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Review

Allosteric modulation of nicotinic acetylcholine receptors

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ABSTRACT

Nicotinic acetylcholine receptors (nAChRs) are receptors for the neurotransmitter acetylcholine and are members of the 'Cys-loop' family of pentameric ligand-gated ion channels (LGICs). Acetylcholine binds in the receptor extracellular domain at the interface between two subunits and research has identified a large number of nAChR-selective ligands, including agonists and competitive antagonists, that bind at the same site as acetylcholine (commonly referred to as the orthosteric binding site). In addition, more recent research has identified ligands that are able to modulate nAChR function by binding to sites that are distinct from the binding site for acetylcholine, including sites located in the transmembrane domain. These include positive allosteric modulators (PAMs), negative allosteric modulators (NAMs), silent allosteric modulators (SAMs) and compounds that are able to activate nAChRs via an allosteric binding site (allosteric agonists). Our aim in this article is to review important aspects of the pharmacological diversity of nAChR allosteric modulators and to describe recent evidence aimed at identifying binding sites for allosteric modulators on nAChRs.

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1. Introduction

Nicotinic acetylcholine receptors (nAChRs) are excitatory receptors for the neurotransmitter acetylcholine and play an important role in the central and peripheral nervous system [1–4]. They are members of the 'Cys-loop' family of pentameric ligand-gated ion channels (LGICs); a family that includes a subset of receptors for 5-hydroxytryptamine (5-HT), γ-aminobutyric acid (GABA) and glycine [5–7].

Nicotinic receptors are widely expressed in the brain in both pre- and post-synaptic locations [8,9]. They are also expressed in both sympathetic and parasympathetic ganglia, where they are responsible for fast synaptic transmission. In addition, nAChRs are expressed in skeletal muscle, epithelial and immune cells [10–13]. Nicotinic receptors have been implicated in a number of neuromuscular, neurological and psychiatric disorders. For example, in recent years, neuronal nAChRs have been identified as important targets for therapeutic drug discovery, in connection with disorders such as Alzheimer's disease and schizophrenia [14,15].

Sixteen human nAChR subunits (α1-α7, α9, α10, β1-β4, γ, δ and ε) have been identified. The α1, β1, γ, δ and ε subunits are

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expressed in muscle, whereas the α2-α7, α9, α10 and β1-β4 subunits are expressed more widely and are commonly referred to as neuronal subunits [16,17]. Receptors expressed at the neuromuscular junction are heteromeric complexes containing two copies of the α1 subunit co-assembled with three non-α subunits, with receptors in embryonic and adult muscle having the subunit composition of $(\alpha1)_2\beta1\gamma\delta$ and $(\alpha1)_2\beta1\delta\varepsilon$, respectively [18,19]. There is, however, considerably greater subunit diversity amongst neuronal nAChRs [8,17]. Some neuronal nAChR subunits, such as α7, can form functional homomeric [$(\alpha7)_5$] nAChRs [20], whereas the majority of neuronal nAChR subunits form heteromeric complexes, consisting of at least two α-type subunits co-assembled with at least two β-type subunits, for example $(\alpha4)_2(\beta2)_3$ and $(\alpha4)_3(\beta2)_2$ [17]. Each nAChR subunit contains an amino-terminal extracellular domain and four transmembrane helices (TM1-TM4). The pore of the channel is lined by the second transmembrane domain (TM2) from five co-assembled subunits [21] (Fig. 1).

2. Allosteric modulation of nAChRs

The endogenous neurotransmitter of nAChRs, acetylcholine, binds in the receptor extracellular domain, at the interface between two subunits [22,23]. Research conducted over many years has identified a large number of nAChR-selective ligands, including agonists and competitive antagonists that bind at the same site as acetylcholine (commonly referred to as the orthosteric binding site). In addition, more recent research has identified ligands that are able to modulate nAChR function by binding to sites that are distinct from the binding site for acetylcholine, including sites located in the transmembrane domain.

As has been discussed previously, there can be some confusion as to the use of the term 'allosteric' in receptor pharmacology [24]. We will use the term 'allosteric site' to describe any nAChR ligand-binding site that is distinct from the conventional acetylcholine binding site and we will use the term 'allosteric modulator' to describe any ligand that alters the functional properties of nAChRs by interacting with a site that is distinct from the orthosteric site. In doing so, we do not necessarily intend to imply a particular mechanism of action for such ligands. Instead, our aim in this review is to describe evidence for receptor modulation that occurs as a consequence of ligands binding to sites that are distinct from that at which acetylcholine acts as an agonist.

Allosteric modulators can either potentiate the effects of agonist-activation (positive allosteric modulators; PAMs), or inhibit agonist-activation (negative allosteric modulators; NAMs). Of course, quite correctly, the term non-competitive antagonist is also used extensively to describe ligands that are capable of inhibiting agonist-evoked responses through a distinct binding site. Possible mechanisms for modulation of nAChRs by allosteric

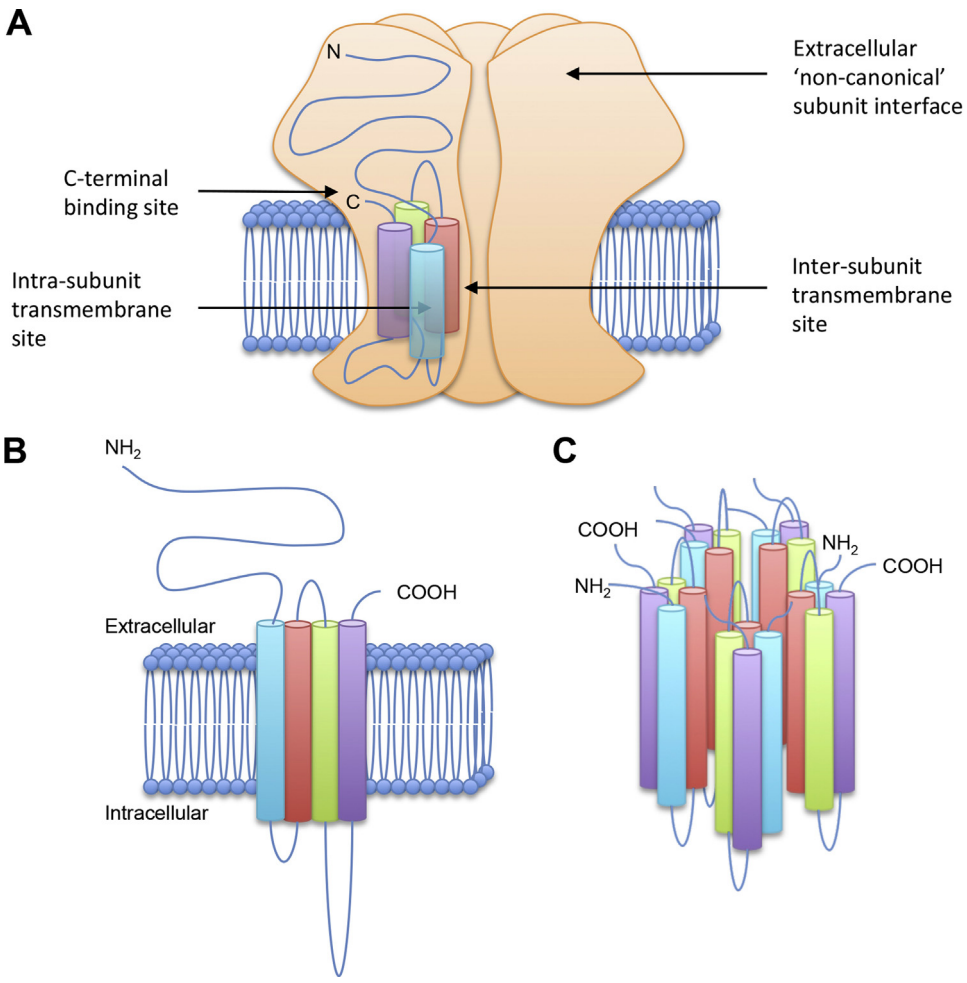

Fig. 1. Cartoon representation of nAChR structure and subunit topology. Five co-assembled nAChR subunits are shown in a lipid bilayer and annotated to show locations that have been proposed as binding sites for allosteric modulators (A). The transmembrane topology of a single nAChR subunit is shown, in which the polypeptide chain is denoted by a blue line and the four transmembrane helices by cylinders (A and B). Also illustrated (C) is the nAChR transmembrane domain, formed by twenty transmembrane helices (four from each of the five co-assembled subunits). The central ion channel pore is lined by the second transmembrane helix (TM2) from each of the five subunits.