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Invited review

Mood and anxiety regulation by nicotinic acetylcholine receptors: A potential pathway to modulate aggression and related behavioral states

Marina R. Picciotto*, Alan S. Lewis, Gerrit I. van Schalkwyk, Yann S. Mineur

Department of Psychiatry, Yale University, New Haven, CT 06508, USA

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ABSTRACT

The co-morbidity between smoking and mood disorders is striking. Preclinical and clinical studies of nicotinic effects on mood, anxiety, aggression, and related behaviors, such as irritability and agitation, suggest that smokers may use the nicotine in tobacco products as an attempt to self-medicate symptoms of affective disorders. The role of nicotinic acetylcholine receptors (nAChRs) in circuits regulating mood and anxiety is beginning to be elucidated in animal models, but the mechanisms underlying the effects of nicotine on aggression-related behavioral states (ARBS) are still not understood. Clinical trials of nicotine or nicotinic medications for neurological and psychiatric disorders have often found effects of nicotinic medications on ARBS, but few trials have studied these outcomes systematically. Similarly, the increase in ARBS resulting from smoking cessation can be resolved by nicotinic agents, but the effects of nicotinic medications on these types of mental states and behaviors in non-smokers are less well understood. Here we review the literature on the role of nAChRs in regulating mood and anxiety, and subsequently on the closely related construct of ARBS. We suggest avenues for future study to identify how nAChRs and nicotinic agents may play a role in these clinically important areas.

This article is part of the Special Issue entitled 'The Nicotinic Acetylcholine Receptor: From Molecular Biology to Cognition'.

1. Introduction

Nicotine consumption through tobacco products is highly co-morbid with mood disorders, including depression, anxiety and irritability; however the connection between nicotine use and behavioral regulation remains unclear and is still debated (Moylan et al., 2012). For instance, the overall incidence of smoking in depressed patients is twice as high as in the general population (Glassman et al., 1990) and the rate of smoking relapse is greater in patients with depression (Covey et al., 1998). The underlying mechanisms mediating the connection between smoking and mood alterations are not yet understood, however. Tobacco use could precipitate mood dysregulation, potentially explaining the higher incidence of depression in smokers (Boden et al., 2010); however, many studies have reported that nicotine can improve symptoms of depression under some conditions (Salin-Pascual et al., 1995; Tizabi et al., 1999). It has therefore been suggested that nicotine in tobacco is used in an effort to self-medicate symptoms of depression and other psychiatric disorders (Markou et al., 1998). In addition, smoking cessation and nicotine withdrawal can be accompanied by depressive episodes, stress-induced anger, and increased tension (al'Absi et al., 2007; Hatsukami et al., 1985). Taken together, these associations suggest that alterations in signaling through nicotinic acetylcholine receptors (nAChRs) might be involved in mood regulation. In this review we discuss potential mechanisms underlying the association between nAChRs and depression and anxiety.

Mood dysregulation, especially depressed mood and co-morbid anxiety states, is influential in regulating the constructs of aggression, irritability, and agitation, an interrelated triad we refer to as aggression-related behavioral states (ARBS). We review studies from both pre-clinical and clinical studies that demonstrate a key role for nAChRs in ARBS, and suggest that nAChR modulation of mood and/or anxiety might account, in part, for its effects on

* Corresponding author. Department of Psychiatry, Yale University School of Medicine, 34 Park Street, Third Floor Research, New Haven, CT 06508, USA. Tel.: +1 203 737 2041.
E-mail address: marina.picciotto@yale.edu (M.R. Picciotto).

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ARBS. Finally, we propose that further study at the pre-clinical and clinical levels might encourage development of novel nicotinic-based agents for treating mood dysregulation as well as ARBS.

2. Preclinical studies of nicotine on mood, anxiety, and aggression-related behavioral states

2.1. Depression and anxiety

While there are variable effects of nicotinic signaling on behaviors related to depression, numerous studies suggest that decreasing activity of α4β2* nAChRs can improve symptoms of depression (for reviews see Mineur and Picciotto, 2009; Picciotto et al., 2008). Chronic nicotine exposure induces up-regulation of nAChRs, but also profound desensitization of these receptors *in vitro* (Fenster et al., 1997; Grady et al., 1994). Studies in slices have shown that α4β2* nAChRs can be rapidly and persistently desensitized in the presence of nicotine, whereas α7 nAChRs can maintain their activity (Mansvelder et al., 2002). These data suggest there is decreased ACh signaling through some nAChR subtypes during ongoing smoking, but likely to be restored and potentially increased over time (because high affinity nAChRs are upregulated by chronic nicotine use as experienced by smokers (Fenster et al., 1999)) as nicotine is cleared during withdrawal. This phenomenon could also underlie the cyclical mood dysregulation experienced by smokers between smoking episodes, and could therefore perpetuate smoking behavior (Watkins et al., 2000). For example, one group has proposed that a single puff of a cigarette results in occupancy of 50% of α4β2* nAChRs for more than 3 h, that blood levels of nicotine in a smoker would saturate almost 90% of these nAChRs for hours and that desensitization of these receptors can suppress craving (Brody et al., 2006). This could explain why nicotinic signaling has seemingly paradoxical effects: low dose chronic nicotine has a comparable effect to an antagonist of high affinity β2 subunit-containing (β2*) nAChRs in a conditioned emotional response task in mice (Anderson and Brunzell, 2012), and both nicotine and the nicotinic antagonist mecamylamine can increase serotonin release in the hippocampus (Kenny et al., 2000). Several pharmacological studies have confirmed that nicotinic blockers (antagonists or partial agonists) can alleviate depression-like behaviors in mice, either alone or in combination with monoaminergic drugs (Andreasen et al., 2009; Bacher et al., 2009; Mineur et al., 2009, 2011; Rollema et al., 2009). Interestingly, commonly used antidepressants can also act as α4β2* nAChR antagonists in cell-based assays (Shytle et al., 2002; Slemmer et al., 2000), suggesting that these medications might also act in synergy with nAChR signaling to be fully effective. Rodent studies have further demonstrated that the effects of selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (NRIs) in models of depression-like behaviors can be potentiated by nAChR antagonists or partial agonists (Andreasen et al., 2009; Andreasen and Redrobe, 2009; Rollema et al., 2009), and that β2* nAChRs are required for antidepressant efficacy of at least one antidepressant medication (Caldarone et al., 2004). Conversely, mice with increased activity of α4β2* nAChRs as a result of a point mutation in the α4 subunit show increased anxiety-like behaviors (Labarca et al., 2001).

These studies suggest that limiting nAChR signaling through α4β2* nAChRs can lead to positive effects on mood symptoms, however other nAChRs also appear to be important for antidepressant responses. A recent study showed that functional β4 nAChRs are required for the full effect of buproprion, an atypical antidepressant (Radhakrishnan et al., 2013). In addition, some reports suggest that *increased* signaling at α7 nAChRs in combination with therapies that increase serotonin signaling can also improve performance in tests of antidepressant efficacy (Andreasen et al., 2012, 2013). These data suggest that a partial agonist, or a mix of agents with differing effects at heteromeric and homomeric nAChRs may be the most promising for developing nicotinic-based antidepressants, because the valence of nAChR signaling can be very different and depends on receptor subtype and brain region (Picciotto et al., 2008, 2012). These apparent discrepancies may also explain some of the controversy about the role of nicotine in mood regulation. Some models have proposed that nicotine use can, in fact, lead to negative effects on mood, for instance through HPA axis activation (Mendelson et al., 2005). Thus, because nicotine can both activate and desensitize different nAChR subtypes, resulting in differential modulation of many brain circuits, the net effect of nicotine on mood will depend on the integration of multiple nicotinic signals. The complexity of this system may suggest that a nicotinic partial agonist that selectively targets specific nAChRs involved in mood regulation could be more useful than a broad spectrum nAChR blocker.

Identifying the brain areas mediating the effects of nAChRs on depression-like behaviors will not be straightforward. nAChRs are expressed on many cell types throughout the central nervous system (Han et al., 2000), and modulate multiple neurotransmitter systems. Nevertheless, there is some evidence that nAChRs in the amygdala could be important for the antidepressant effect of nAChR blockade (Mineur et al., 2007). Cholinergic cells projecting to the amygdala exhibit high firing rates (Whalen et al., 1994) and hyperactivity of the amygdala is a hallmark of arousal and stress reactivity (Davidson et al., 2002; Drevets, 2001). Thus, decreasing amygdala cholinergic activity through α4β2* nAChR blockade could decrease stress reactivity and depression-like symptoms (LeDoux, 2003; Mineur et al., 2007). Conversely, activation of α7 nAChRs in the amygdala can also lead to an overall decrease in activity as a result of heightened GABAergic inhibition (Pidoplichko et al., 2013), suggesting a potential mechanism for α7 agonism in mediating an antidepressant-like response. This also highlights the need to consider the effects of different nAChR subtypes on specific cell-types in microcircuits throughout the brain involved in mood regulation. In the hippocampus, another brain region critical for antidepressant response (Santarelli et al., 2003), increasing cholinergic tone induces anxiety- and depression-like behaviors that can be reversed by systemic administration of a nicotinic antagonist (Mineur et al., 2013). Further, as mentioned above, both chronic nicotine and the nicotinic antagonist mecamylamine can facilitate serotonin transmission in the hippocampus, while the effects of monoamine depletion can be partially reversed by nicotine administration and can lead to changes in anxiety-like behavior in the elevated plus maze (File et al., 2000a, 2000b; Fu et al., 1998; Kenny et al., 2000). We recently found that serotonin depletion could prevent antidepressant-like effects induced by the nicotinic partial agonist cytisine in the forced swim and the social defeat tests, while the effects of serotonergic drugs could be potentiated by this nicotinic compound (Mineur et al., 2014). Thus, changes in nAChR signaling, and more specifically, decreasing nAChR activity, can facilitate monoamine transmission and this may mediate the ability of nicotinic drugs to alter depression-like behaviors.

Nicotinic drugs may also have effects on mood-related behaviors through actions on the mesolimbic dopamine system. Nicotine reinforcement and reward is mediated through nAChRs in the mesolimbic system (Maskos et al., 2005; McGranahan et al., 2011; Tolu et al., 2012) and numerous studies have now demonstrated that alterations of neuronal activity in the mesolimbic system can result in antidepressant-like effects (Nestler, 2014; Nestler and Carlezon, 2006; Warner-Schmidt et al., 2012). For instance, mice lacking β2* nAChRs in dopamine neurons of the VTA lack anxiolytic