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Review

Multiple binding sites in the nicotinic acetylcholine receptors: An opportunity for polypharmacolgy

Patricio Iturriaga-Vásquez[a,*], Jans Alzate-Morales[b], Isabel Bermudez[c], Rodrigo Varas[e], Miguel Reyes-Parada[d,e,**]

[a] Facultad de Ingeniería y Ciencias, Universidad de la Frontera, Temuco, Chile
[b] Centro de Bioinformática y Simulación Molecular, Facultad de Ingeniería, Universidad de Talca, Talca, Chile
[c] Department of Biological & Medical Sciences, Faculty of Health & Life Sciences, Oxford Brookes University, Oxford, UK
[d] Escuela de Medicina, Facultad de Ciencias Médicas, Universidad de Santiago de Chile, Chile
[e] Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Chile

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ABSTRACT

For decades, the development of selective compounds has been the main goal for chemists and biologists involved in drug discovery. However, diverse lines of evidence indicate that polypharmacological agents, i.e. those that act simultaneously at various protein targets, might show better profiles than selective ligands, regarding both efficacy and side effects. On the other hand, the availability of the crystal structure of different receptors allows a detailed analysis of the main interactions between drugs and receptors in a specific binding site.

Neuronal nicotinic acetylcholine receptors (nAChRs) constitute a large and diverse family of ligand-gated ion channels (LGICs) that, as a product of its modulation, regulate neurotransmitter release, which in turns produce a global neuromodulation of the central nervous system. nAChRs are pentameric protein complexes in such a way that expression of compatible subunits can lead to various receptor assemblies or subtypes. The agonist binding site, located at the extracellular region, exhibits different properties depending on the subunits that conform the receptor. In the last years, it has been recognized that nAChRs could also contain one or more allosteric sites which could bind non-classical nicotinic ligands including several therapeutically useful drugs. The presence of multiple binding sites in nAChRs offers an interesting possibility for the development of novel polypharmacological agents with a wide spectrum of actions.

Contents

* Corresponding author.
** Corresponding author at: Facultad de Ingeniería y Ciencias, Universidad de la Frontera, Temuco, Chile.
E-mail addresses: patricio.iturriaga@ufrontera.cl (P. Iturriaga-Vásquez), miguel.reyes@usach.cl (M. Reyes-Parada).

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1. Introduction

High levels of attrition and a paucity of truly novel agents have characterized drug discovery in the last decade. This has led to the search of novel strategies such as polypharmacology, allosterism or drug repurposing in order to develop new drugs or to find novel uses for known compounds. At the same time, an enormous progress has been done regarding the structure and function of nicotinic acetylcholine receptors. Thus, they still remain as exceptionally attractive targets for drug design. In the present article we will briefly discuss some general topics about these ubiquitous proteins and will outline the characteristics that make them particularly suitable for the development of novel polypharmacological agents with a wide spectrum of actions.

2. The concept of polypharmacology

For years, medicinal chemists and pharmacologists have considered selectivity as a property of paramount importance when designing and evaluating compounds with potential therapeutic usefulness. This has been based on the idea that drugs acting on a single target involved in disease progression (either a gene or a protein receptor) will have minimum side effects and maximal efficacy. Recent observations coming from systems biology, however, increasingly indicate that "promiscuous" drugs, i.e. targeting multiple receptors (or the use of selective drug mixtures), might show better profiles regarding both efficacy and side effects [1–8]. The basic biological concept underlying these findings is that robust phenotypes such as those observed in mood or neurodegenerative disorders, are often the result of a complex network of molecular events rather than changes on a single target functioning. Thus, if only one node of the system is selectively addressed, even if it is a critical one, in most of cases the dynamics of the network will compensate that pharmacological action, affecting therefore drug efficacy [3,8–10].

Even though it is known that many currently used drugs act via interaction with multiple receptors [9,11], the realization that these properties can be proactively pursued has generated a new trend in drug discovery, called polypharmacology, in which a desired therapeutic effect can be achieved by compounds acting on a selected range of pharmacological targets [12–14]. However, the rational design of multitarget drugs faces considerable challenges in the understanding and optimization of multiple structure-activity relationships [3,4,14,15]. In fact, it is unclear to what extent rational design of polypharmacological drugs can be achieved for proteins functionally and/or structurally divergent [1,8,15]. In this context, although different drug discovery strategies have been used in the last six decades, the availability of high resolution crystal structures of important biological targets has shifted the emphasis towards structure-based design (SBD) [16] and fragment-based design (FBD) [17,18]. Moreover, fishing approaches have emerged as an interesting alternative for finding multitarget hits that facilitate rational optimization [19,20]. Thus, it has been shown that the use of SBD, FBD and/or fishing strategies (alone or in combination) leads to promising results regarding the rational design of polypharmacological drugs [see for example [14,18,21–24].

3. Ligand-gated ion channel family

Ligand-gated ion channels (LGICs) are defined as a group of transmembrane proteins which open when a ligand binds to an external region of the channel, allowing ions such as Na^+, K^+, Ca^{2+}, or Cl^- to pass through the membrane [25,26]. Members of the cys-loop LGIC family mediate both fast excitatory and inhibitory synaptic neurotransmission in the nervous system. The LGIC proteins include homomeric and heteromeric cation permeable nicotinic acetylcholine receptors and the serotonin type 3 receptor (5-HT_3R), and anionic permeable channels such as $GABA_A$ [27] and $GABA_C$ receptors [28], glycine receptors [29], some invertebrate glutamate receptors (GluR) [30] and histamine-gated chloride channels (HisCls) [31,32]. The cys-loop LGICs are considered as pentamers containing homologous subunits, and it is assumed that the genes coding for these subunits are derived from a common ancestor gene [33,34]. Each subunit is defined by a large extracellular N-terminal domain, three transmembrane segments, an intracellular loop of variable length and a fourth transmembrane segment, with an extracellular C-terminal end (Fig. 1) [35].

4. Neuronal nicotinic acetylcholine receptors

Neuronal nicotinic acetylcholine receptors (nAChRs) are involved in different central nervous system (CNS) functions and disorders such as cognition, analgesia, nicotine addiction [36–38], stroke, Tourette's syndrome, Parkinson's and Alzheimer's diseases, schizophrenia, anxiety, depression, epilepsy, autism and attention-deficit hyperactivity disorder (Fig. 2) [39–41]. There are at least 11 different subunits (α2–α7, α9, α10, β2–β4) known to constitute neuronal nAChRs, isolated from bird, rodent and human neurons [42,43]. Since the subunits arrangement defines the pharmacological and biophysical properties of a given nAChR subtype, it is essential to identify those subunits in order to understand the role of endogenous nAChRs and to rationally design new drugs [44]. The α4β2* nAChR subtype is the most abundant in the CNS and represents about 90% of the [^{3}H]cytisine binding sites in rat brain [45]. This subtype exists in two different stoichiometries, the low sensitivity form $(\alpha4\beta2)_{2\alpha}4$ and the high sensitivity form $(\alpha4\beta2)_{2\beta}2$. The diversity in the subunit interfaces and in the number of binding sites confer striking differences in potency and efficacy for nicotinic ligands [46]. Another dominant nAChR subtype found in brain is the homomeric (i.e. composed of five identical subunits) α7 nAChR [47]. In addition, several other subtypes have been reported to be present in the CNS [48].

Despite this complex diversity, there is a consensus about the predominant role of presynaptic nAChRs as modulators of neurotransmitter release throughout all types of chemical synapses in the CNS [49]. Different nAChR subtypes involved in the regulation of neurotransmitter release in several areas of the brain have been described. For instance, it has been shown that noradrenaline release in hippocampus and prefrontal cortex is regulated by α3β4 nAChR [50]. Furthermore, dopamine (DA) appears to be the most important neurotransmitter released upon exposure to nicotine in different zones of the brain, such as cortex [51,52], hippocampus [49], midbrain [50], striatum [42,53] and thalamus [54]. In the DAergic neurons of the midbrain (VTA and subtantia nigra, mainly) the α4β2 nAChR subtype is the most important receptor involved in DA release (Fig. 2) [38].

A wide range of animal and plant toxins targeting nAChRs can be found in nature. Thus, natural agonists include nicotine, cytisine, anatoxin-A and epibatidine [55], while a few small molecule (non-peptide) natural products act as antagonists, e.g. methyllycaconitine for the α7 subtype [56] and erysodine or dihydro-β-erythroidine for the α4β2 subtype [57,58]. The increased interest in neuronal nAChRs as therapeutic targets has prompted the appearance of several novel synthetic ligands to add to this pharmacopoeia. Nevertheless, there is still a need for truly subunit-selective ligands, especially antagonists [49,59].

As an example of the wide variety of nAChRs ligands developed thus far, a selected number of natural and synthetic α4β2 nAChR agonists and their properties are listed below.