Functional and structural interactions between selective serotonin reuptake inhibitors and nicotinic acetylcholine receptors

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Neuronal nicotinic acetylcholine receptors (nAChRs) are involved in the regulation of mood and their related disorders such as anxiety and major depressive disorder. For instance, there is a clear and strong association between major depression and smoking, where depressed patients smoke twice more than the non-depressed population, and opposite to that, nicotine consumption may lead to depressive symptoms. In patients with major depressive disorder, although the number of nAChRs is not altered, there is a low availability of nAChRs, possibly caused by higher endogenous ACh levels and the consequent nAChR desensitization, consistent with the cholinergic hypothesis of depression, in which the cholinergic systems is hypersensitive. Moreover, studies using animal models of depression reveal that nicotine-evoked serotonin release is mediated by nAChR activation compensating the deficiency of serotonin in depressed conditions. It was also reported that several common clinically prescribed antidepressants, including selective serotonin reuptake inhibitors (SSRIs), inhibit different nAChRs by non-competitive mechanisms, including ion channel blockade and accelerating nAChR desensitization. More specifically, SSRIs decrease channel open time without changing the single-channel conductance, indicating that these antidepressants act as open-channel blockers. Furthermore, inactive doses of citalopram, a SSRI antidepressant, and of PNU-28298, an α7 nAChR agonist, exert antidepressant-like effects. According with functional and structural results, SSRIs (e.g., fluoxetine) and tricyclic antidepressants (e.g., imipramine) bind to overlapping sites located within the nAChR ion channel in the desensitized and resting states.

Keywords: Selective serotonin reuptake inhibitors; antidepressants; nicotinic acetylcholine receptors; fluoxetine; non-competitive antagonists; molecular modeling

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Introduction

Nicotinic acetylcholine receptors (nAChRs) are physiologically involved in the regulation of mood, and consequently its functional imbalance is implicated in the development of anxiety states and depressive disorders [1-3]. Along the same concept, the cholinergic-adrenergic hypothesis proposes that depression is developed by an imbalance between the noradrenergic and cholinergic systems, where the latter system is more sensitive or more stimulated than the former system [4]. In this regard, nAChR inhibition by antidepressants could be relevant for its clinical efficacy [5]. Although the causality between nicotine exposure and depression remains unclear, it is important to highlight the association between smoking and depression, where depressed patients smoke twice more than the average population, probably to control their mood symptoms.

Paradoxically, however, the use of nicotine may lead to the development of depressive symptoms [1, 2-7]. One possibility that smoking could induce depression is that nicotine would hyperactivate nAChRs, and consequently the cholinergic signaling, breaking the balance between cholinergic and noradrenergic systems [4]. Additionally, chronic smoking leads to long-term upregulation of high affinity nAChRs containing the β2 subunit, potentially increasing nAChR activity, that in turn could contribute to depressive symptoms [8].

Although there is no difference in the number of β2*-nAChRs (i.e., β2-containing nAChRs) between patients with major depressive disorder and healthy subjects, a comparative lower availability of β2*-nAChRs has been observed across several brain regions (i.e., parietal, frontal, anterior cingulate, temporal and occipital cortices, thalamus, cerebellum, striatum, hippocampus, amygdale and brainstem) from depressive patients. This lower receptor availability could be caused by higher levels of endogenous acetylcholine (ACh) that may result in receptor desensitization [9], consistent with the cholinergic hypothesis of depression. In addition to inhibiting different neurotransmitter transporters, several common prescribed antidepressants also inhibit nAChRs in a non-competitive fashion. In this review, we focus on the functional and structural interactions exerted by selective inhibitors of the serotonin reuptake system, the so-called “selective serotonin reuptake inhibitors (SSRIs)”, on different nAChR subtypes. Among SSRIs, we can include fluoxetine, nor-fluoxetine, sertraline, paroxetine, zimelidine, and citalopram (see molecular structures in Fig. 1). The best characterized SSRIs in terms of their interaction with nAChRs are fluoxetine and paroxetine, whereas fewer studies have been performed with other SSRIs [10-22]. The common pharmacological action of SSRIs consists in the inhibition of both muscle and neuronal nAChRs in a non-competitive manner, presumably by interacting within the ion channel (for more details see the section BINDING SITES FOR SSRIs AT DIFFERENT nAChRs). The effects elicited by SSRIs on nAChRs may restore the cholinergic imbalance occurring during depressive states.

Hypothesis of depression

Major depression is a deep alteration of mood, manifested by anxiety, anhedonia, disturbed sleep, cognitive impairment, suicidal ideation, among others [23]. This devastating mood disorder is very complex and depends on genetic, neuronal, cognitive, psychological, and sociocultural aspects [24-26].

Although the etiology of depression is not well understood, the dysfunction of certain brain regions has been implicated in the physiopathology of this disease, and consequently in the clinical action of antidepressants. The most important brain areas related to depression are the cortical, subcortical, limbic, basal ganglia, and brain stem regions [27]. Interestingly, the size and the number of synapses at several areas, including amygdala, nucleus accumbens, hippocampus, prefrontal cortex, and cingulate cortex, are reduced in animal models of depression and in depressed patients [24-26].

Monoamine hypothesis of depression

Several hypotheses have been proposed to explain the etiology of depression, which include some neurotransmitter systems. Moreover, each of them may take part in this complex disorder [28, 29]. One of the first and more extended hypothesis of depression consists in the deficit of extracellular monoamines, including the neurotransmitters serotonin (5-HT), noradrenaline (NA), and dopamine (DA) [30]. In this regard, substances that increase monoamines would be useful as an aid for the treatment of depression. Since the 1950s, patients with major depressive disorder have been treated with substances that inhibit the reuptake and/or metabolism of monoamines (i.e., monoamine oxidase inhibitors; e.g., selegiline) [31, 32]. Among monoamine reuptake inhibitors, the most recent and effective have been classified as SSRIs (see Fig. 1) [29].

The cholinergic-adrenergic hypothesis of depression

The cholinergic-adrenergic hypothesis of depression emerged later on, proposing that an imbalance between the activity of NA and ACh is the main cause [4]. ACh signalling in the brain is mediated by two classes of receptors, muscarinic and nicotinic, and has been associated to several
physiological and pathological processes, including learning, memory, attention, food-intake, mood, and consequently, to mood disorders such as anxiety and major depression [7, 33, 34]. For instance, an increase of the extracellular levels of both ACh and choline (the precursor and hydrolysis metabolite of ACh) has been observed during depression, suggesting overactivity of the nAChR system [3, 7, 35]. In addition, the administration of the acetylcholinesterase (AChE) inhibitor physostigmine, which increases the synaptic levels of ACh, induced symptoms of depression in humans [36–38] and increased depression-like behavior in mice [39].

Role of nicotinic acetylcholine receptors in depression

Neuronal nAChRs are a heterogeneous family of pentameric ligand-gated ion channels that are widely expressed throughout the brain and are involved in several physiological and pathological processes. Postsynaptic nAChRs mediate the transmission of fast signals across central and peripheral synapses [40, 41], whereas presynaptic nAChRs modulate the release of a variety of neurotransmitters, including those implicated in depression [42, 43]. For instance, nicotine-evoked 5-HT release is dependent on α7 nAChR stimulation [44, 45].

Several lines of preclinical and clinical evidence support the involvement of nAChRs in depression [3, 39, 46, 47]. Additional evidence supports a bidirectional association between smoking and depression, in which depressive states increase the rate of smoking due to mood changes positively correlated with the quantity of tobacco used; and vice versa, smoking increases the risk for major depression, probably due to overactivation of nAChRs [1, 7, 48, 49]. There is also comorbidity between depression/anxiety states and nicotine addiction [2], highlighting the relationship between these diseases and nAChRs.

Although antidepressants are successfully used in the treatment of both depression and anxiety, only bupropion and nortriptyline are beneficial in long-term smoking cessation, whereas fluoxetine (a SSRI) is effective only in smokers with strong depressive symptoms [50, 52] (reviewed in [51]). However, monoamine oxidase inhibitors do not benefit during smoking cessation [50]. Additional studies also point out the importance of the cholinergic system in the development of depression, and more specifically that nAChR inhibition produces antidepressant-like effects. For example, augmenting ACh content by decreasing the AChE activity, using the inhibitor physostigmine or virally delivered shRNAs, produces depression-like behavior in animal models, which is reversed by nAChR antagonists [39]. On the other hand, nAChR antagonists, which limit the activity of these receptors, produce antidepressant-like effects [7, 46, 47]. This is in accordance with the fact that depressed subjects have a higher endogenous ACh content that may be overactivating the cholinergic system [9].

Figure 1. Molecular structures of SSRIs that inhibit different nAChR subtypes.
Selective serotonin reuptake inhibitors also inhibit nAChR function

The best characterized mechanism of action for SSRIs is based on the inhibition of 5-HT reuptake toward presynaptic terminals, increasing the synaptic concentration of 5-HT with the consequent changes on 5-HT neurotransmission \[13, 16\]. Here, we review the effects of SSRIs when interacting with nAChRs (Table 1). The most common action of SSRIs at different nAChRs consists in the non-competitive inhibition of nAChR function. Thus, the immediate consequence is a decrease in the cholinergic activity mediated by nAChRs, alleviating the exacerbated cholinergic activity observed during depressive conditions, consistent with the cholinergic hypothesis of depression \[4, 36-39\].
Fluoxetine inhibits all nAChR subtypes studied to date and is one of the best characterized SSRI regarding its action on nAChRs (Table 1).

**Inhibitory mechanisms of nAChR by SSRIs**

It has been proposed that nAChRs exist in allosteric transitions between different conformational states: a resting state, an active open-channel state, and one or more high-affinity desensitized state(s) with a non-conducting ion channel [40, 57]. Although not all functional properties of SSRIs have been studied on every nAChR subtype, experimental evidence indicates that the activity of SSRIs depends on the nAChR conformational state, modulating each nAChR state in different fashions. For instance, fluoxetine allosterically modulates nAChRs by interacting with the resting (closed), activated (open), and desensitized (non-conducting) states of the receptor [11, 13, 20]. Although the pharmacological activity of fluoxetine with different nAChRs depends on the receptor subtype, its functional effects can be summarized as follows: (a) reduces the channel opening frequency, (b) increases the channel closed times, (c) decreases the channel open times, (d) does not change single-channel conductance [13, 20]. Consequently, the activity of fluoxetine on the nAChR response, at the whole-cell level, results in the reduction of the amplitude and acceleration of decay (desensitization) of the agonist-induced currents, and reduction of Ca$^{2+}$ entry [10, 13, 20].

Fluoxetine accelerates nAChR desensitization, and has stronger inhibitory potency at elevated agonist concentrations, suggesting higher affinity to desensitized nAChRs [13, 19]. This pharmacological feature has been also observed for other structurally different antidepressants [58], suggesting a common mode of activity. A similar correlation (i.e., higher affinity at higher concentrations) has been determined for nicotinic agonists [59]. Based on this evidence, we can suggest a potential mechanism for the clinical activity of antidepressants. In depressed conditions, where higher concentrations of ACh are expected, most AChRs are probably in the desensitized state. As previously shown, this conformational state is strongly inhibited by antidepressants, reducing synergistically the nAChR-related signaling, that may ultimately help in the improvement of depressive states.

**Binding affinity of selective serotonin reuptake inhibitors to nAChRs**

The binding affinities of SSRIs and other antidepressants at various nAChRs in different conformational states were determined by radioligand competition experiments [11, 19, 60, 61]. More specifically, the influence of fluoxetine and paroxetine on the maximal binding of either [3H]imipramine (tricyclic antidepressant and NCA of nAChRs [12, 58]) to each human (h) neuronal (hα4β2, hα3β4, and hα7) nAChRs subtype or [3H]TCP (the structural and functional analogue of phenycyclidine (PCP), a NCA of Torpedo nAChRs [62]) to Torpedo nAChR, in the resting (bungarotoxin-bound) and desensitized (agonist-bound) states was determined. Thus, fluoxetine and paroxetine completely inhibit the specific binding of either [3H]imipramine to each neuronal nAChR subtype [19] or [3H]TCP to Torpedo nAChRs [11] with higher affinity when the nAChRs are in the desensitized states compared to the resting states (Table 2). The $n_H$ values are close to unity (Table 2), suggesting that fluoxetine and paroxetine inhibit [3H]imipramine and [3H]TCP binding to nAChRs in a non-cooperative manner, suggesting that these NCAs bind to overlapping sites.

**Implications of SSRIs affecting nAChRs**

It was commonly thought that therapeutic effects of SSRIs are essentially due to the inhibition of serotonin transporters, finally increasing the concentration of 5-HT in the synaptic cleft. Note that among these SSRIs, the most potent inhibitor of nAChRs is fluoxetine (Table 1). In particular, fluoxetine inhibits serotonin transporters (IC$_{50}$ ~ 6-17 nM) [63-65] with higher potency compared to other potential targets, including voltage-gated ion channels (IC$_{50}$s in the μM range) [66, 67].

Of particular interest in this review is the possible clinical implication of the inhibitory effects of SSRIs on nAChRs. It has been suggested that ACh levels are elevated in patients with major depression [3, 7, 35]. In this sense, SSRIs counteract
the possible overactivity of the cholinergic system in different ways: (1) According with the affinity and actions of SSRIs, they firstly act on serotonin transporters, increasing the extracellular levels of 5-HT up to 7-fold the basal concentrations in many brain areas, including the nucleus accumbens, striatum, thalamus, and hypothalamus [68–70]. The increase in the endogenous concentration of 5-HT may be high enough to inhibit nAChRs [71, 72]; (2) SSRIs directly interact with the closed, activated, and/or desensitized states of nAChRs inhibiting their function, having higher affinity for the desensitized state (see Table 2) [11–13, 15, 20]; and finally, (3) the SSRI fluoxetine also increases directly the activity of AChE throughout the brain, reducing extracellular ACh levels, and consequently reducing nAChR-related signaling [39].

The plasma concentration of fluoxetine during clinically effective treatments may reach 0.29–0.97 µM, and in some patients up to 1.6 µM after administration of 40 mg/day during 30-days treatment [73, 74]. A wide range of brain to plasma ratios (2.6-20) has been calculated for fluoxetine [75,76], concurrent with the determined relatively high fluoxetine brain concentration (13 µM) [77]. Accordingly, it is very feasible that all nAChR subtypes can be inhibited by fluoxetine (Table 1). Potentially, this antidepressant might alter those physiological (i.e., attention, memory, and learning) and pathological (i.e., epilepsy, schizophrenia, Alzheimer’s disease, addiction, anxiety, and major depression) processes in which nAChRs are involved [33, 41–43, 78–80].

In addition to be used for depression, fluoxetine is also used to treat slow-channel congenital myasthenic syndromes. A common feature in both conditions is that the concentration of ACh is higher than that in the normal population [8,20,39]. For instance, in slow-channel congenital myasthenic syndromes, the high synaptic ACh levels are associated with long-lasting opening of slow-channel mutant nAChRs, enhancing cation influx into the endplate [20, 81]. Accordingly, the actions of fluoxetine (decreases channel opening frequency and open times, and increases closed times) may restore the pathological conditions observed in congenital myasthenic syndromes. A reasonable question arise: do long-lasting opening of nAChRs occur in depressed patients, or in animal models of depression?

There is some evidence showing the involvement of nAChRs in major depression using animal models [47]. More specifically, nicotine-evoked 5-HT release depends on α7 nAChR activation, and monoamine release is facilitated by nAChR stimulation [47]. For instance, the combined administration of the α7 nAChR agonist PNU-282987 (30 mg/kg, a dose that causes full occupancy of α7 nAChRs [82]) with a sub-active dose of citalopram (3 mg/kg, which inhibits ~50% serotonin reuptake but is unable to produce antidepressant activity using the forced swim and tail suspension tests in mice [47, 83]) causes antidepressant-like effects. Since PNU-282987 alone showed no antidepressant-like activity, it is possible that the combined α7 nAChR agonism and partial serotonin transporter inhibition seems to be responsible for the antidepressant-like effect, confirming the involvement of nAChRs in the treatment of major depression.

Additional data indicated that serotonergic neurons express functional nAChRs (i.e., α4β2 and α7 nAChR subtypes) [84, 85]. Postsynaptic nAChRs increase firing frequency of serotonergic neurons that may result in changing 5-HT levels, whereas presynaptic nAChRs would mediate nicotine-evoked 5-HT release in serotonergic neuron projections [45, 84–86]. In addition, nicotine alone or in combination with sertraline reversed the impairment induced by chronic mild stress in the spontaneous alternation behavior in mice [46]. These data provide additional support for the involvement of nAChRs in depression.

In certain conditions such as smoking and depression, nAChRs (from treated patients) may be exposed, at the same time, to endogenous agonists (ACh, choline), the exogenous agonist nicotine, high levels of 5-HT, and/or to antidepressants, such as fluoxetine. Consequently, ACh through the interaction of nAChRs may produce a variety of effects, depending on the nAChR subtype and functional state, cellular location, and neuronal pathway, among other factors [78]. One example may be the activation of presynaptic nAChRs that modulates the release of several neurotransmitters involved in mood regulation, and thus, its malfunctioning might be related to mood disorders [42, 43]. All these panoramas add to the complexity of the nAChRs functioning and their modulation by antidepressants.

**Binding sites for SSRIs at different nAChRs**

The comparative/homology modeling and molecular docking simulations have been used to determine the molecular interactions of SSRIs and other antidepressants, specifically fluoxetine and paroxetine, with a variety of nAChR subtypes [11, 19, 60, 61, 87, 88]. In this regard, based on the Torpedo nAChR molecular model (PDB id: 2BG9) [89], muscle and neuronal nAChRs were constructed, including the hz1β1γδ, hz1β1εδ, hz4β2, hz3β4, and ha7 subtypes [11, 60, 61, 87, 90, 91]. In addition, SSRIs and other antidepressants were built in the protonated and neutral forms, and subsequently docked to each nAChR model [11, 90, 91].
Docking simulations indicated that fluoxetine, in the protonated and neutral forms, interacts within the middle portion of the ion channel from each nAChR subtype (Fig. 2). Considering that each subunit has one transmembrane M2 segment, the ion channel is formed by five M2 segments (reviewed in [92]). Although the ion channel is highly conserved among species, differences are also apparent among nAChR subunit sequences (reviewed in [92]), producing variations in the nAChR ion channel structure. For example, in the α4β2 nAChR the amino acid rings are named: outer or extracellular (position 20'), nonpolar (position 17'), valine (position 13'), leucine (position 9'), serine (position 6'), threonine (position 2'), intermediate (position -2'), and cytoplasmic or inner (position -5'), whereas in the α7 nAChR the polar rings (positions 2' and 6') are switched: the threonine ring occurs at position 6' and the serine ring at position 2'. In the case of the α3β4 nAChR, the α4 subunit carries an additional essential change: phenylalanine residues are located at position 13', forming together with α3 subunit the valine/phenylalanine ring. This substitution dramatically changes the overall binding properties of the channel in docking simulations. Fluoxetine docking results, presented below, support this statement.

The docking simulations for neutral and protonated forms, interacts within the middle portion of the ion channel from each nAChR subtype (Fig. 2). Considering that each subunit has one transmembrane M2 segment, the ion channel is formed by five M2 segments (reviewed in [92]). Although the ion channel is highly conserved among species, differences are also apparent among nAChR subunit sequences (reviewed in [92]), producing variations in the nAChR ion channel structure. For example, in the α4β2 nAChR the amino acid rings are named: outer or extracellular (position 20'), nonpolar (position 17'), valine (position 13'), leucine (position 9'), serine (position 6'), threonine (position 2'), intermediate (position -2'), and cytoplasmic or inner (position -5'), whereas in the α7 nAChR the polar rings (positions 2' and 6') are switched: the threonine ring occurs at position 6' and the serine ring at position 2'. In the case of the α3β4 nAChR, the α4 subunit carries an additional essential change: phenylalanine residues are located at position 13', forming together with α3 subunit the valine/phenylalanine ring. This substitution dramatically changes the overall binding properties of the channel in docking simulations. Fluoxetine docking results, presented below, support this statement.

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To contrast the docking results between fluoxetine and imipramine, the docking of imipramine to different nAChRs was also studied in the neutral and protonated states [11, 91]. The results suggested that imipramine interacts within the middle portion of the channel of α4β2 and αβ4 nAChRs with all five M2 helices, but not with other transmembrane segments. A more detailed analysis indicated that, in the case of α4β2 nAChRs imipramine interacts with residues forming the valine and leucine rings via van der Waals contacts, and no contact was observed to the serine ring [90].

The molecular docking results for the αβ4 nAChR-imipramine complexes suggest that this antidepressant interacts predominantly by van der Waals contacts with non-polar residues in the domain formed by the valine/phenylalanine (position 13') and leucine rings, and by...
forming π-π interactions between its aromatic rings and the three β4-Phe residues at position 13. These docking results are in agreement with radioligand binding data, indicating that the SSRI binding site at both Torpedo and neuronal nAChR subtypes (Table 2) overlaps the imipramine locus in both desensitized and resting states. Moreover, the observed nH values from the competition binding experiments are close to unity (see Table 2), suggesting that SSRIs may be interacting with the [3H]imipramine binding site in a steric fashion, and possibly that SSRIs and tricyclic antidepressants, in general, interact with the same site(s) on nAChRs.

Conflicting interests

The authors have declared that no conflict of interests exist.

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Author contributions

J.G.C., K.M.T.D. and H.R. conceived the work and wrote the manuscript.

Abbreviations

[^3]H]TCP: [piperidyl-3,4-3H(N)]-(N-(1-(2-thienyl)cyclohexyl)-3,4-piperidine); 5-HT: serotonin; ACh: acetylcholine; nAChR: nicotinic acetylcholine receptor; AChE: acetylcholinesterase; DA, dopamine; IC50, ligand concentration that inhibits 50% binding; Kᵢ, inhibition constant; NA: noradrenaline; NCA: non-competitive antagonist; SSRIs: selective serotonin reuptake inhibitors.

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