAChR, PAMs that reduce desensitization or destabilize the desensitized state may, through that action, also increase the apparent peak response amplitude. Negative allosteric modulators (NAMs) may have the opposite effects. Indirect modulation may occur through other processes, such as via phosphorylation of the LGIC or modified association with other membrane proteins. By definition, a modulator should not itself be an agonist. However, under some conditions, a PAM may appear to have partial agonist properties, as the small but finite probability for LGIC to exist in the activated state in the absence of bound agonist could be enhanced by the PAM.^{128,129}

Even in the simplistic scheme depicted in Figure 2, several types of modulators could be envisioned. One may facilitate transition from resting to open channel state upon activation by agonist, increasing agonist response amplitude without significant effect on response decay rate (see L_0 modification^{129,130}). Examples of such modulators have appeared and are referred to as type I PAMs. Other modulators may stabilize the open channel state, in theory, to the point where it has the lowest free energy in the presence of agonist plus modulator. This would not only enhance response amplitude but also reduce receptor desensitization and potentially allow reactivation from the desensitized state. Indeed, compounds producing such effects at $\alpha 7$ nAChR have been identified recently and are referred to as type II PAMs (see below). However, it should be recognized that these broad classifications are largely phenomenological. They serve to categorize modulator effects and direct medicinal chemistry, but the specific molecular mechanism(s) underlying each type of effect remains to be established. Given the intricacies of LGIC states and kinetics, it should be anticipated that more than one mechanism could underlie the broad modulator categories identified to date.

For GABA_A LGIC, homologous to nAChR, PAM binding sites have been identified and binding interactions between PAM and orthosteric ligand have been characterized and utilized in drug discovery efforts. However, among other members of the Cys-loop LGIC family, PAMs generally have been characterized more by function than binding. At $\alpha 7$ nAChR, there are numerous examples of highly effective PAMs that have no apparent direct effect on orthosteric ligand binding. Several factors may contribute to this: (a) binding generally is determined at equilibrium and probably reflects the desensitized nAChR state, while function reflects the open-channel state; i.e., there is a large kinetic disparity between function and binding measurements; (b) increasing the rate of transition from resting (closed channel) to activated (open channel) states could increase response amplitude while having little effect on orthosteric ligand binding at equilibrium; (c) the $\alpha 7$ nAChR desensitizes

rapidly such that slowing the rate of desensitization could increase the amplitude of the response while having little effect on orthosteric ligand binding at equilibrium; (d) binding typically is measured with radiolabeled antagonist (MLA or α -bungarotoxin), while for PAM it may be more relevant to measure agonist binding and to measure individual kinetic parameters rather than equilibrium binding; (e) orthosteric ligands may be differentially affected by a given PAM,¹³¹ and too few examples have been studied for $\alpha 7$ nAChR. Models to differentiate orthosteric ligand from allosteric modulator effect on binding have been developed,^{131,132} but little has been done to apply such models to $\alpha 7$ nAChR.

Recently described $\alpha 7$ nAChR PAMs can have profound effects not only on the agonist response amplitude but also on the apparent Hill coefficient in the agonist concentration–response relationship. Some have suggested that the increase in Hill coefficient may reflect the number of agonist molecules required to activate the receptor. This may be the case, but it is difficult to determine from the measurements and models typically applied. In a mathematical model, the apparent Hill coefficient also could be altered by changing the free energy of isomerization between certain allosteric states without altering the number of orthosteric ligand sites.^{129,130} Indeed, $\alpha 7$ nAChR activation and desensitization rates are sufficiently rapid that the ligand and receptor do not reach steady state in most response measurements, and thus, application of the Hill equation may be inappropriate in a formal sense. Such measurements may serve to compare one agonist to another under similar conditions but should not be taken too far in studies of receptor mechanism. Nondesensitizing mutagenized $\alpha 7$ nAChR may be helpful, but whether recent PAMs affect the mutagenized and wild-type nAChR similarly needs further study.

Among other recombinant nAChR, $\beta 2$ -containing nAChRs desensitize more slowly than $\alpha 7$, and $\beta 4$ -containing nAChRs desensitize even more slowly. Estradiol acts as an $\alpha 4\beta 2$ PAM,¹³³ but its effect is relatively weak. Both $\alpha 3\beta 2$ and $\alpha 4\beta 2$ nAChR demonstrate high- and low-sensitivity subforms,²⁵ which would complicate the evaluation of PAM mechanisms unless the subform could be isolated or the PAM could be demonstrated to be highly selective for one subform. Zinc modulates nAChR and affects the relatively slowly desensitizing $\alpha 4\beta 4$ nAChR recombinant most profoundly,¹³⁴ providing perhaps a simpler substrate for evaluation of nAChR PAM mechanisms. However, nAChR PAMs of current therapeutic interest may act through different sites and mechanisms.

Finally, as noted before, under some conditions, an $\alpha 7$ nAChR PAM, particularly at higher concentrations, may produce an agonist-like effect. This does not necessarily represent a second mechanism of nAChR activation, however. Modeling predicts that even a pure PAM mechanism could produce *apparent* receptor activation by augmenting the effect of spontaneous allosteric transitions.^{129,130} Further, under some conditions $\alpha 7$ nAChR activation could result from the combined effects of PAM plus choline, a weak but effective $\alpha 7$ agonist present in blood and cerebrospinal fluid ($\sim 10 \mu\text{M}$) and released from cells into bathing media *in vitro*.

Endogenous nAChR Modulators

nAChRs may be regulated physiologically by endogenous PAMs, possibly including serum albumin or associated substances.^{135,136} Zinc, found in high concentrations in specific neurons of brain, spinal cord, and sensory ganglia,^{137,138} modulates nAChR function, with the most profound actions on $\alpha 4^*$ nAChR.¹³⁴ The role of neuronal zinc remains unclear but

is potentially relevant to the pathology of AD.¹³⁹ Other endogenous nAChR modulators are proteins belonging to the Ly-6/urokinase plasminogen activator receptor (uPAR) superfamily of receptor and secreted proteins, which participate in signal transduction, cellular adhesion, and immune cell activation. These include SLURP (-1 and -2), a secreted protein found in the circulation,^{140,141} and lynx (-1 and -2),^{142–144} which contains a glycosylphosphatidylinositol (GPI) membrane anchor and is found in the brain. Interestingly, these proteins bear striking homology to the snake toxin α -bungarotoxin, a nAChR selective antagonist. The plasma concentration of SLURP-1 is sufficient to serve as an $\alpha 7$ nAChR PAM,¹⁴⁵ raising the possibility that these LGIC may be regulated by endogenous PAM, in addition to choline and low concentrations of ACh released as a paracrine factor. Consistent with this speculation, mutations in SLURP have been linked to a human dermatological disorder¹⁴⁵ and both SLURP-1 and the $\alpha 7$ nAChR have been implicated in epidermal cell function.^{64,146} Under such conditions, synthetic $\alpha 7$ nAChR PAMs may serve as replacement therapeutics as well as a means to adjust the gain on cholinergic synaptic transmission.

Indirect nAChR Modulators

nAChRs, like many other receptors, may be modulated through phosphorylation or engagement of other intracellular pathways. Taking advantage of such processes could provide significant therapeutic utility, if done in a reasonably selective manner. Mechanisms and opportunities for selectivity are not entirely clear at present. Thus, although one can modulate $\alpha 7$ nAChR through such pathways, indirectly acting compounds are not allosteric modulators in a strict sense. Examples of such compounds are provided in Figure 3 (top row).

The nootropics **12** (nefracetam) and **13** (aniracetam) have been found to potentiate $\alpha 7$ and $\alpha 4\beta 2$ nAChR (Figure 3).^{147–152} Additionally, a metabolite of aniracetam has been found to modulate $\alpha 7$ nAChRs¹⁵³ and compound **12** has been reported to also potentiate NMDA-sensitive LGIC.¹⁵⁴ Compounds **12** and **13** have been reported to enhance hippocampal transmission and behavioral performance.^{151,155,156} The molecular mechanism(s) underlying these effects is not fully elucidated but apparently involves G protein activation and kinase-mediated pathways.^{147,153,154,157} While interesting in the context of nAChR mechanisms, these compounds are not $\alpha 7$ nAChR selective and their protein kinase pathway activation could produce a multitude of other effects.

The tyrosine kinase inhibitor **14** (genistein) modulates $\alpha 7$ nAChR function through kinase pathways and possibly by direct receptor interaction. A study involving measurements of receptor phosphorylation, use of other kinase and phosphatase inhibitors, and overexpression of Src kinase indicated that compound **14**, acting as a tyrosine kinase inhibitor, could potentiate $\alpha 7$ nAChR responses.¹⁵⁸ Further, mutagenesis of the $\alpha 7$ nAChR localized the effect to Tyr-386 and Tyr-442 of the TM3–TM4 cytoplasmic loop. Other studies have suggested that **14**, again as a kinase inhibitor, could increase $\alpha 7$ nAChR responses by up-regulating membrane insertion of the receptor.¹⁵⁹ However, some effects of **14** can be quite rapid, seemingly more consistent with a direct interaction with the $\alpha 7$ nAChR than with a mechanism requiring cellular permeation and alteration of receptor phosphorylation.¹²⁵ Thus, compound **14** may potentiate $\alpha 7$ nAChR responses by more than one mechanism and may point toward another class of direct-acting $\alpha 7$ PAM. However, the varied effects of compound **14** complicate its utility as an *in vivo* tool and the structural aspects responsible for direct $\alpha 7$ PAM as opposed to

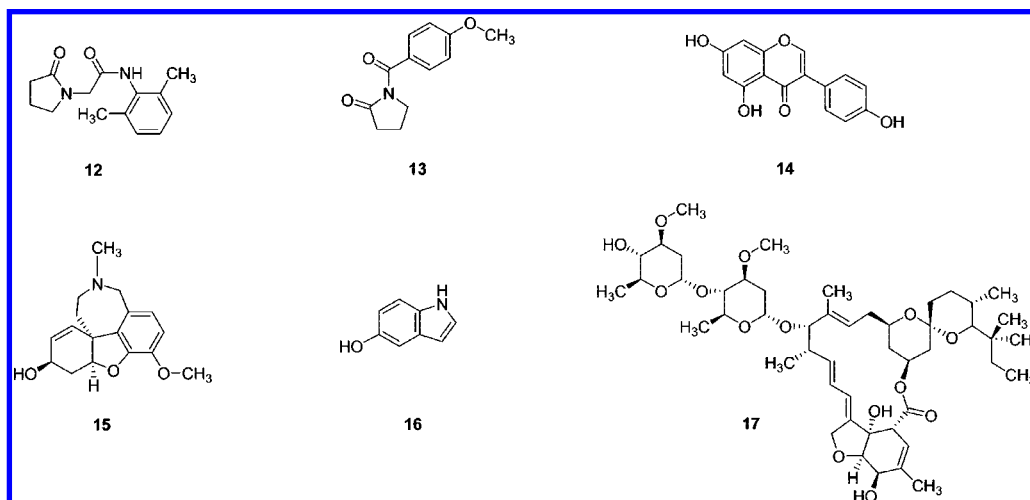


Figure 3. Indirect (first row) and direct (second row) allosteric modulators of $\alpha 7$ nAChR.

the indirect modulation of $\alpha 7$ nAChR expression or function remain to be determined. Although limited information regarding structure–activity relationships of genistein related to its kinase inhibition properties are available,¹⁶⁰ no SAR studies related to its PAM activity at $\alpha 7$ nAChRs have surfaced.

Direct-Acting nAChR PAMs

Early studies identified codeine and certain acetylcholinesterase inhibitors (physostigmine and **15** (galantamine) but not donepezil or rivastigmine) as nAChR modulators.^{161–166} Compound **15** (Figure 3), depending on the concentration tested, was reported to potentiate or inhibit type IA currents evoked by choline in cultured hippocampal neurons. Because these currents are thought to be mediated by the activation of $\alpha 7$ containing receptors, it was proposed that compound **15** effects are partially mediated by the allosteric potentiation of $\alpha 7$ nAChRs. The binding site, identified with the aid of a blocking antibody, was localized to a region of the nAChR N-terminal extracellular domain close to, but not within, the agonist binding site. However, as nAChR PAMs, the effects of agents like compound **15** are subtle and not selective. Furthermore, effects associated with acetylcholinesterase inhibition limit and confound the ability to use these agents as tools for proof of principle studies, and there is not a clear pharmacophore model for the design of potent and selective PAMs based on these agents.

Earlier known PAMs interacting directly with the $\alpha 7$ nAChR include compounds such as **16** (5-hydroxyindole)¹⁶⁷ and the anthelmintic ivermectin (**17**).¹⁶⁸ Compound **17**, one of the first $\alpha 7$ PAMs described, increases maximal ACh-evoked current, reduces the EC_{50} value of ACh, and increases the slope of the concentration–activation curve. Likewise, compound **16** causes a significant increase of subsequent ACh-evoked current at the $\alpha 7$ nAChR. There is some evidence that **16**, but not **15** or **17**, modestly enhances agonist binding potency, as assessed by radiolabeled antagonist displacement.^{169,170} Both compounds **16** and **17** are neither potent nor highly selective. For example, high concentrations (1–20 mM) of **16** are required for potentiating ACh evoked $\alpha 7$ nAChR mediated current, calcium or glutamate release.¹⁶⁷ With regard to receptor selectivity, compound **16** is reported to also modulate 5-HT₃ LGIC,¹⁷¹ and **17** modulates mammalian and invertebrate chloride LGIC.^{172–175}

$\alpha 7$ nAChR Selective PAMs

Novel $\alpha 7$ nAChR-selective PAMs belonging to diverse chemotypes have more recently emerged. The binding sites for these compounds have not been elucidated, but the fact that

their effects are rapid suggests a direct effect. As mentioned earlier, two profiles of PAMs may be recognized: type I that predominately affects the apparent peak current and type II that increases both the apparent peak current and slows the desensitization profile of the agonist response.

Type I PAMs

In addition to compounds like **16** and **14** mentioned above, a number of compounds have recently been reported as positive allosteric modulators with little effect on desensitization kinetics. Scientists at University of California—Irvine, taking advantage of the sequence homology between GABA_A and nAChR, hypothesized that compounds acting as positive allosteric modulators at GABA_A receptors also may modulate $\alpha 7$ nAChRs.¹⁷⁶ To this end they screened, for $\alpha 7$ PAM activity, a series of enaminones previously identified as PAMs of GABA_A receptors evoking modulation at a site distinct from the benzodiazepine, neuroactive steroid, and isosteric binding sites.^{177,178} Compound **18** (compound 6 or XY4083) was identified as an $\alpha 7$ nAChR PAM (Figure 4). Although detailed SAR remains to be described, the amide moiety of enaminones appears to be critical for $\alpha 7$ PAM activity. Currents enhanced by this PAM retained the fast kinetic and desensitization properties of the $\alpha 7$ nAChR. In rodent models, compound **18** normalized sensory-gating deficits in DBA/2 mice and improved working memory in the eight-arm radial maze.¹⁷⁹ Pharmacokinetic studies suggested that the brain levels achieved were adequate to modulate $\alpha 7$ nAChRs in these behavioral tests. For example, in the sensory-gating studies, the brain level of the compound corresponded to 0.3 μ M after intravenous administration of 0.3 mg/kg. This exposure level correlated with positive modulation of $\alpha 7$ nAChRs by 20% (120% of control) as measured by analysis of peak current response.

More recently, a urea derivative **19** (NS1738) has been described as an $\alpha 7$ nAChR PAM (Figure 4). In this series almost invariably one of the phenyl moieties of the urea is substituted by one or more electron-withdrawing groups.¹⁸⁰ Oocyte and patch clamp electrophysiology experiments reveal that this compound augmented the $\alpha 7$ nAChR response to ACh by about 2- to 3-fold, increasing both potency and maximal efficacy of the neurotransmitter, with an EC_{50} value for modulator activity of 3.4 μ M. Urea **19** had only marginal effects on the decay kinetics of the $\alpha 7$ nAChR response, reflecting minimal effect on receptor desensitization. Nevertheless, compound **19** was found to improve recognition memory and reverse impairments

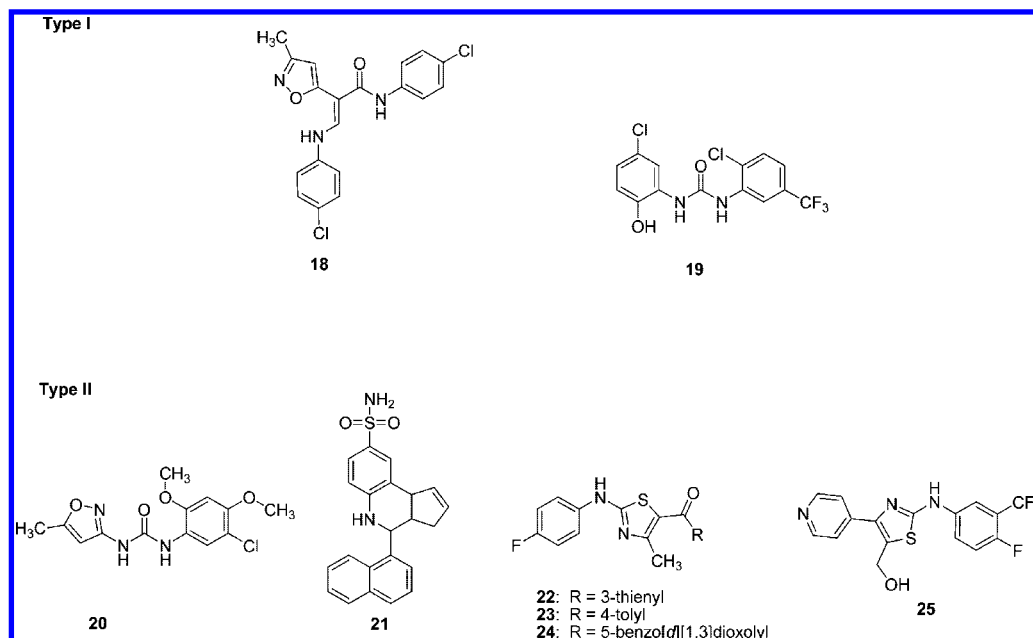


Figure 4. Examples of type I and type II allosteric modulators of $\alpha 7$ nAChR.

in water maze performance by (–)-scopolamine in rats.¹⁸¹ The minimal effective dose was 30 mg/kg and was associated with a brain concentration of $\sim 1 \mu\text{M}$.

Type II PAMs

Compound **20** (PNU-120596) remains one of the better characterized type II PAMs.¹⁸² These urea analogues possess phenyl-substituted electron-donating groups on one nitrogen of the urea and a five-membered heterocycle bearing an electron-withdrawing group on the other nitrogen. Compound **20** not only increased peak ACh-evoked $\alpha 7$ nAChR current by ~ 4 -fold (modulation $\text{EC}_{50} = 1.5 \mu\text{M}$) but also substantially increased the duration of the response by suppressing desensitization.^{125,182}

Like other type II PAMs, compound **20** is capable of restoring current responses at an already desensitized $\alpha 7$ nAChR. Although ureas **19** and **20** are structurally related, it is interesting to note that their characteristics as $\alpha 7$ nAChR PAMs are quite different. Both compounds enhance response amplitudes, but only **20** demonstrated a profound effect on the desensitization kinetics. The differential profiles of **19** and **20** suggest that these molecules may have distinct modes of action. In vivo, compound **20** improved sensory gating deficits induced by amphetamine in rats, a pharmacological model proposed to reflect circuit disturbance associated with schizophrenia. Compound **20** also improved performance in a rodent short-term recognition memory model.¹⁸³ Brain concentrations of **20** associated with the minimally effective dose were $\sim 80 \text{ nM}$ following intravenous and subcutaneous administration (0.3 mg/kg). This exposure is comparable to the concentration that produced a measurable modulation of ACh-evoked currents (by $\sim 25\%$) in hippocampal neurons or in $\alpha 7$ nAChR expressing cells, suggesting that a relatively low level of modulator activity is sufficient for evoking in vivo efficacy. At a behaviorally efficacious dose range, compound **20** also increased the phosphorylation of key biochemical markers such as cyclic AMP response element binding protein (CREB), a well-recognized signaling mechanism implicated in learning and memory.

More recently described quinoline sulfonamides exemplified by **21** are reported as PAMs of $\alpha 7$ nAChR, increasing the peak

current amplitude and substantially slowing the desensitization kinetics.¹²⁵ On the basis of peak current amplitude measurements, the cyclopentaquinoline analogue has been found to have potency (modulation $\text{EC}_{50} = 1.3 \mu\text{M}$) comparable to that of urea **20**, and both compounds are considerably more potent than indole **16** (modulation $\text{EC}_{50} = 1 \text{ mM}$). It is interesting to note that fused tetrahydroquinolines reported in this series as $\alpha 7$ PAMs are substituted at the 8-position with a sulfonamide group.¹⁸⁴

Representing another chemical class, three thiazoles (Figure 4) were initially reported as PAMs.¹⁸⁵ These compounds potentiated $\alpha 7$, $\alpha 2\beta 4$, $\alpha 4\beta 2$, and $\alpha 4\beta 4$ but not peripheral ganglionic $\alpha 3^*$, muscle $\alpha 1$ -containing nAChRs, or other ion channels such as NMDA, AMPA, and GABA_A. Thus, the compounds do not appear to be selective for $\alpha 7$ nAChR but show a remarkably favorable selectivity for CNS nAChRs. By selection of the thiazole analogue **22** (LY-2087101) as a prototype and using a chimeric $\alpha 7/5\text{-HT}_3$ receptor hosting the N-terminal extracellular domain and the transmembrane and C-terminal regions of the 5-HT₃ receptor, it was revealed that the site of allosteric potentiation by this compound lies in regions other than the N-terminal extracellular domain, unlike **16** and **15**.^{179,186} More recently, a thiazole derivative **25** (JNJ1930942) has been reported as an $\alpha 7$ nAChR PAM¹⁸⁶ (Figure 4). Compound **25** increases the peak current amplitude and substantially slows the desensitization kinetics, with a modulation EC_{50} value of $4.2 \mu\text{M}$.

Perspectives and Future Directions

The past 40 years or so have witnessed a rising interest in allosteric modulation as a means of regulating receptor and ion channel function. Prominent examples directly relevant to the Cys-loop family of LGIC are the varied GABA_A allosteric modulators, including widely successful sleep medicines. Here, subunit selective pharmacological fine-tuning has been realized with drugs acting allosterically. Allosteric modulators of $\alpha 7$ nAChRs such as those reviewed here are introductory examples of a novel emerging pharmacology that will hold our attention in the future.

The results summarized above show that a variety of chemotypes could modulate $\alpha 7$ nAChRs through interaction at distinct sites on the protein that may or may not be located extracellularly. Quite simplistically, at least two different profiles of PAMs may be envisaged: type I PAMs that predominately affect the peak current and agonist sensitivity exemplified by compounds such as **18** and **19**, and type II PAMs that, in addition, cause modification of the desensitization profile of agonist responses exemplified by compound **20**. Both types of PAMs have been reported to show in vivo efficacy in animal models of cognition. In some cases, in vitro properties and physiochemical properties remain to be further optimized because compounds are limited by relatively low potency, low solubility, metabolic stability, and/or adequate CNS penetration. Accordingly, identification of selective, potent, and pharmacokinetically acceptable PAMs continues to be an active area of discovery research.

From a mechanistic sense, PAMs of differential in vitro profiles should prove to be valuable tools with which to further define the physiology and pharmacology of $\alpha 7$ nAChR transmission and with which to interrogate biophysical models of nAChR function along the lines of the Monod–Wyman–Changeux model of allosteric receptor function.^{4,129,187–189} Information regarding the complexity of PAM binding sites is emerging, but the molecular mechanisms are not well understood. It is also unclear whether PAMs with differential in vitro profiles, e.g., type I vs type II, exhibit differences in the spectrum of in vivo efficacy, safety, and tolerability profiles. In particular, whether the type II profile is desirable or undesirable in view of potential consequences of sustained Ca^{2+} influx is a question yet to be completely resolved.

Mechanistic differences between PAMs and agonists could be critical for drug development. Orthosteric agonists could trigger continued activation of the receptor even in the absence of physiological activity by the corresponding neuronal network. Or in the case of a rapidly desensitizing receptor such as the $\alpha 7$ nAChR, such compounds could actually attenuate endogenous transmission while activating only a small fraction of the channels. PAMs, on the other hand, are limited by the nature of the receptor modulation, and their actions are dependent on the availability of endogenously available agonist. Some of the immediate challenges to expedite drug discovery and development in this area include identifying modulator binding sites, clarifying desirable in vitro functional profiles, determining the optimal selectivity profile, and establishing the ability to expediently screen the varied functional effects of PAMs. Finally, it remains to be determined whether PAMs, in reality, display additional advantages compared to agonists in terms of efficacy, tolerance, or compensatory mechanisms preclinically and, ultimately, in the clinic. Addressing these challenging questions, a significant new focus in the field of nAChR research, should pave the way for attractive novel therapeutics with which to address neuropsychiatric and neurodegenerative diseases without unwanted side effects.

Biographies

Ramin Faghih received his Ph.D. (Doctorat D'Etat) in Organic Chemistry from the Université Paris-Sud (Centre D'Orsay). Following postdoctoral work with Prof. Bert Fraser-Reid at Duke University, he joined Abbott Laboratories. Dr. Faghih's research interests lie in the area of synthetic and medicinal chemistry and drug design. He is currently focusing his research efforts on the identification of novel agents for the treatment of neuropsychiatric disorders.

Clark A. Briggs received his Sc.B. in Chemistry from Brown University and a Ph.D. in Pharmacology from Yale University. Following a postdoctoral fellowship and a Research Scientist position at the Beckman Research Institute at the City of Hope Medical Center, he joined Abbott Neuroscience Research where he has been engaged in drug discovery programs pertaining to G-protein-coupled receptors and ligand- and voltage-gated ion channel targets for neuropsychiatric and analgesic and urologic indications.

Murali Gopalakrishnan received his B.Pharmacy degree from Banaras Hindu University, India, and a Ph.D. degree in Biochemical Pharmacology from the State University of New York at Buffalo with Prof. David J. Triggle. Following a postdoctoral fellowship at the Department of Physiology at Baylor College of Medicine, he joined Abbott. Since then, he has been engaged in drug discovery programs in the areas of central nervous system, urology, and pain, focusing on voltage- and ligand-gated ion channels. Currently, Dr. Gopalakrishnan is Project Leader in Neuroscience Research Area within the Global Pharmaceutical Research and Development Division of Abbott.

Note Added after ASAP Publication. This paper posted ASAP on January 17, 2008 before corrections were incorporated. The revised version posted ASAP on January 24, 2008.

References

- (1) Levin, E. D. *Nicotinic Receptors in the Nervous System*; CRC Press: Boca Raton, FL, 2002.
- (2) Paterson, D.; Nordberg, A. Neuronal nicotinic receptors in the human brain. *Prog. Neurobiol.* **2000**, *61*, 75–111.
- (3) Gahring, L. C.; Rogers, S. W. Neuronal nicotinic acetylcholine receptor expression and function on nonneuronal cells. *Am. Assoc. Pharm. Sci. J.* **2006**, *7*, E885–E894.
- (4) Hogg, R. C.; Raggenbass, M.; Bertrand, D. Nicotinic acetylcholine receptors: from structure to brain function. *Rev. Physiol. Biochem. Pharmacol.* **2003**, *147*, 1–46.
- (5) Lee, C. Conformation, action, and mechanism of action of neuromuscular blocking muscle relaxants. *Pharmacol. Ther.* **2003**, *98*, 143–169.
- (6) McGehee, D. S.; Role, L. W. Physiological diversity of nicotinic acetylcholine receptors expressed by vertebrate neurons. *Annu. Rev. Physiol.* **1995**, *57*, 521–546.
- (7) Lippiello, P. M.; Bencherif, M.; Hauser, T. A.; Jordan, K. G.; Letchworth, S. R.; Mazurov, A. A. Nicotinic receptors as targets for therapeutic discovery. *Expert Opin. Drug Discovery* **2007**, *2*, 1185–1203.
- (8) Romanelli, M. N.; Gratter, P.; Guandalini, L.; Martini, E.; Bonaccini, C.; Gualtieri, F. Central nicotinic receptors: structure, function, ligands, and therapeutic potential. *ChemMedChem* **2007**, *2*, 746–767.
- (9) Jensen, A. A.; Frolund, B.; Liljefors, T.; Krosgaard-Larsen, P. Neuronal nicotinic acetylcholine receptors: structural revelations, target identifications, and therapeutic inspirations. *J. Med. Chem.* **2005**, *48*, 4705–4745.
- (10) Edelstein, S. J.; Changeux, J.-P. Allosteric transitions of the acetylcholine receptor. *Adv. Protein Chem.* **1998**, *51*, 121–184.
- (11) Bertrand, D.; Gopalakrishnan, M. Allosteric modulation of nicotinic acetylcholine receptors. *Biochem. Pharmacol.* **2007**, *74*, 1155–1163.
- (12) Mohler, H.; Fritschy, J. M.; Rudolph, U. A new benzodiazepine pharmacology. *J. Pharmacol. Exp. Ther.* **2002**, *300*, 2–8.
- (13) Dani, J. A.; Bertrand, D. Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. *Annu. Rev. Pharmacol. Toxicol.* **2007**, *47*, 699–729.
- (14) Hogg, R. C.; Bertrand, D. Partial agonists as therapeutic agents at neuronal nicotinic acetylcholine receptors. *Biochem. Pharmacol.* **2007**, *73*, 459–468.
- (15) Lukas, R. J.; Changeux, J.-P.; Le Novère, N.; Albuquerque, E. X.; Balfour, D. J. K.; Berg, D. K.; Bertrand, D.; Chiappinelli, V. A.; Clarke, P. B. S.; Collins, A. C.; Dani, J. A.; Grady, S. R.; Kellar, K. J.; Lindstrom, J. M.; Marks, M. J.; Quik, M.; Taylor, P. W.; Wonnacott, S. International Union of Pharmacology. XX. Current status of the nomenclature for nicotinic acetylcholine receptors and their subunits. *Pharmacol. Rev.* **1999**, *51*, 397–401.
- (16) Gao, F.; Mer, G.; Tonelli, M.; Hansen, S. B.; Burghardt, T. P.; Taylor, P.; Sine, S. M. Solution NMR of acetylcholine binding protein reveals ACh-mediated conformational change of the C-loop. *Mol. Pharmacol.* **2006**, *70*, 1230–1235.

- (17) Bouzat, C.; Gumilar, F.; Spitzmaul, G.; Wang, H. L.; Rayes, D.; Hansen, S. B.; Taylor, P.; Sine, S. M. Coupling of agonist binding to channel gating in an ACh-binding protein linked to an ion channel. *Nature* **2004**, *430*, 896–900.
- (18) Lee, W. Y.; Sine, S. M. Principal pathway coupling agonist binding to channel gating in nicotinic receptors. *Nature* **2005**, *438*, 243–247.
- (19) Keiger, C. J. H.; Prevette, D.; Conroy, W. G.; Oppenheim, R. W. Developmental expression of nicotinic receptors in the chick and human spinal cord. *J. Comp. Neurol.* **2003**, *455*, 86–99.
- (20) Gotti, C.; Hanke, W.; Maury, K.; Moretti, M.; Ballivet, M.; Clementi, F.; Bertrand, D. Pharmacology and biophysical properties of $\alpha 7$ and $\alpha 7$ - $\alpha 8$ α -bungarotoxin receptor subtypes immunopurified from the chick optic lobe. *Eur. J. Neurosci.* **1994**, *6*, 1281–1291.
- (21) Azam, L.; Winzer-Serhan, U.; Leslie, F. M. Co-expression of $\alpha 7$ and $\beta 2$ nicotinic acetylcholine receptor subunit mRNAs within rat brain cholinergic neurons. *Neuroscience* **2003**, *119*, 965–977.
- (22) Blumenthal, E. M.; Shoop, R. D.; Berg, D. K. Developmental changes in the nicotinic responses of ciliary ganglion neurons. *J. Neurophysiol.* **1999**, *81*, 111–120.
- (23) Pugh, P. C.; Corriveau, R. A.; Conroy, W. G.; Berg, D. K. Novel subpopulation of neuronal acetylcholine receptors among those binding α -bungarotoxin. *Mol. Pharmacol.* **1995**, *47*, 717–725.
- (24) Elgoyhen, A. B.; Vetter, D. E.; Katz, E.; Rothlin, C. V.; Heinemann, S. F.; Boulter, J. $\alpha 10$: a determinant of nicotinic cholinergic receptor function in mammalian vestibular and cochlear mechanosensory hair cells. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 3501–3506.
- (25) Briggs, C. A.; Gubbins, E. J.; Marks, M. J.; Putman, C. B.; Thimmapaya, R.; Meyer, M. D.; Surowy, C. S. Untranslated region dependent exclusive expression of high-sensitivity subforms of $\alpha 4\beta 2$ and $\alpha 3\beta 2$ nicotinic acetylcholine receptors. *Mol. Pharmacol.* **2006**, *70*, 227–240.
- (26) Zhou, Y.; Nelson, M. E.; Kuryatov, A.; Choi, C.; Cooper, J.; Lindstrom, J. Human $\alpha 4\beta 2$ acetylcholine receptors formed from linked subunits. *J. Neurosci.* **2003**, *23*, 9004–9015.
- (27) Zwart, R.; Vijverberg, H. P. M. Four pharmacologically distinct subtypes of $\alpha 4\beta 2$ nicotinic acetylcholine receptor expressed in *Xenopus laevis* oocytes. *Mol. Pharmacol.* **1998**, *54*, 1124–1131.
- (28) Tapia, L.; Kuryatov, A.; Lindstrom, J. M. Ca^{2+} permeability of the $(\alpha 4)_3(\beta 2)_2$ stoichiometry greatly exceeds that of $(\alpha 4)_2(\beta 2)_3$ human AChRs. *Mol. Pharmacol.* **2007**, *71*, 769–776.
- (29) Quirk, M.; Kulak, J. M. Nicotine and nicotinic receptors: relevance to Parkinson's disease. *Neurotoxicology* **2002**, *23*, 581–594.
- (30) Quirk, M.; Polonskaya, Y.; McIntosh, J. M.; Kulak, J. M. Differential nicotinic receptor expression in monkey basal ganglia: effects of nigrostriatal damage. *Neuroscience* **2002**, *112*, 619–630.
- (31) Leonard, S.; Breese, C.; Adams, C.; Benhammou, K.; Gault, J.; Stevens, K.; Lee, M.; Adler, L.; Olincy, A.; Ross, R.; Freedman, R. Smoking and schizophrenia: abnormal nicotinic receptor expression. *Eur. J. Pharmacol.* **2000**, *393*, 237–242.
- (32) Couturier, S.; Bertrand, D.; Matter, J.-M.; Hernandez, M.-C.; Bertrand, S.; Millar, N.; Valera, S.; Barkas, T.; Ballivet, M. A neuronal nicotinic acetylcholine receptor subunit ($\alpha 7$) is developmentally regulated and forms a homo-oligomeric channel blocked by α -BTX. *Neuron* **1990**, *5*, 847–856.
- (33) D'Andrea, M. R.; Nagle, R. G. Targeting the $\alpha 7$ nicotinic acetylcholine receptor to reduce amyloid accumulation in Alzheimer's disease pyramidal neurons. *Curr. Pharm. Des.* **2006**, *12*, 677–684.
- (34) Mazurov, A.; Hauser, T.; Miller, C. H. Selective $\alpha 7$ nicotinic acetylcholine receptor ligands. *Curr. Med. Chem.* **2006**, *13*, 1567–1584.
- (35) Dajas-Bailador, F.; Wonnacott, S. Nicotinic acetylcholine receptors and the regulation of neuronal signalling. *Trends Pharmacol. Sci.* **2004**, *25*, 317–324.
- (36) Castro, N. G.; Albuquerque, E. X. α -Bungarotoxin-sensitive hippocampal nicotinic receptor channel has a high calcium permeability. *Biophys. J.* **1995**, *68*, 516–524.
- (37) Seguela, P.; Wadiche, J.; Dineley-Miller, K.; Dani, J. A.; Patrick, J. W. Molecular cloning, functional properties, and distribution of rat brain $\alpha 7$: a nicotinic cation channel highly permeable to calcium. *J. Neurosci.* **1993**, *13*, 596–604.
- (38) Sands, S. B.; Costa, A. C. S.; Patrick, J. W. Barium permeability of neuronal nicotinic receptor $\alpha 7$ expressed in *Xenopus* oocytes. *Biophys. J.* **1993**, *65*, 2614–2621.
- (39) Lohmann, T. H. O.; Torrao, A. S.; Britto, L. R. G.; Lindstrom, J.; Hamassaki-Britto, D. E. A comparative non-radioactive *in situ* hybridization and immunohistochemical study of the distribution of $\alpha 7$ and $\alpha 8$ subunits of the nicotinic acetylcholine receptors in visual areas of the chick brain. *Brain Res.* **2000**, *852*, 463–469.
- (40) Sgard, F.; Charpentier, E.; Bertrand, S.; Walker, N.; Caput, D.; Graham, D.; Bertrand, D.; Besnard, F. A novel human nicotinic receptor subunit, $\alpha 10$, that confers functionality to the $\alpha 9$ subunit. *Mol. Pharmacol.* **2002**, *61*, 150–159.
- (41) Lustig, L. R.; Peng, H.; Hiel, H.; Yamamoto, T.; Fuchs, P. A. Molecular cloning and mapping of the human nicotinic acetylcholine receptor $\alpha 10$ (CHRNA10). *Genomics* **2001**, *73*, 272–283.
- (42) Keiger, C. J. H.; Walker, J. C. Individual variation in the expression profiles of nicotinic receptors in the olfactory bulb and trigeminal ganglion and identification of $\alpha 2$, $\alpha 6$, $\alpha 9$, and $\beta 3$ transcripts. *Biochem. Pharmacol.* **2000**, *59*, 233–240.
- (43) Glowatzki, E.; Wild, K.; Brandle, U.; Fakler, G.; Fakler, B.; Zenner, H. P.; Ruppersberg, J. P. Cell-specific expression of the $\alpha 9$ nACh receptor subunit in auditory hair cells revealed by single-cell RT-PCR. *Proc. R. Soc. London, Ser. B* **1995**, *262*, 141–147.
- (44) Buhler, A. V.; Dunwiddie, T. V. Regulation of the activity of hippocampal stratum oriens interneurons by $\alpha 7$ nicotinic acetylcholine receptors. *Neuroscience* **2001**, *106*, 55–67.
- (45) Frazier, C. J.; Rollins, Y. D.; Breese, C. R.; Leonard, S.; Freedman, R.; Dunwiddie, T. V. Acetylcholine activates an α -bungarotoxin sensitive nicotinic current in rat hippocampal interneurons, but not pyramidal cells. *J. Neurosci.* **1998**, *18*, 1187–1195.
- (46) Jones, S.; Yakel, J. L. Functional nicotinic ACh receptors on interneurons in the rat hippocampus. *J. Physiol. (London)* **1997**, *504*, 603–610.
- (47) Alkondon, M.; Albuquerque, E. X. Diversity of nicotinic acetylcholine receptors in rat hippocampal neurons. I. Pharmacological and functional evidence for distinct structural subtypes. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 1455–1473.
- (48) Alkondon, M.; Pereira, E. F. R.; Barbosa, C. T. F.; Albuquerque, E. X. Neuronal nicotinic acetylcholine receptor activation modulates gamma-aminobutyric acid release from CA1 neurons of rat hippocampal slices. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 1396–1411.
- (49) Barik, J.; Wonnacott, S. Indirect modulation by $\alpha 7$ nicotinic acetylcholine receptors of noradrenaline release in rat hippocampal slices: interaction with glutamate and GABA systems and effect of nicotine withdrawal. *Mol. Pharmacol.* **2006**, *69*, 618–628.
- (50) Girod, R.; Barazangi, N.; McGehee, D. S.; Role, L. W. Facilitation of glutamatergic neurotransmission by presynaptic nicotinic acetylcholine receptors. *Neuropharmacology* **2000**, *39*, 2715–2725.
- (51) Gray, R.; Rajan, A. S.; Radcliffe, K. A.; Yakehiro, M.; Dani, J. A. Hippocampal synaptic transmission enhanced by low concentrations of nicotine. *Nature* **1996**, *383*, 713–716.
- (52) Li, X.; Rainnie, D. G.; McCarley, R. W.; Greene, R. W. Presynaptic nicotinic receptors facilitate monoaminergic transmission. *J. Neurosci.* **1998**, *18*, 1904–1912.
- (53) Schilström, B.; Fagerquist, M. V.; Zhang, X.; Hertel, P.; Panagis, G.; Nomikos, G. G.; Svensson, T. H. Putative role of presynaptic $\alpha 7^*$ nicotinic receptors in nicotine stimulated increases of extracellular levels of glutamate and aspartate in the ventral tegmental area. *Synapse* **2000**, *38*, 375–383.
- (54) Summers, K. L.; Kem, W. R.; Giacobini, E. Nicotinic agonist modulation of neurotransmitter levels in the rat frontoparietal cortex. *Jpn. J. Pharmacol.* **1997**, *74*, 139–146.
- (55) O'Neill, M. J.; Murray, T. K.; Lakics, V.; Visanji, N. P.; Duty, S. The role of neuronal nicotinic acetylcholine receptors in acute and chronic neurodegeneration. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 399–411.
- (56) Belluardo, N.; Mudo, G.; Blum, M.; Fuxe, K. Central nicotinic receptors, neurotrophic factors and neuroprotection. *Behav. Brain Res.* **2000**, *113*, 21–34.
- (57) Kem, W. R. The brain $\alpha 7$ nicotinic receptor may be an important therapeutic target for the treatment of Alzheimer's disease: studies with DMXB (GTS-21). *Behav. Brain Res.* **2000**, *113*, 169–181.
- (58) Broide, R. S.; Leslie, F. M. The $\alpha 7$ nicotinic acetylcholine receptor in neuronal plasticity. *Mol. Neurobiol.* **1999**, *20*, 1–16.
- (59) Saeed, R. W.; Varma, S.; Peng-Nemereff, T.; Sherry, B.; Balakhaneh, D.; Huston, J.; Tracey, K. J.; Al Abed, Y.; Metz, C. N. Cholinergic stimulation blocks endothelial cell activation and leukocyte recruitment during inflammation. *J. Exp. Med.* **2005**, *201*, 1113–1123.
- (60) Kawashima, K.; Fujii, T. Expression of non-neuronal acetylcholine in lymphocytes and its contribution to the regulation of immune function. *Front. Biosci.* **2004**, *9*, 2063–2085.
- (61) Bruggmann, D.; Lips, K. S.; Pfeil, U.; Haberberger, R. V.; Kummer, W. Multiple nicotinic acetylcholine receptor α -subunits are expressed in the arterial system of the rat. *Histochem. Cell Biol.* **2002**, *118*, 441–447.
- (62) Heesch, C.; Weis, M.; Aicher, A.; Dimmeler, S.; Cooke, J. P. A novel angiogenic pathway mediated by non-neuronal nicotinic acetylcholine receptors. *J. Clin. Invest.* **2002**, *110*, 527–536.
- (63) Proskocil, B. J.; Sekhon, H. S.; Jia, Y.; Savchenko, V.; Blakely, R. D.; Lindstrom, J.; Spindel, E. R. Acetylcholine is an autocrine or paracrine hormone synthesized and secreted by airway bronchial epithelial cells. *Endocrinology* **2004**, *145*, 2498–2506.
- (64) Arredondo, J.; Nguyen, V. T.; Chernyavsky, A. I.; Bercovich, D.; Orr-Urtreger, A.; Vetter, D. E.; Grando, S. A. Functional role of $\alpha 7$

- nicotinic receptor in physiological control of cutaneous homeostasis. *Life Sci.* **2003**, *72*, 2063–2067.
- (65) Suzuki, T.; Hide, I.; Matsubara, A.; Hama, C.; Harada, K.; Miyano, K.; Andra, M.; Matsubayashi, H.; Sakai, N.; Kohsaka, S.; Inoue, K.; Nakata, Y. Microglial $\alpha 7$ nicotinic acetylcholine receptors drive a phospholipase C/IP3 pathway and modulate the cell activation toward a neuroprotective role. *J. Neurosci. Res.* **2006**, *83*, 1461–1470.
 - (66) Yoshikawa, H.; Kurokawa, M.; Ozaki, N.; Nara, K.; Atou, K.; Takada, E.; Kamochi, H.; Suzuki, N. Nicotine inhibits the production of proinflammatory mediators in human monocytes by suppression of I- κ B phosphorylation and nuclear factor- κ B transcriptional activity through nicotinic acetylcholine receptor $\alpha 7$. *Clin. Exp. Immunol.* **2006**, *146*, 116–123.
 - (67) Ulloa, L. The vagus nerve and the nicotinic anti-inflammatory pathway. *Nat. Rev. Drug Discovery* **2005**, *4*, 673–684.
 - (68) Son, J. H.; Meizel, S. Evidence suggesting that the mouse sperm acrosome reaction initiated by the zona pellucida involves an $\alpha 7$ nicotinic acetylcholine receptor. *Biol. Reprod.* **2003**, *68*, 1348–1353.
 - (69) Orr-Urtreger, A.; Göldner, F. M.; Saeki, M.; Lorenzo, I.; Goldberg, L.; De Biasi, M.; Dani, J. A.; Patrick, J. W.; Beaudet, A. L. Mice deficient in the $\alpha 7$ neuronal nicotinic acetylcholine receptor lack α -bungarotoxin binding sites and hippocampal fast nicotinic currents. *J. Neurosci.* **1997**, *17*, 9165–9171.
 - (70) Keller, J. J.; Keller, A. B.; Bowers, B. J.; Wehner, J. M. Performance of $\alpha 7$ nicotinic receptor null mutants is impaired in appetitive learning measured in a signaled nose poke task. *Behav. Brain Res.* **2005**, *162*, 143–152.
 - (71) Bowers, B. J.; McClure-Begley, T. D.; Keller, J. J.; Paylor, R.; Collins, A. C.; Wehner, J. M. Deletion of the $\alpha 7$ nicotinic receptor subunit gene results in increased sensitivity to several behavioral effects produced by alcohol. *Alcohol: Clin. Exp. Res.* **2005**, *29*, 295–302.
 - (72) Wehner, J. M.; Keller, J. J.; Keller, A. B.; Picciotto, M. R.; Paylor, R.; Booker, T. K.; Beaudet, A.; Heinemann, S. F.; Balogh, S. A. Role of neuronal nicotinic receptors in the effects of nicotine and ethanol on contextual fear conditioning. *Neuroscience* **2004**, *129*, 11–24.
 - (73) Dineley, K. T.; Xia, X. F.; Bui, D.; Sweatt, J. D.; Zheng, H. Accelerated plaque accumulation, associative learning deficits, and up-regulation of $\alpha 7$ nicotinic receptor protein in transgenic mice co-expressing mutant human presenilin 1 and amyloid precursor proteins. *J. Biol. Chem.* **2002**, *277*, 22768–22780.
 - (74) Gotti, C.; Zoli, M.; Clementi, F. Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Trends Pharmacol. Sci.* **2006**, *27*, 482–491.
 - (75) Levin, E. D.; Rezvani, A. H. Nicotinic-antipsychotic drug interactions and cognitive function. *Experientia, Suppl.* **2006**, *98*, 185–205.
 - (76) Martin, L. F.; Kem, W. R.; Freedman, R. $\alpha 7$ nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. *Psychopharmacology (Berlin)* **2004**, *174*, 54–64.
 - (77) Ripoll, N.; Bronnec, M.; Bourin, M. Nicotinic receptors and schizophrenia. *Curr. Med. Res. Opin.* **2004**, *20*, 1057–1074.
 - (78) Hogg, R. C.; Bertrand, D. Nicotinic acetylcholine receptors as drug targets. *Curr. Drug Targets: CNS Neurol. Disord.* **2004**, *3*, 123–130.
 - (79) Olincy, A.; Harris, J. G.; Johnson, L. L.; Pender, V.; Kongs, S.; Allensworth, D.; Ellis, J.; Zerbe, G. O.; Leonard, S.; Stevens, K. E.; Stevens, J. O.; Martin, L.; Adler, L. E.; Soti, F.; Kem, W. R.; Freedman, R. Proof-of-concept trial of an $\alpha 7$ nicotinic agonist in schizophrenia. *Arch. Gen. Psychiatry* **2006**, *63*, 630–638.
 - (80) Kitagawa, H.; Takenouchi, T.; Azuma, R.; Wesnes, K. A.; Kramer, W. G.; Clody, D. E.; Burnett, A. L. Safety, pharmacokinetics, and effects on cognitive function of multiple doses of GTS-21 in healthy, male volunteers. *Neuropsychopharmacology* **2003**, *28*, 542–551.
 - (81) Levin, E. D. Nicotinic receptor subtypes and cognitive function. *J. Neurobiol.* **2002**, *53*, 633–640.
 - (82) de Jonge, W. J.; van der Zanden, E. P.; The, F. O.; Bijlsma, M. F.; van Westerloo, D. J.; Bennink, R. J.; Berthoud, H. R.; Uematsu, S.; Akira, S.; van den Wijngaard, R. M.; Boeckxstaens, G. E. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nat. Immunol.* **2005**, *6*, 844–851.
 - (83) Wang, H.; Liao, H.; Ochani, M.; Justiniani, M.; Lin, X.; Yang, L.; Al Abed, Y.; Wang, H.; Metz, C.; Miller, E. J.; Tracey, K. J.; Ulloa, L. Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. *Nat. Med.* **2004**, *10*, 1216–1221.
 - (84) Wang, H.; Yu, M.; Ochani, M.; Amella, C. A.; Tanovic, M.; Susarla, S.; Li, J. H.; Wang, H. C.; Yang, H.; Ulloa, L.; Al Abed, Y.; Czura, C. J.; Tracey, K. J. Nicotinic acetylcholine receptor $\alpha 7$ subunit is an essential regulator of inflammation. *Nature* **2003**, *421*, 384–388.
 - (85) Ng, M. K. C.; Wu, J.; Chang, E.; Wang, B. y.; Katzenberg-Clark, R.; Ishii-Watabe, A.; Cooke, J. P. A central role for nicotinic cholinergic regulation of growth factor-induced endothelial cell migration. *Arterioscler., Thromb., Vasc. Biol.* **2007**, *27*, 106–112.
 - (86) Heeschen, C.; Weis, M.; Cooke, J. P. Nicotine promotes arteriogenesis. *J. Am. Coll. Cardiol.* **2003**, *41*, 489–496.
 - (87) Newhouse, P. A.; Potter, A.; Singh, A. Effects of nicotinic stimulation on cognitive performance. *Curr. Opin. Pharmacol.* **2004**, *4*, 36–46.
 - (88) Fratiglioni, L.; Wang, H. X. Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. *Behav. Brain Res.* **2000**, *113*, 117–120.
 - (89) Stitzel, J. A.; Lu, Y.; Jimenez, M.; Tritto, T.; Collins, A. C. Genetic and pharmacological strategies identify a behavioral function of neuronal nicotinic receptors. *Behav. Brain Res.* **2000**, *113*, 57–64.
 - (90) Cooper, R. G. Effect of tobacco smoking on renal function. *Indian J. Med. Res.* **2006**, *124*, 261–268.
 - (91) Hanna, S. T. Nicotine effect on cardiovascular system and ion channels. *J. Cardiovasc. Pharmacol.* **2006**, *47*, 348–358.
 - (92) Wu, W. K.; Cho, C. H. The pharmacological actions of nicotine on the gastrointestinal tract. *J. Pharmacol. Sci.* **2004**, *94*, 348–358.
 - (93) Kem, W. R.; Mahnir, V. M.; Prokai, L.; Papke, R. L.; Cao, X.; LeFrancis, S.; Wildeboer, K.; Prokai-Tatrai, K.; Porter-Papke, J.; Soti, F. Hydroxy metabolites of the Alzheimer's drug candidate 3-[(2,4-dimethoxy)benzylidene]-anabaseine dihydrochloride (GTS-21): their molecular properties, interactions with brain nicotinic receptors, and brain penetration. *Mol. Pharmacol.* **2004**, *65*, 56–67.
 - (94) Levin, E. D. Nicotinic agonist and antagonist effects on memory. *Drug Dev. Res.* **1996**, *38*, 188–195.
 - (95) Briggs, C. A.; McKenna, D. G.; Piattoni-Kaplan, M. Human $\alpha 7$ nicotinic acetylcholine receptor responses to novel ligands. *Neuropharmacology* **1995**, *34*, 583–590.
 - (96) Meyer, E. M.; de Fiebre, C. M.; Hunter, B. E.; Simpkins, C. E.; Frauworth, N.; De Fiebre, N. E. C. Effects of anabaseine-related analogs on rat brain nicotinic receptor binding and on avoidance behaviors. *Drug Dev. Res.* **1994**, *31*, 127–134.
 - (97) Woodruff-Pak, D. S.; Li, Y.-T.; Kem, W. R. A nicotinic agonist (GTS-21), eyeblink classical conditioning, and nicotinic receptor binding in rabbit brain. *Brain Res.* **1994**, *645*, 309–317.
 - (98) Radek, R. J.; Miner, H. M.; Bratcher, N. A.; Decker, M. W.; Gopalakrishnan, M.; Bitner, R. S. $\alpha 4\beta 2$ nicotinic receptor stimulation contributes to the effects of nicotine in the DBA/2 mouse model of sensory gating. *Psychopharmacology (Berlin)* **2006**, *187*, 47–55.
 - (99) Romanelli, M. N.; Gualtieri, F. Cholinergic nicotinic receptors: competitive ligands, allosteric modulators, and their potential applications. *Med. Res. Rev.* **2003**, *23*, 393–426.
 - (100) Bunnelle, W. H.; Dart, M. J.; Schrimpf, M. R. Design of ligands for the nicotinic acetylcholine receptors: the quest for selectivity. *Curr. Top. Med. Chem.* **2004**, *4*, 299–334.
 - (101) Van Kampen, M.; Selbach, K.; Schneider, R.; Schiegel, E.; Boess, F.; Schreiber, R. AR-R 17779 improves social recognition in rats by activation of nicotinic $\alpha 7$ receptors. *Psychopharmacology (Berlin)* **2004**, *172*, 375–383.
 - (102) Papke, R. L.; Porter Papke, J. K.; Rose, G. M. Activity of $\alpha 7$ -selective agonists at nicotinic and serotonin 5HT₃ receptors expressed in *Xenopus* oocytes. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1849–1853.
 - (103) Grottick, A. J.; Higgins, G. A. Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. *Behav. Brain Res.* **2000**, *117*, 197–208.
 - (104) Grottick, A. J.; Trube, G.; Corrigan, W. A.; Huwyler, J.; Malherbe, P.; Wyler, R.; Higgins, G. A. Evidence that nicotinic $\alpha 7$ receptors are not involved in the hyperlocomotor and rewarding effects of nicotine. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 1112–1119.
 - (105) Boess, F. G.; De Vry, J.; Erb, C.; Flessner, T.; Hendrix, M.; Luthile, J.; Methfessel, C.; Riedl, B.; Schnizler, K.; van der Staay, F.-J.; van Kampen, M.; Wiese, W. B.; Koenig, G. The novel $\alpha 7$ nicotinic acetylcholine receptor agonist *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-7-[2-(methoxy)phenyl]-1-benzofuran-2-carboxamide improves working and recognition memory in rodents. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 716–725.
 - (106) Feuerbach, D.; Nozulak, J.; Lingenhoeft, K.; McAllister, K.; Hoyer, D. JN403, *in vitro* characterization of a novel nicotinic acetylcholine receptor $\alpha 7$ selective agonist. *Neurosci. Lett.* **2007**, *416*, 61–65.
 - (107) Shaffer, C. L.; Gunduz, M.; Scialis, R. J.; Fang, A. F. Metabolism and disposition of a selective $\alpha 7$ nicotinic acetylcholine receptor agonist in humans. *Drug Metab. Dispos.* **2007**, *35*, 1188–1195.
 - (108) Tatsumi, R.; Fujio, M.; Satoh, H.; Katayama, J.; Takanashi, S.; Hashimoto, K.; Tanaka, H. Discovery of the $\alpha 7$ nicotinic acetylcholine receptor agonists. (R)-3'-(5-Chlorothiophen-2-yl)spiro-1-azabicyclo[2.2.2]octane-3,5'-[1'3'] oxazolidin-2'-one as a novel, potent, selective, and orally bioavailable ligand. *J. Med. Chem.* **2005**, *48*, 2678–2686.
 - (109) Jordan, K. J.; Gatto, G. J.; Hauser, T. A. Assessment of a full $\alpha 7$ nicotinic acetylcholine receptor agonist, TC-5619, in animal models of schizophrenia. *Soc. Neurosci. Abstr.* **2005**, *31*, 952.10.
 - (110) Hajos, M. Targeting information-processing deficit in schizophrenia: a novel approach to psychotherapeutic drug discovery. *Trends Pharmacol. Sci.* **2006**, *27*, 391–398.

- (111) Hajos, M.; Hurst, R. S.; Hoffmann, W. E.; Krause, M.; Wall, T. M.; Higdon, N. R.; Groppi, V. E. The selective $\alpha 7$ nicotinic acetylcholine receptor agonist PNU-282987 enhances GABAergic synaptic activity in brain slices and restores auditory gating deficits in anesthetized rats. *J. Pharmacol. Exp. Ther.* **2004**, *312*, 1213–1222.
- (112) Pichat, P.; Bergis, O. E.; Terranova, J. P.; Urani, A.; Duarte, C.; Santucci, V.; Gueudet, C.; Voltz, C.; Steinberg, R.; Stemmelin, J.; Oury-Donat, F.; Avenet, P.; Griebel, G.; Scatton, B. SSR180711, a novel selective $\alpha 7$ nicotinic receptor partial agonist: (II) efficacy in experimental models predictive of activity against cognitive symptoms of schizophrenia. *Neuropsychopharmacology* **2007**, *32*, 17–34.
- (113) Wishka, D. G.; Walker, D. P.; Yates, K. M.; Reitz, S. C.; Jia, S.; Myers, J. K.; Olson, K. L.; Jacobsen, E. J.; Wolfe, M. L.; Groppi, V. E.; Hanchar, A. J.; Thornburgh, B. A.; Cortes-Burgos, L. A.; Wong, E. H. F.; Staton, B. A.; Raub, T. J.; Higdon, N. R.; Wall, T. M.; Hurst, R. S.; Walters, R. R.; Hoffmann, W. E.; Hajos, M.; Franklin, S.; Carey, G.; Gold, L. H.; Cook, K. K.; Sands, S. B.; Zhao, S. X.; Soglia, J. R.; Kalgutkar, A. S.; Arneric, S. P.; Rogers, B. N. Discovery of *N*-(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]furo[2,3-*c*]pyridine-5-carboxamide, an agonist of the $\alpha 7$ nicotinic acetylcholine receptor, for the potential treatment of cognitive deficits in schizophrenia: synthesis and structure–activity relationship. *J. Med. Chem.* **2006**, *49*, 4425–4436.
- (114) Radek, R. J.; Robb, H. M.; Bunnelle, W. H.; Decker, M. W.; Gopalakrishnan, M.; Bitner, R. S. Improved preattention and information processing by $\alpha 7$ neuronal nicotinic receptor agonism in models of sensory gating. *Soc. Neurosci. Abstr.* **2006**, *32*, 325.20.
- (115) Bitner, R. S.; Bunnelle, W. H.; Anderson, D. J.; Briggs, C. A.; Buccafusco, J.; Curzon, P.; Decker, M. W.; Frost, J. M.; Grønlien, J. H.; Gubbins, E.; Li, J.; Malysz, J.; Markosyan, S.; Marsh, K.; Meyer, M. D.; Nikkel, A. L.; Radek, R. J.; Robb, H. M.; Timmermann, D.; Sullivan, J. P.; Gopalakrishnan, M. Broad-spectrum efficacy across cognitive domains by $\alpha 7$ nicotinic acetylcholine receptor agonism correlates with activation of ERK1/2 and CREB phosphorylation pathways. *J. Neurosci.* **2007**, *27*, 10578–10587.
- (116) Buccafusco, J. J.; Terry, J.; Decker, M. W.; Gopalakrishnan, M. Profile of nicotinic acetylcholine receptor agonists ABT-594 and A-582941 with differential subtype selectivity on delayed matching accuracy by young monkeys. *Biochem. Pharmacol.* **2007**, *74*, 1202–1211.
- (117) Lambert, J. J.; Belelli, D.; Peden, D. R.; Vardy, A. W.; Peters, J. A. Neurosteroid modulation of GABA_A receptors. *Prog. Neurobiol.* **2003**, *71*, 67–80.
- (118) Sigel, E.; Buhr, A. The benzodiazepine binding-site of GABA_A receptors. *Trends Pharmacol. Sci.* **1997**, *18*, 425–429.
- (119) Olsen, R. W.; Chang, C. S.; Li, G.; Hanchar, H. J.; Wallner, M. Fishing for allosteric sites on GABA_A receptors. *Biochem. Pharmacol.* **2004**, *68*, 1675–1684.
- (120) Chen, Z. W.; Olsen, R. W. GABA_A receptor associated proteins: a key factor regulating GABA_A receptor function. *J. Neurochem.* **2007**, *100*, 279–294.
- (121) Toyoda, H.; Yamada, J.; Ueno, S.; Okabe, A.; Kato, H.; Sato, K.; Hashimoto, K.; Fukuda, A. Differential functional expression of cation–Cl[−] cotransporter mRNAs (KCC1, KCC2, and NKCC1) in rat trigeminal nervous system. *Mol. Brain Res.* **2005**, *133*, 12–18.
- (122) Ueno, S.; Tsutsui, M.; Toyohira, Y.; Minami, K.; Yanagihara, N. Sites of positive allosteric modulation by neurosteroids on ionotropic gamma-aminobutyric acid receptor subunits. *FEBS Lett.* **2004**, *566*, 213–217.
- (123) Harris, J. G.; Kongs, S.; Allensworth, D.; Martin, L.; Tregellas, J.; Sullivan, B.; Zerbe, G.; Freedman, R. Effects of nicotine on cognitive deficits in schizophrenia. *Neuropsychopharmacology* **2004**, *29*, 1378–1385.
- (124) Changeux, J.-P. The TiPS Lecture. The nicotinic acetylcholine receptor. An allosteric protein prototype of ligand-gated ion channels. *Trends Pharmacol. Sci.* **1990**, *11*, 485–492.
- (125) Grønlien, J. H.; Haakerud, M.; Ween, H.; Thorin-Hagene, K.; Briggs, C. A.; Gopalakrishnan, M.; Malysz, J. Distinct profiles of $\alpha 7$ nAChR positive allosteric modulation revealed by structurally diverse chemotypes. *Mol. Pharmacol.* **2007**, *72*, 715–724.
- (126) Revah, F.; Bertrand, D.; Galzi, J.-L.; Devillers-Thiéry, A.; Mulle, C.; Hussy, N.; Bertrand, S.; Ballivet, M.; Changeux, J.-P. Mutations in the channel domain alter desensitization of a neuronal nicotinic receptor. *Nature* **1991**, *353*, 846–849.
- (127) Bertrand, D.; Devillers-Thiéry, A.; Revah, F.; Galzi, J.-L.; Hussy, N.; Mulle, C.; Bertrand, S.; Ballivet, M.; Changeux, J.-P. Unconventional pharmacology of a neuronal nicotinic receptor mutated in the channel domain. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 1261–1265.
- (128) Changeux, J. P.; Edelstein, S. J. Allosteric mechanisms in normal and pathological nicotinic acetylcholine receptors. *Curr. Opin. Neurobiol.* **2001**, *11*, 369–377.
- (129) Edelstein, S. J.; Schaad, O.; Henry, E.; Bertrand, D.; Changeux, J.-P. A kinetic mechanism for nicotinic acetylcholine receptors based on multiple allosteric transitions. *Biol. Cybern.* **1996**, *75*, 361–379.
- (130) Hogg, R. C.; Bertrand, D. Nicotinic Receptors. In *Allosteric Receptor Modulation in Drug Targeting*; Bowery, N. G., Ed.; Taylor & Francis Group: New York, 2006; pp 155–178.
- (131) Kenakin, T. P. Characteristics of Allosterism in Drug Action. In *Allosteric Receptor Modulation in Drug Targeting*; Bowery, N. G., Ed.; Taylor & Francis Group: New York, 2006; pp 19–37.
- (132) Hall, D. A. Predicting Dose-Response Curve Behavior. In *Allosteric Receptor Modulation in Drug Targeting*; Bowery, N. G., Ed.; Taylor & Francis Group: New York, 2006; pp 39–78.
- (133) Curtis, L.; Buisson, B.; Bertrand, S.; Bertrand, D. Potentiation of human $\alpha 4 \beta 2$ neuronal nicotinic acetylcholine receptor by estradiol. *Mol. Pharmacol.* **2002**, *61*, 127–135.
- (134) Hsiao, B.; Mihalak, K. B.; Repicky, S. E.; Everhart, D.; Mederos, A. H.; Malhotra, A.; Luetje, C. W. Determinants of zinc potentiation on the $\alpha 4$ subunit of neuronal nicotinic receptors. *Mol. Pharmacol.* **2006**, *69*, 27–36.
- (135) Conroy, W. G.; Liu, Q. S.; Nai, Q.; Margiotta, J. F.; Berg, D. K. Potentiation of $\alpha 7$ -containing nicotinic acetylcholine receptors by select albumins. *Mol. Pharmacol.* **2003**, *63*, 419–428.
- (136) Butt, C. M.; Hutton, S. R.; Marks, M. J.; Collins, A. C. Bovine serum albumin enhances nicotinic acetylcholine receptor function in mouse thalamic synaptosomes. *J. Neurochem.* **2002**, *83*, 48–56.
- (137) Weiss, J. H.; Sensi, S. L.; Koh, J. Y. Zn²⁺: a novel ionic mediator of neural injury in brain disease. *Trends Pharmacol. Sci.* **2000**, *21*, 395–401.
- (138) Velazquez, R. A.; Cai, Y. J.; Shi, Q. Y.; Larson, A. A. The distribution of zinc selenite and expression of metallothionein-III mRNA in the spinal cord and dorsal root ganglia of the rat suggest a role for zinc in sensory transmission. *J. Neurosci.* **1999**, *19*, 2288–2300.
- (139) Mocchegiani, E.; Bertoni-Freddari, C.; Marcellini, F.; Malavolta, M. Brain, aging and neurodegeneration: role of zinc ion availability. *Prog. Neurobiol.* **2005**, *75*, 367–390.
- (140) Tsuji, H.; Okamoto, K.; Matsuzaka, Y.; Iizuka, H.; Tamiya, G.; Inoko, H. SLURP-2, a novel member of the human Ly-6 superfamily that is up-regulated in *Psoriasis vulgaris*. *Genomics* **2003**, *81*, 26–33.
- (141) Adermann, K.; Wattler, F.; Wattler, S.; Heine, G.; Meyer, M.; Forssmann, W. G.; Nehls, M. Structural and phylogenetic characterization of human SLURP-1, the first secreted mammalian member of the Ly-6/uPAR protein superfamily. *Protein Sci.* **1999**, *8*, 810–819.
- (142) Miwa, J. M.; Stevens, T. R.; King, S. L.; Caldarone, B. J.; Ibanez-Tallon, I.; Xiao, C.; Fitzsimonds, R. M.; Pavlides, C.; Lester, H. A.; Picciotto, M. R.; Heintz, N. The prototoxin lynx1 acts on nicotinic acetylcholine receptors to balance neuronal activity and survival in vivo. *Neuron* **2006**, *51*, 587–600.
- (143) Dessaud, E.; Salaun, D.; Gayet, O.; Chabbert, M.; Delapeyrière, O. Identification of lynx2, a novel member of the ly-6/neurotoxin superfamily, expressed in neuronal subpopulations during mouse development. *Mol. Cell. Neurosci.* **2006**, *31*, 232–242.
- (144) Miwa, J. M.; Ibanez-Tallon, I.; Crabtree, G. W.; Sanchez, R.; Sali, A.; Role, L. W.; Heintz, N. Lynx1, an endogenous toxin-like modulator of nicotinic acetylcholine receptors in the mammalian CNS. *Neuron* **1999**, *23*, 105–114.
- (145) Chimienti, F.; Hogg, R. C.; Plantard, L.; Lehmann, C.; Brackch, N.; Fischer, J.; Huber, M.; Bertrand, D.; Hohl, D. Identification of SLURP-1 as an epidermal neuromodulator explains the clinical phenotype of Mal de Meleda. *Hum. Mol. Genet.* **2003**, *12*, 3017–3024.
- (146) Arredondo, J.; Chernyavsky, A. I.; Webber, R. J.; Grando, S. A. Biological effects of SLURP-1 on human keratinocytes. *J. Invest. Dermatol.* **2005**, *125*, 1236–1241.
- (147) Zhao, X. L.; Kuryatov, A.; Lindstrom, J. M.; Yeh, J. Z.; Narahashi, T. Nootropic drug modulation of neuronal nicotinic acetylcholine receptors in rat cortical neurons. *Mol. Pharmacol.* **2001**, *59*, 674–683.
- (148) Oyaizu, M.; Narahashi, T. Modulation of the neuronal nicotinic acetylcholine receptor-channel by the nootropic drug nefiracetam. *Brain Res.* **1999**, *822*, 72–79.
- (149) Nomura, T.; Nishizaki, T. Nefiracetam facilitates hippocampal neurotransmission by a mechanism independent of the piracetam and aniracetam action. *Brain Res.* **2000**, *870*, 157–162.
- (150) Nishizaki, T.; Matsuoka, T.; Nomura, T.; Sumikawa, K.; Shiotani, T.; Watabe, S.; Yoshii, M. Nefiracetam modulates acetylcholine receptor currents via 2 different signal transduction pathways. *Mol. Pharmacol.* **1998**, *53*, 1–5.
- (151) Nishizaki, T.; Nomura, T.; Matsuoka, T.; Kondoh, T.; Enikolopov, G.; Sumikawa, K.; Watabe, S.; Shiotani, T.; Yoshii, M. The anti-dementia drug nefiracetam facilitates hippocampal synaptic transmission by functionally targeting presynaptic nicotinic ACh receptors. *Brain Res.* **2000**, *80*, 53–62.

- (152) Narahashi, T.; Marszalec, W.; Moriguchi, S.; Yeh, J. Z.; Zhao, X. Unique mechanism of action of Alzheimer's drugs on brain nicotinic acetylcholine receptors and NMDA receptors. *Life Sci.* **2003**, *74*, 281–291.
- (153) Miyamoto, H.; Yaguchi, T.; Ohta, K.; Nagai, K.; Nagata, T.; Yamamoto, S.; Nishizaki, T. 2-Pyrrolidinone induces a long-lasting facilitation of hippocampal synaptic transmission by enhancing $\alpha 7$ ACh receptor responses via a PKC pathway. *Mol. Brain Res.* **2003**, *117*, 91–96.
- (154) Moriguchi, S.; Shioda, N.; Maejima, H.; Zhao, X.; Marszalec, W.; Yeh, J. Z.; Fukunaga, K.; Narahashi, T. Nefiracetam potentiates N-methyl-D-aspartate (NMDA) receptor function via protein kinase C activation and reduces magnesium block of NMDA receptor. *Mol. Pharmacol.* **2007**, *71*, 580–587.
- (155) Matsumoto, S.; Kanno, T.; Nomura, T.; Shiotani, T.; Watabe, S.; Nabeshima, T.; Nishizaki, T. Nefiracetam induces a long-lasting facilitation of hippocampal postsynaptic responses in mice lacking the NMDA receptor epsilon-1 subunit. *Brain Res.* **2002**, *956*, 178–181.
- (156) Kolta, A.; Lynch, G.; Ambros-Ingerson, J. Effects of aniracetam after LTP induction are suggestive of interactions on the kinetics of the AMPA receptor channel. *Brain Res.* **1998**, *788*, 269–286.
- (157) Nishizaki, T.; Matsumura, T. The aniracetam metabolite 2-pyrrolidinone induces a long-term enhancement in AMPA receptor responses via a CaMKII pathway. *Mol. Brain Res.* **2002**, *98*, 130–134.
- (158) Charpentier, E.; Wiesner, A.; Huh, K. H.; Ogier, R.; Hoda, J. C.; Allaman, G.; Ragenbass, M.; Feuerbach, D.; Bertrand, D.; Fuhrer, C. $\alpha 7$ neuronal nicotinic acetylcholine receptors are negatively regulated by tyrosine phosphorylation and Src-family kinases. *J. Neurosci.* **2005**, *25*, 9836–9849.
- (159) Cho, C. H.; Song, W.; Leitzell, K.; Teo, E.; Meleth, A. D.; Quick, M. W.; Lester, R. A. J. Rapid upregulation of $\alpha 7$ nicotinic acetylcholine receptors by tyrosine dephosphorylation. *J. Neurosci.* **2005**, *25*, 3712–3723.
- (160) Traxler, P.; Green, J.; Mett, H.; Sequin, U.; Furet, P. Use of a pharmacophore model for the design of EGFR tyrosine kinase inhibitors: isoflavones and 3-phenyl-4(H)-quinolones. *J. Med. Chem.* **1999**, *42*, 1018–1026.
- (161) Pereira, E. F. R.; Reinhardt-Maelicke, S.; Schrattenholz, A.; Maelicke, A.; Albuquerque, E. X. Identification and functional characterization of a new agonist site on nicotinic acetylcholine receptors of cultured hippocampal neurons. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 1474–1491.
- (162) Pereira, E. F. R.; Alkondon, M.; Reinhardt, S.; Maelicke, A.; Peng, X.; Lindstrom, J.; Whiting, P.; Albuquerque, E. X. Physostigmine and galanthamine: probes for a novel binding site on the $\alpha 4\beta 2$ subtype of neuronal nicotinic acetylcholine receptors stably expressed in fibroblast cells. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 768–778.
- (163) Samochocki, M.; HOFFE, A.; Fehrenbacher, A.; Jostock, R.; Ludwig, J.; Christner, C.; Radina, M.; Zerlin, M.; Ullmer, C.; Pereira, E. F. R.; Lubbert, H.; Albuquerque, E. X.; Maelicke, A. Galantamine is an allosterically potentiating ligand of neuronal nicotinic but not of muscarinic acetylcholine receptors. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 1024–1036.
- (164) Santos, M. D.; Alkondon, M.; Pereira, E. F. R.; Aracava, Y.; Eisenberg, H. M.; Maelicke, A.; Albuquerque, E. X. The nicotinic allosteric potentiating ligand galantamine facilitates synaptic transmission in the mammalian central nervous system. *Mol. Pharmacol.* **2002**, *61*, 1222–1234.
- (165) Schrattenholz, A.; Coban, T.; Schröder, B.; Okonjo, K. O.; Kuhlmann, J.; Pereira, E. F.; Albuquerque, E. X.; Maelicke, A. Biochemical characterization of a novel channel-activating site on nicotinic acetylcholine receptors. *J. Recept. Res.* **1993**, *13*, 393–412.
- (166) Schrattenholz, A.; Pereira, E. F. R.; Roth, U.; Weber, K. H.; Albuquerque, E. X.; Maelicke, A. Agonist responses of neuronal nicotinic acetylcholine receptors are potentiated by a novel class of allosterically acting ligands. *Mol. Pharmacol.* **1996**, *49*, 1–6.
- (167) Zwart, R.; De Filippi, G.; Broad, L. M.; McPhie, G. I.; Pearson, K. H.; Baldwinson, T.; Sher, E. 5-Hydroxyindole potentiates human $\alpha 7$ nicotinic receptor-mediated responses and enhances acetylcholine-induced glutamate release in cerebellar slices. *Neuropharmacology* **2002**, *43*, 374–384.
- (168) Krause, R. M.; Buisson, B.; Bertrand, S.; Corringer, P.-J.; Galzi, J.-L.; Changeux, J.-P.; Bertrand, D. Ivermectin: a positive allosteric effector of the $\alpha 7$ neuronal nicotinic acetylcholine receptor. *Mol. Pharmacol.* **1998**, *53*, 283–294.
- (169) MacDougall, K. N.; Wildeboer, K. M.; Soti, F.; Kem, W. R. Hydroxyindole enhancement of benzylidene-anabaseine binding to rat brain $\alpha 7$ nicotinic acetylcholine receptors. *Soc. Neurosci. Abstr.* **2005**, *31*, 952.7.
- (170) Grantham, C. J.; Berben, M.; Ashton, D.; Lesage, A.; Langlois, X. Indole analogues increase $\alpha 7$ nicotinic receptor affinity for nicotinic agonists. *Soc. Neurosci. Abstr.* **2004**, *30*, 956.13.
- (171) van Hooft, J. A.; van der, H. E.; Vijverberg, H. P. Allosteric potentiation of the 5-HT₃ receptor-mediated ion current in N1E-115 neuroblastoma cells by 5-hydroxyindole and analogues. *Neuropharmacology* **1997**, *36*, 649–653.
- (172) Feng, X. P.; Hayashi, J.; Beech, R. N.; Prichard, R. K. Study of the nematode putative GABA type-A receptor subunits: evidence for modulation by ivermectin. *J. Neurochem.* **2002**, *83*, 870–878.
- (173) Ludmerer, S. W.; Warren, V. A.; Williams, B. S.; Zheng, Y. C.; Hunt, D. C.; Ayer, M. B.; Wallace, M. A.; Chaudhary, A. G.; Egan, M. A.; Meinke, P. T.; Dean, D. C.; Garcia, M. L.; Cully, D. F.; Smith, M. M. Ivermectin and noduliporic acid receptors in *Drosophila melanogaster* contain both gamma-aminobutyric acid-gated Rdl and glutamate-gated GluCl alpha chloride channel subunits. *Biochemistry* **2002**, *41*, 6548–6560.
- (174) Shan, Q.; Haddrill, J. L.; Lynch, J. W. Ivermectin, an unconventional agonist of the glycine receptor chloride channel. *J. Biol. Chem.* **2001**, *276*, 12556–12564.
- (175) Adelsberger, H.; Lepier, A.; Dudel, J. Activation of rat recombinant $\alpha 1\beta 2\gamma 2S$ GABA_A receptor by the insecticide ivermectin. *Eur. J. Pharmacol.* **2000**, *394*, 163–170.
- (176) Connolly, C. N.; Wafford, K. A. The Cys-loop superfamily of ligand-gated ion channels: the impact of receptor structure on function. *Biochem. Soc. Trans.* **2004**, *32*, 529–534.
- (177) Johnstone, T. B.; Hogenkamp, D. J.; Coyne, L.; Su, J.; Halliwell, R. F.; Tran, M. B.; Yoshimura, R. F.; Li, W. Y.; Wang, J.; Gee, K. W. Modifying quinolone antibiotics yields new anxiolytics. *Nat. Med.* **2004**, *10*, 31–32.
- (178) Hogenkamp, D. J.; Johnstone, T. B.; Huang, J. C.; Li, W. Y.; Tran, M.; Whitmore, E. R.; Bagnara, R. E.; Gee, K. W. Enaminone amides as novel orally active GABA_A receptor modulators. *J. Med. Chem.* **2007**, *50*, 3369–3379.
- (179) Ng, H. J.; Whitmore, E. R.; Tran, M. B.; Hogenkamp, D. J.; Broide, R. S.; Johnstone, T. B.; Zheng, L.; Stevens, K. E.; Gee, K. W. Nootropic $\alpha 7$ nicotinic receptor allosteric modulator derived from GABA_A receptor modulators. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 8059–8064.
- (180) Dahl, B. H.; Peters, D.; Olsen, G. M.; Jørgensen, T. D.; Timmermann, D. B. Novel Urea Derivatives and Their Medical Use. WO 2005/092843 A1, 2005.
- (181) Timmermann, D. B.; Grønlien, J. H.; Kohlhaas, K. L.; Nielsen, E. Ø.; Dam, E.; Jørgensen, T. D.; Ahring, P. K.; Peters, D.; Holst, D.; Christensen, J. K.; Malysz, J.; Briggs, C. A.; Gopalakrishnan, M.; Olsen, G. M. An allosteric modulator of the $\alpha 7$ nicotinic acetylcholine receptor displaying memory enhancing properties. *J. Pharmacol. Exp. Ther.* **2007**, *323*, 294–307.
- (182) Hurst, R. S.; Hajos, M.; Ragenbass, M.; Wall, T. M.; Higdon, N. R.; Lawson, J. A.; Rutherford-Root, K. L.; Berkenpas, M. B.; Hoffmann, W. E.; Piotrowski, D. W.; Groppi, V. E.; Allaman, G.; Ogier, R.; Bertrand, S.; Bertrand, D.; Arneric, S. P. A novel positive allosteric modulator of the $\alpha 7$ neuronal nicotinic acetylcholine receptor in vitro and in vivo characterization. *J. Neurosci.* **2005**, *25*, 4396–4405.
- (183) Kohlhaas, K. L.; Bitner, R. S.; Robb, H. M.; Radek, R. J.; Markosyan, S.; Gopalakrishnan, M. Improved pre-attention and short-term memory via positive allosteric modulation of the $\alpha 7$ neuronal nicotinic receptor. *Int. J. Neuropsychopharmacol.* **2006**, *9*, S202.
- (184) Becker, C.; Comstock, J.; Michne, W. F.; Murphy, M.; Phillips, E. Positive Modulators of Nicotinic Acetylcholine Receptors. WO 2004/098600 A1, 2004.
- (185) Broad, L. M.; Zwart, R.; Pearson, K. H.; Lee, M.; Wallace, L.; McPhie, G. I.; Emkey, R.; Hollinshead, S. P.; Dell, C. P.; Baker, S. R.; Sher, E. Identification and pharmacological profile of a new class of selective nicotinic acetylcholine receptor potentiators. *J. Pharmacol. Exp. Ther.* **2006**, *318*, 1108–1117.
- (186) Dinklo, T.; Meeus, K.; Peeters, L.; Lavreysen, H.; van Roosbroeck, Y.; Grantham, C.; Vandenberk, I.; Pouzet, B.; Stevens, K. E.; Zheng, L.; Mackie, C.; Macdonald, G.; Lesage, A.; Thuring, J. In vitro and in vivo evaluation of JNJ1930942, a novel $\alpha 7$ nAChR selective positive allosteric modulator. *Biochem. Pharmacol.* **2007**, *74*, SMA-33.
- (187) Changeux, J. P.; Edelman, S. J. Allosteric receptors after 30 years. *Neuron* **1998**, *21*, 959–980.
- (188) Bertrand, D.; Changeux, J.-P. Nicotinic receptor: an allosteric protein specialized for intercellular communication. *Semin. Neurosci.* **1995**, *7*, 75–90.
- (189) Changeux, J.-P.; Revah, F. The acetylcholine receptor molecule: allosteric sites and the ion channel. *Trends Neurosci.* **1987**, *10*, 245–250.