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Commentary

Partial agonists as therapeutic agents at neuronal nicotinic acetylcholine receptors

Ron C. Hogg *, *Daniel Bertrand*

Department of Neurosciences, Medical Faculty, CMU, 1 rue Michel Servet, CH-1211 Geneva 4, Switzerland

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ABSTRACT

Improved understanding of how brain function is altered in neurodegenerative disease states, pain and conditions, such as schizophrenia and attention deficit disorder, has highlighted the role of nicotinic acetylcholine receptors (nAChRs) in these conditions and identified them as promising therapeutic targets. nAChRs are widely expressed throughout the peripheral and central nervous system, and this widespread nature underlines the need for new ligands with different selectivities and pharmacological profiles if we are to avoid the adverse side effects associated with many of the nAChR modulators currently identified. Partial agonists have the unique property of being able to act both as agonists or antagonists depending on the concentration of endogenous neurotransmitter. Moreover, the agonist action of partial agonists has a 'ceiling' effect, giving them a large safety margin and making them an attractive proposition for therapeutic molecules. Partial agonists of nAChRs are currently being developed as a nicotine replacement therapy for smoking cessation and for the treatment of a number of neurological diseases associated with a loss of cholinergic function. This commentary will discuss the pharmacological properties of partial agonists and review recent research developments in the field of partial agonists acting at nicotinic receptors.

1. Introduction

1.1. nAChRs

The neuronal nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated ion channels, which are expressed throughout the central and peripheral nervous systems (see reviews [1,2]). Neuronal nAChRs are made up from pentameric assemblies of α and β subunits. In mammals eight α (α2–α7, α9 and α10) and three β subunits (β2–β4) have been identified to date, which combine to form functional channels. Most commonly, functional channels are made up of a single type of α and a single type of β subunit, however, there is evidence that 'triplet' channels containing two different types of α and a single type of β subunit, or two types of β and one type of α subunit exist [3–6]. α7 and α9 subunits can form functional homomeric channels, however, α9 preferentially co-assembles with α10 to form heteromeric channels [7]. nAChR dysfunction is believed to be at the origin of a number of neurological diseases, including: schizophrenia, Alzheimer's and Parkinson's diseases and there is increasing evidence that nAChRs play an important role in the response to pain [8–10]. As a result these receptors have become important therapeutic targets, with the development of a wide range of allosteric

* *Corresponding author*. Tel.: +41 22 379 53 55; fax: +41 22 379 54 02.
E-mail address: Ronald.Hogg@medecine.unige.ch (R.C. Hogg).
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modulators and full and partial agonists currently being developed for therapeutic use.

1.2. *Neuronal nAChRs in disease*

Diseases affecting neuronal nAChR function can lead to serious impairment of physiological processes and their importance in pathologies of the human nervous system has been the subject of several recent reviews [11–14]. Diseases involving neuronal nAChRs can be broadly divided into two categories: those in which receptor function is altered, by for example, mutations in the gene coding for the receptor, as is the case in autosomal dominant frontal lobe epilepsy (ADNFLE), and diseases involving a loss of nAChR function, which make up the bulk of diseases involving nAChRs that have been presently identified and include the neurodegenerative conditions such as Alzheimer's and Parkinson's diseases. Although the involvement of nAChRs in some CNS conditions is incomplete, the beneficial effect of drugs acting at these receptors implicates them in these disease states. Autoradiograpy of post-mortem brain tissue from individuals suffering from certain neurodegenerative conditions reveals that the levels of binding of selective nAChR ligands is reduced in some brain areas [15]. Moreover, reduced binding to nAChRs is closely associated with primary histopathological changes in Parkinson's disease, Alzheimer's disease and Lewy body dementia, suggesting that a reduction of nAChR density precedes neurodegeneration in these diseases [15].

Alzheimer's disease affects almost 10% of individuals over the age of 65 and is characterized by a progressive loss of short-term memory and higher cognitive functions [16,17]. Individuals suffering from Alzheimer's disease display progressive degeneration of the cholinergic innervation of the hippocampus and cerebral cortex [18] with a significant reduction in choline acetyl transferase activity in these regions [19]. Binding studies using labelled ligands, indicate the loss of $\alpha4\beta2$ nAChRs [20]. In addition, β-amyloid peptides (1–42) and (1–40), which are found in high concentrations in neuritic plaques have been reported to have neurotoxic effects via $\alpha7$ nAChRs [21–27], however, it was recently reported that hippocampal slices from mice over-expressing the human β-amyloid peptide (1–42) had functional $\alpha7$-mediated currents, despite the fact that *in vitro*, mouse $\alpha7$ receptors were inhibited by similar concentrations of human β-amyloid (1–42) [28]. This result casts some doubts over the direct effects of β-amyloid peptides on nAChRs in the aetiology of Alzheimer's disease. The goal in the treatment of Alzheimer's disease is to prevent the loss of cholinergic function and neuronal death in the hippocampus and cerebral cortex and to compensate for any loss in cholinergic neurotransmission.

Parkinson's disease is characterized by central motor dysfunction resulting in muscular rigidity, tremor and difficulty in initiating and sustaining movement and is associated with a progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, which project to the striatum. Neuronal degeneration is paralleled by the loss of high-affinity nicotine binding sites in these regions and there is increasing evidence that the nAChRs lost in the striatum contain the $\alpha6$ subunit together with other α and β subunits [29–32]. Experimental results from animal models of Parkinson's disease demonstrate that this neuronal degeneration can be prevented by prolonged nicotine administration [33–35]. Nicotine has been shown to markedly improve the symptoms of patients suffering from Parkinson's disease [36] with the beneficial effects being due to increased synaptic dopamine levels in the mesolimbic system and substantia nigra [37,38]. Moreover, the incidence of Parkinson's disease was reported to be 50% lower amongst smokers than in the general population even when taking into account the higher mortality rate of smokers [39,40]. Furthermore, a study in monozygotic twins has shown that the risk of developing Parkinson's disease is inversely correlated with the number of cigarettes smoked, suggesting that stimulation of nicotinic receptors by nicotine may have a protective effect [41]. The possible mechanism of these neuroprotective effects will be discussed in the following section. Two goals in the treatment of Parkinson's disease are (a) to prevent progressive neurodegeneration and the subsequent loss of high affinity cholinergic receptors and (b) to provide symptomatic relief, possibly by selective stimulation of remaining nAChRs containing the $\alpha6$ subunit.

Schizophrenia affects around 1% of the population and is characterised by disturbances of perception and thought. Abnormalities in dopaminergic synaptic transmission are thought to cause excessive release of dopamine, which leads to overactivity at synapses in the mesolimbic system. The involvement of nAChRs in schizophrenia was first suggested by the high percentage of smokers among individuals suffering from this disease [42]. This higher proportion of smokers amongst the schizophrenic population has given rise to the hypothesis that nicotine intake may represent a form of self-medication to compensate for a deficit in nicotinic neurotransmission [43]. Binding studies on post-mortem brain tissue from schizophrenics show that whereas high-affinity nicotinic binding sites are increased in the brains of smokers, in the brains of schizophrenics, binding to $\alpha7$ receptors is reduced in the CA3 region of the hippocampus [44] suggesting that nicotinic function may be reduced. Although this theory remains controversial, it is possible that nicotine present in cigarette smoke activates central nAChRs and an increase central nicotinic neurotransmission may be beneficial. Indeed, nasal nicotine spray has been reported to provide mild benefits in cognitive function in schizophrenics [45]. This theory has been the subject of two recent reviews [46,47].

2. Definition of molecules acting at the ligand-binding site

Several models have been proposed to describe the relationship between receptor occupation and biological response. Receptor occupancy theory describes the quantitative relationships between the binding of a ligand to a receptor and the resulting response. According to this theory an agonist is a substance that binds to a receptor and causes a measurable response. The amplitude of this response depends on the number of receptors occupied, which in turn is dependent on the concentration of agonist and its affinity for the receptor

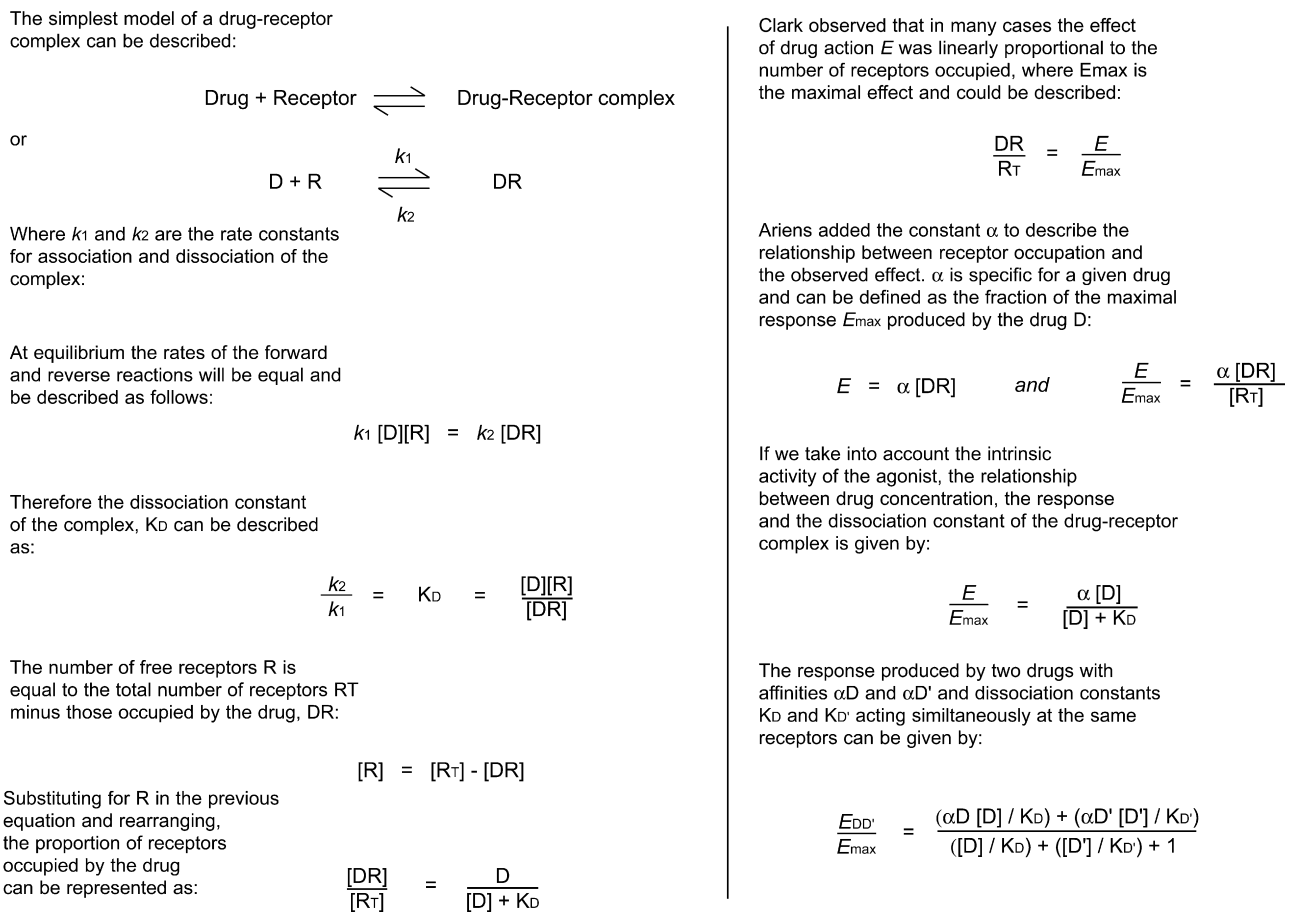

Fig. 1 – Kinetic description of drug-receptor interactions with a linear relationship between receptor occupation and response.

(see Fig. 1). The affinity for the receptor is an intrinsic property of the agonist. Receptor occupancy theory was first elaborated by A.J. Clark in the 1930s and became the basis for describing drug receptor interactions [48]. However, the observation that not all agonists elicited the same maximal response (E_{max}), even at saturating concentrations where all receptors are occupied, and the fact that a maximal response can be produced by different agonists at a concentration when only a fraction of receptors are occupied, indicated that the relationship between receptor occupation and response was more complicated that previously assumed, and Clark's equations (see Fig. 1) could not explain the effects of all ligands. To account for these observations, in the 1950s, Ariëns et al. introduced a scaling factor, α, which they called the intrinsic activity of the agonist [49], and is proportional to the amplitude of the maximal response produced by receptor occupation for a given agonist (Fig. 1). Highly active agonists that produce the maximal potential response from receptor occupation have an $\alpha = 1$, and antagonists, which bind to the receptor but do not elicit a response have an $\alpha = 0$. 'Weak' agonists that produce a fraction of the maximal response have a value of α between 0 and 1. Thus, an agonist can be described by two independent properties, its affinity for the receptor, and its intrinsic activity (see Fig. 2A). In practice, it is difficult to know the maximal response that a receptor is capable of producing, for many receptors the endogenous neurotransmitter is regarded as being a full agonist, however, often the endogenous neurotransmitter is not the most potent agonist, and in addition, new agonists with higher efficacy are continually being discovered. Moreover, some receptors are sensitive to several endogenous molecules each with its own affinity and intrinsic activity; for example, adrenoceptors are activated by endogenous adrenaline, noradrenaline and dopamine.

Weak agonists were termed dualist by Ariëns since they have weak agonist activity but also act as antagonists, reducing the amplitude of responses to more active agonists [50] (Fig. 2B and D). Stephenson introduced the term partial agonist to describe these weak agonists, when a partial agonist produces its maximal response all receptors are occupied, however, it is not capable of eliciting a response as large as the maximum response of a highly active agonist. Since a partial agonist occupies the binding site of the receptor, it can compete with the binding of more active agonists, thus reducing the response of the more active agonist. Since, this antagonism is competitive and depends on the relative affinities of the full and partial agonist, the antagonist effect can be overcome by increasing the concentration of full agonist (Fig. 2C).

Another class of compound acting at the ligand-binding site of ligand-gated ion channels are inverse-agonists.

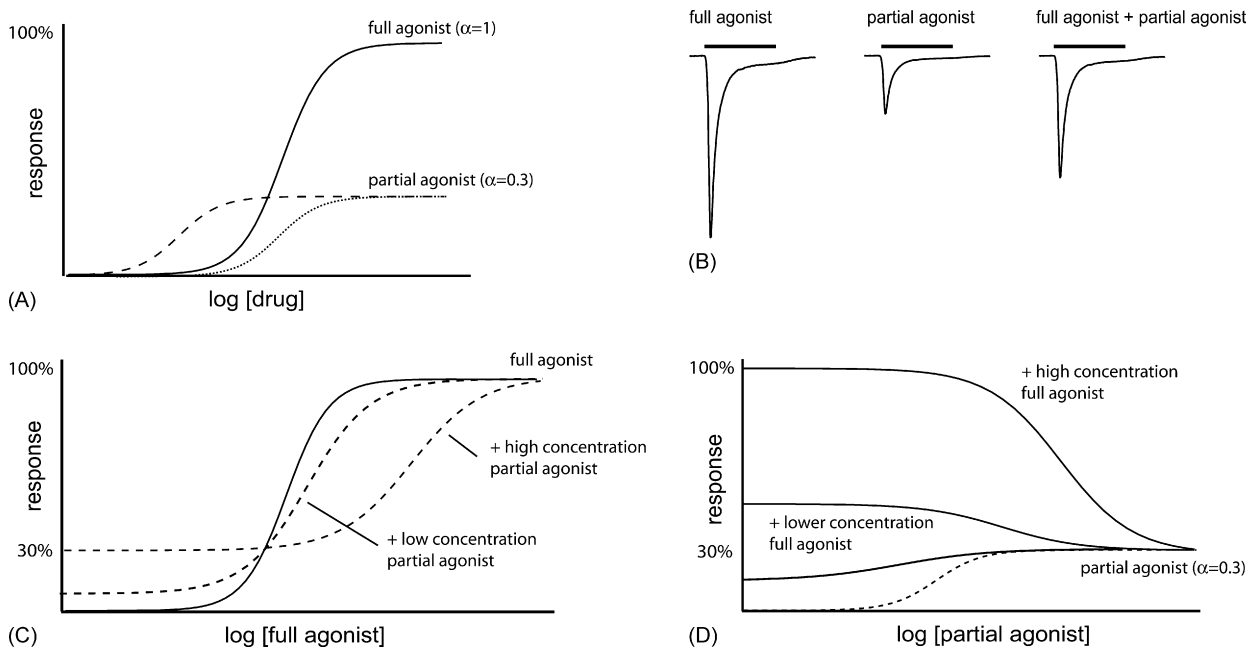

Fig. 2 – Characteristics of full and partial agonists. (A) The concentration–response relationship for a full agonist (α = 1, solid line) and a partial agonist (α = 0.3) with the same affinity (dotted line) and higher affinity (dashed line) for the receptor than the full agonist. (B) Maximal responses of a ligand-gated ion channel to a full and partial agonist, simultaneous application of both drugs reduces the maximal response of the full agonist. (C) Concentration–response curves for the application of a full agonist (α = 1, solid line) in the presence of a low and high concentration of a partial agonist (α = 0.3) where the affinities of the two drugs for the receptor are equal. (D) concentration–response curves for a partial agonist (α = 0.3) in the presence of a full agonist (α = 1) both with equal affinities for the receptor. Curves are shown in the presence of increasing concentrations of full agonist.

An inverse-agonist has an effect that is opposite to that of an agonist, but differs from an antagonist in that it does not attenuate the response of a receptor to agonist stimulation, rather, it can reduce the activity of a receptor that has a basal activity in the absence of agonist. The effects of an inverse-agonist are attenuated by an antagonist.

Ariëns' description of the relation between receptor occupancy and response is linear, however, Stephenson proposed a hyperbolic relationship and introduced the term efficacity to describe the ability of an agonist to evoke a response when the receptor is occupied [51]. Efficacity is similar to Ariëns' intrinsic activity factor (α), differing only in its relationship between stimulus and response.

3. Insights from single ion channels

Ligand-gated ion channels such as nAChRs have the ligand-binding site and the ion-conducting pore located within the same protein structure, therefore, agonist binding and channel opening are directly coupled and it can be considered that this macromolecule constitutes a complete pharmacological system. It is possible to record the activity of a single or small number of ion channels in a membrane patch or reconstituted lipid bilayer. This approach offers several advantages: the most important is that because the measurements are obtained from a single receptor, there can be no heterogeneity in the population of receptors that produce the response. In addition, the concentrations of all soluble substances at both the intra- and extra-cellular side of the membrane can be controlled. Although sub-conductance states are observed for some channels, ion channels generally have a single conductance level that is independent of the agonist concentration. As the concentration of agonist is increased the channel spends a greater fraction of time in the open state. For many channels, openings occur in bursts and the relationship between the probability that the channel is in the open state (P_{open}) and agonist concentration, plotted on log–concentration axes, resembles that of concentration–response relationships for cellular and tissue responses. The duration of channel opening is not only dependent on agonist concentration, but the distributions of open and closed states also depend on the individual agonist, each agonist evokes a unique pattern, with partial agonists evoking fewer and shorter channel openings than more potent agonists [52]. Although single channel records of nAChRs show spontaneous receptor openings, these occur with a low probability and are thought not to play a physiological role, thus, nAChRs are not good candidates for modulation by inverse-agonist compounds.

4. The allosteric model

The patch clamp technique has enabled researchers to study the functioning of ion channels on the same microsecond timescale as the binding and dissociation of agonist molecules,

these insights have helped to refine the models describing receptor occupation and response. It has been observed that many ion channels close even when agonist remains bound to the receptor. Single channel recordings have also revealed that it is not necessary for an agonist to bind to the receptor in order for the channel to open, and spontaneous channel openings have been observed at muscle [53] and α7 mutant nAChRs in the absence of agonist [54]. One model that takes these spontaneous openings into account, is the allosteric model of receptor function. The allosteric theory, initially formulated by Monod et al. [55], was adapted by Karlin [56] to describe the functioning of ligand-gated ion channels. This model predicts that the receptor can exist in multiple conformational states and undergoes spontaneous transitions between different states [57]. Each state displays a different affinity for a given ligand, and transitions from one state to another depend upon both the presence of a ligand and/or the isomerization coefficients L_0–L_2 (Fig. 3) (see [58] for a more thorough review on allosteric theory). The presence of a ligand with a high affinity for a particular state will stabilise the receptor in this state. To describe the functioning of the nAChR a minimum of three states must be included (Fig. 3). In the absence of agonist, the equilibrium between the states is in favour of the resting (R) closed state. According to the allosteric theory agonists are ligands that have a high affinity for the active (A) conformation and consequently stabilise the receptor in this state. Antagonists have a high affinity for either the R or D conformation, stabilising the receptor in one of these closed states. Partial agonists have only a slightly higher affinity for the active state over the closed (R and D) states and will stabilise a smaller number of receptors in the active state than a full agonist, or at the single channel level will stabilise the receptor in the A state for a shorter time, therefore evoking a smaller response. A partial agonist also has a higher affinity for closed states than a full agonist and explains the antagonistic effect versus a more potent agonist.

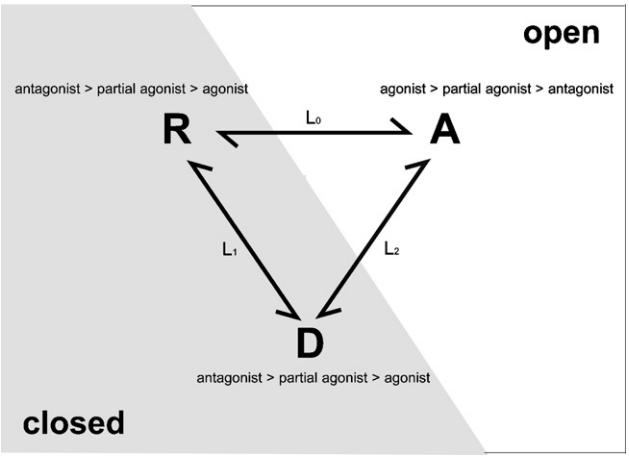

Fig. 3 – Minimal allosteric model for a desensitising ligand-gated ion channel. Letters represent the resting (R), active (A) and desensitised (D), states of the receptor. In the R and D states the receptor is in the closed state, in the A state the ion channel is open and gives rise to a measurable response. The relative order of affinity for agonists, partial agonists and antagonists of each receptor conformation is indicated. In the absence of ligand the equilibrium between the different receptor conformations are determined by the isomerization coefficients L_0–L_2.

5. Treatment strategies for neurodegenerative diseases

5.1. *Neuroprotection*

In the treatment of neurodegenerative diseases drugs targeted to nAChRs should compensate for the deficit of receptor function and improve neurone survival. In addition to its agonist effect, nicotine has been demonstrated to have neuroprotective effects in the CNS, delaying the aging process of nigrostriatal neurons [59] and protecting against exocytotic cell death [60]. These effects have been attributed to various mechanisms, including, an increase in expression of neurotrophic factors [61], inhibition of nitric oxide production [62] and activation of protein kinase C [63]. It was also reported that neuroprotective effects were correlated with the ability to activate α7 nAChRs [64] and could be blocked by inhibition of α7 receptors by MLA [65] leading to the hypothesis that Ca^{2+} entry through α7 nAChRs can promote neurone survival [65].

5.2. *Upregulation*

Chronic nicotine administration was first reported to increase the number of acetycholine binding sites in the brains of mice [66,67]. Immunoprecipitation studies of rat brain showed that this effect was pronounced in the cortex, and reported that the α4 and β2 subunits were upregulated [68]. The ability of nAChR ligands to increase the density of ACh binding sites in the CNS was also observed in the brains of smokers, which show significant upregulation of high affinity binding sites for nicotine [69,70]. Subsequent studies demonstrated that full and partial agonists, such as DMPP, (−)-cytisine, ABT-418, A-85380 and (±)-epibatidine also produced upregulation, with no direct correlation between binding affinity for nAChRs and increase in high affinity binding sites [71]. In addition, it was reported that the competitive antagonists DHβE, D-tubocurarine and the open channel blocker mecamylamine cause upregulation of α4β2 nAChRs in HEK cells and a fibroblast cell line [71,72], indicating that activation of receptors is not required for upregulation. The α7 partial agonists (±)-epibatidine, GTS-21, DMPP and the antagonist MLA, also caused upregulation of [^{125}I]-α-BgTX binding in HEK cells expressing α7 receptors [73]. It is not clear if the increase in high affinity binding sites reflects an increase in the number of receptors, or a change in the affinity of existing receptors, however, this increase in binding, has been associated with enhanced receptor functioning, termed functional upregulation [74–76]. The mechanisms underlying the upregulation of ligand-binding sites and functional upregulation remain unclear, the observation that upregulation is not related to the efficacy of the ligand to activate the receptor suggests that ligand binding to the extracellular domain of the nAChR alone, without receptor activation, may either slow down the removal of receptors from the membrane or to stabilize the receptor in a state which is consistent with the presence of a high affinity ligand-binding site. Nicotine, carbamylcholine,

DHβE and choline were shown to act intracellularly to enhance the rate of maturation of α4β2 nAChRs in HEK293 and SH-SY5Y neuroblastoma cells [77]. Using epitope-tagged subunits, Vallejo et al. reported that functional upregulation of α4β2 responses in HEK cells was not associated with a significant change in the number of surface receptors or changes in the assembly, trafficking, or cell-surface turnover of receptors [78]. They observed, however, that nicotine exposure altered the functional state of the receptor, slowing desensitization and enhancing sensitivity to acetylcholine. Based on these findings, they proposed that nicotine exposure slowly stabilizes α4β2 receptors in a high-affinity state that is more easily activated by subsequent nicotine exposure. Due to their ceiling effect on receptor activation the use of partial agonists to induce upregulation is likely to be associated with fewer adverse side effects than more potent full agonists.

6. Advantages of a partial agonist versus a full agonist or competitive inhibitor

A partial agonist can act as an agonist or an antagonist at a given receptor depending on the surrounding concentration of endogenous neurotransmitter. When endogenous neurotransmitter levels are high, a partial agonist will have a net antagonist effect, reducing the maximal response to the endogenous neurotransmitter (Fig. 2B and C). When endogenous neurotransmitter concentrations are low, the partial agonist will have an agonist effect and activate receptors (Fig. 2C). The maximum response evoked by the partial agonist will depend on its efficacy, so even if the concentration is increased the maximal response is limited. This 'ceiling effect' gives partial agonists a larger safety margin compared to full agonists and makes these molecules attractive for the development of therapeutics. Moreover, it has been claimed that partial agonists of nAChRs, may avoid addiction that could otherwise result from stimulation of the mesolimbic dopamine system with a full agonist. For example, the use of the partial agonists varenicline and dianicline (SSR591813) in clinical trials for smoking cessation do not produce the same addictive effects as the full agonist nicotine [79–81]. It is possible that partial agonists at α4β2 receptors provide a low-to-moderate level of stimulation of dopaminergic neurones, which reduce craving and withdrawal symptoms during smoking cessation, while strong stimulation of these receptors by nicotine is inhibited. This continued low level of dopamine release may be less dependence forming than the large spikes in dopamine release caused by acute nicotine intake from cigarette smoke [79].

7. *In vitro* and *in vivo* effects of partial agonists

The number of partial agonists targeted to nAChRs is steadily increasing, the compounds discussed hereafter provide examples of the effects and possible advantages of partial agonists acting at nAChRs. An area of treatment that has seen the development of several partial agonists is as nicotine replacement therapy for smoking cessation. Nicotine absorbed from tobacco smoke stimulates α4β2 receptors in the ventral tegmentum and causes the release of dopamine from mesolimbic neurones [82,83], this dopamine release is thought to be responsible for the rewarding effects of nicotine. Abrupt cessation of nicotine intake leads to withdrawal symptoms, with severity increasing with the level of dependence. The plant alkaloid cytisine, a partial agonist of α4β2 nAChRs is marketed in eastern Europe under the brand name Tabex® (http://www.tabex.net/) as a nicotine substitute, however, its effects are limited due to poor CNS access [79]. Varenicline (7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-*h*][3]benzazepine) an analogue of cytisine, developed by Pfizer, and a selective partial agonist of α4β2 nAChRs has been reported to be effective in counteracting the withdrawal symptoms associated with smoking cessation [80,81]. The rationale behind the use of partial agonists for smoking cessation is that their binding to central α4β2 nAChRs in the reward pathway results in a modicum of dopamine release from meso-limbic dopamine neurones, providing some relief from withdrawal symptoms, without a strong level of stimulation sufficient to evoke the reinforcing effect.

ABT-089 (2-methyl-3-(2-(S)-pyrrolindinylmethoxy)pyridine dihydrochloride) is a selective partial agonist at α4β2 receptors, with good oral bioavailability and penetration of the blood-brain barrier [84,85]. Systemic administration of ABT-089 has been reported to have positive effects on cognitive performance in rats and monkeys and to reduce distractibility in adult monkeys [84]. Recently, ABT-089 was tested for the treatment of attention-deficit/hyperactivity disorder in human adults [86], and was shown to be superior to placebo for improvement of total symptoms and the ADHD severity score [86]. ABT-089 was well tolerated at clinically effective doses with no serious side effects reported. *In vitro* ABT-089 was observed to have a neuroprotective effect against glutamate-induced excitotoxic effects in rat cortical cell cultures and differentiated IMR 32 cells. This effect appears to be due to stimulation of α7 nAChRs, as these neuroprotective effects could be attenuated by block of α7 receptors with the antagonist α-bungarotoxin. ABT-089 had more than 1000-fold less affinity for α7 nAChRs ($K_i > 10{,}000$ nM) compared to α4β2 ($K_i = 16$ nM) receptors and 1 mM ABT-089 evoked approximately 1% of the current evoked by 100 μM nicotine [87]. It is likely that the high selectivity for α4β2 subtypes over muscle receptors ($K_i > 1000$ nM), and ganglionic α3-containing receptors contributes to its reduced side effects profile. Agonists and partial agonists of nAChRs have been shown to have neuroprotective effects in many different experimental protocols. The precise mechanism of this effect is not known and given the diversity of the experimental conditions; the mechanism may be system dependant. It has been proposed the calcium entry through α7 receptors may be responsible for this effect, however, this is also known to be neurotoxic. It is possible that the degree of calcium influx is important in determining if the outcome is neuroprotective or neurotoxic. In spite of their low efficacy partial agonists show good neuroprotective effects, suggesting that weaker receptor stimulation may favour neuroprotection.

The anabaseine derivative 3-(2,4-dimethoxybenzylidene)-anabaseine (GTS-21) is a weak partial agonist of α7 nAChRs evoking approximately 10% of the maximal current evoked by nicotine [88]. Low concentrations of GTS-21 antagonised

responses to 100 μM nicotine, whereas at higher concentrations GTS-21 evoked a fraction of the nicotine-evoked current [88]. GTS-21 bound to human α4β2 nAChRs 100-fold more potently than to human α7 subtypes but did not cause activation of this heteromeric receptor [89]. Stimulation of α7 nAChRs by GTS-21 has neuroprotective effects against glutamate-induced and ischemic neurotoxicity [90,91], prevented loss of neocortical neurons in lesioned rats [92,93] and protected against ethanol-induced cytotoxicity *in vitro* [94]. GTS-21 also normalized the auditory gating deficit in rat and mouse models of schizophrenia, moreover, another α7-selective partial agonist, tropisetron [95,96], also improves the auditory gating deficit in mouse models and in humans with schizophrenia [97,98], suggesting that partial stimulation of central α7 nAChRs could be useful in the treatment of schizophrenia [99–101]. In humans GTS-21 had positive effects on cognition, with no significant adverse side effects [102] and in addition has been reported to protect against β-amyloid-induced cytotoxicity [103] making it candidate for the treatment of Alzheimer's disease. A conformationally restricted analogue of nicotine SIB-1663 was a selective partial agonist at human recombinant α2β4 and α4β4 nAChRs and produced positive results in animal models of Parkinson's disease and pain [104]. Another partial agonist SIB-1553A, which has low affinity for α7 nAChRs and shows greater selectivity for β4-containing over β2-containing nAChRs in calcium flux studies [105,106] was reported to improve attention and memory in animal models [107–109]. However, SIB-1553A was also reported to have a modest affinity for H_3, 5HT-1, 5HT-2 and sigma receptors [105,106], suggesting that its cognitive enhancing effects may not be mediated solely by nAChRs.

8. Conclusions

Partial agonists of nAChRs have been shown to be effective in a number of animal models of disease and consequently in trials in human subjects. *In vitro* investigation of the pharmacological characteristics of partial agonists revealed that, depending on the concentration of the endogenous agonist, they can have either a facilitatory or inhibitory effect on the biological response. In the absence of precise measurements of the concentration of endogenous neurotransmitters in the brain at a given moment, it is difficult to know which property of a partial agonist is most important for its activity. In addition, some partial agonists can lead to an upregulation of nicotine binding sites and receptor function, suggesting that this property could play a beneficial role during chronic treatment of disease states involving loss of nicotinic function. An important characteristic of many of the partial agonists mentioned above is the lack of serious side effects associated with their use, which is in contrast with the toxicity of more potent nicotinic receptor agonists such as epibatidine and nicotine. This is likely attributable to the ceiling effect of agonist activity.

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