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Biological basis for the co-morbidity between smoking and mood disorders

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Abstract

Nicotine dependence is still the major preventable cause of death in the developed world, and has strong comorbidity with mood disorders including major depression. Depressed patients are more likely to smoke cigarettes, and quitting can precipitate an episode of depression in some subjects. Interestingly, antidepressants, particularly the atypical antidepressant bupropion, are therapeutics that can help smokers quit. Despite these observations, the underlying biological factors of the relationship between smoking and depression remain unclear. Results from clinical and pre-clinical studies have seemed somewhat paradoxical because heightened cholinergic activity can induce depression while both nicotine and nicotinic antagonists can be antidepressant-like. These observations can be reconciled by considering that high affinity nicotinic receptors in the brain can be desensitized by chronic nicotine use, leading to blunted cholinergic activity. Based on this hypothesis, nicotinic antagonists have recently been tested as treatments for depression in human subjects, particularly as adjunct therapy along with classical antidepressants. These data suggest that the relationship between smoking and depression may be partially explained by the fact that depressed patients smoke in an effort to self-medicate depressive symptoms by desensitizing their nicotinic receptors. This possibility suggests new avenues for treatment of both nicotine dependence and depressive disorders.

Keywords

Translational science; mouse models; human studies; review; depression; major depressive disorder; knockout mice; nicotine; nicotinic acetylcholine receptors

Smoking and Depression

Approximately 20-25% of the US population smokes currently, but this percentage increases to 35-65% in patients with mood disorders (Diwan et al., 1998, Glassman et al., 1990, Kessler, 1995). Depressed smokers are also less likely to quit, and are more prone to withdrawal symptoms (reviewed in Kalman et al., 2005). Cigarette smoke contains more than 4,000 chemicals, but nicotine is thought to be the primary addictive compound in smoked tobacco (US Department of Health and Human Services, 1988). In the central and autonomic nervous system nicotine binds to, activates, and can desensitize nicotinic acetylcholine receptors (nAChRs) (Picciotto, 1998). The activation of nAChRs, by the endogenous neurotransmitter acetylcholine (ACh) or other compounds such as nicotine, leads to neuronal firing. nAChRs are pentameric cation channels composed of combinations of α (2 to 9) and β (2 to 4) subunits. Three main families can be distinguished based on their pharmacological and physiological

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profiles: $\alpha 4\beta 2$ -containing nAChRs ($\alpha 4\beta 2^*$, where * denotes other subunits) combined with $\alpha 5$, $\alpha 6$ or $\beta 3$ are the most widespread family in the central nervous system and have the highest affinity for nicotine (Zoli et al., 1998). The $\alpha 7^*$ nAChRs have a lower affinity for nicotine, but do not desensitize in the presence of low levels of nicotine (Mansvelder & McGehee, 2000). The $\alpha 3\beta 4^*$ nAChRs are intermediate in affinity and are the primary receptors in the autonomic ganglia (Gotti et al., 2006).

The relationship between smoking and mood disorders remains unclear: does smoking lead to the onset of depression? Does depression increase the likelihood that people will smoke? Do smoking and depression share common environmental/genetic factors? Twin studies have shown that there are shared susceptibility genes for smoking and depression (Kendler et al., 1993, McCaffery et al., 2003). In addition, chronic nicotine intake through smoking leads to neuroadaptations that affect many brain circuits, including those related to affect (Paterson & Markou, 2007). Thus, it may not be surprising that acutely abstinent smokers have reported symptoms similar to those of depression (Glassman et al., 1990), while depressed patients report heightened mood after smoking a cigarette compared to non-depressed volunteers (Kinnunen et al., 1996). Similarly, nicotine patch can reduce symptoms of depression, even in non-smokers (Salin-Pascual et al., 1995). Finally, studies in pre-clinical rodent models corroborate these clinical observations: chronic administration of nicotine can elicit antidepressant-like effects in rats in various well-established paradigms (Semba et al., 1998; Djuric et al., 1999, Tizabi et al., 1999). These data strongly suggest that nicotine intake can regulate mood, and that some smokers may use nicotine to self-medicate depressive mood symptoms.

Whereas chronic nicotine exposure can be antidepressant, classical antidepressants can affect smoking behavior as well. One of the most effective pharmacological treatments for smoking cessation, bupropion, was originally developed as an antidepressant (Fava et al., 2005). Furthermore, several classical antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and norepinephrine reuptake inhibitors (NRIs) (reviewed in Hughes et al., 2004) can help smokers to quit (Hall et al., 1998, Hayford et al., 1999, Hurt et al., 1997). Thus, nicotine can be antidepressant and relieving mood symptoms can help with smoking cessation.

The Cholinergic Hypothesis of Depression

The fact that nAChRs can modulate depressive symptoms suggests that acetylcholine, the endogenous ligand for nicotinic receptors, is also critical in regulating mood. In the early 1970's, a clinical study suggested that depression may be triggered by cholinergic hyperactivity (Janowsky et al., 1972). In that study, physostigmine (an acetylcholinesterase inhibitor that can increase ACh levels in the brain) increased depressive symptoms in a subset of subjects (Janowsky et al., 1972). Rat studies also support the hypothesis that increased cholinergic tone can lead to depressive symptoms. The Flinders sensitive and resistant lines (FSL and FRL) were genetically selected based on their differential sensitivity to a cholinesterase inhibitor. FSL rats are more sensitive to cholinesterase inhibitors and show a constellation of depression-like (Overstreet, 1993).

The conclusion that increased cholinergic function results in depressive symptoms may seem paradoxical since nicotine, a cholinergic agonist, has antidepressant properties. These observations can be reconciled when one considers that nicotine and nicotinic compounds administered chronically (as in animal models or with nicotine patches in human), can transiently activate, but subsequently desensitize, nAChRs for relatively long periods (up to several hours in some cases (Gentry & Lukas, 2002, Paradiso & Steinbach, 2003)). Thus, desensitization, and not activation, of nAChRs may result in antidepressant effects. In accord

with this possibility, chronic (which would be more likely to lead to desensitization), but not subchronic, nicotine treatment had antidepressant effects in initial studies (Semba et al., 1998). Similarly, increased nAChR stimulation as a result of cholinesterase blockade has depressant effects in human patients and animal models (Fava et al., 2005).

Consistent with the cholinergic hypothesis of depression, mecamylamine, a non-selective nAChR antagonist, can decrease symptoms of depression and anxiety in patients (Dursun & Kutcher, 1999, Mihaiescu & Drucker-Colin, 2000, Salin-Pascual et al., 2003). Mecamylamine can also result in decreased depressive symptoms when added to an SSRI in patients who were resistant to the SSRI alone (George et al., 2008). Similarly, mouse studies also show that mecamylamine has antidepressant-like properties in several behavioral paradigms (Mineur et al., 2007, Rabenstein et al., 2006) and can also potentiate the effects of classical antidepressants such as amitriptyline (Caldarone et al., 2004) and imipramine (Popik et al., 2003) (two TCAs), or citalopram (Popik et al., 2003) (an SSRI). These studies suggest that decreasing nAChR activity may affect the same monoamine systems that are affected by classical antidepressants. Consistent with this possibility, both nicotine and mecamylamine can increase serotonin release in the rat hippocampus (Kenny et al., 2000).

An increasing body of evidence also shows that classical antidepressants, in addition to their ability to block monoamine transporters, can inhibit nAChR function (Fryer & Lukas, 1999, Garcia-Colunga et al., 1997, Lopez-Valdes & Garcia-Colunga, 2001, Schofield et al., 1981). The majority of antidepressants tested can block nAChRs at nanomolar concentrations, at clinically relevant doses reached in depressed patients after chronic treatment (for review, see Shytle et al., 2002). Thus, while increased monoaminergic tone is clearly important for antidepressant efficacy, these data suggest that nicotinic receptor blockade by antidepressants might also contribute.

Evidence for specific nicotinic receptor modulation of mood from genetic mouse models

Studies in transgenic mouse models have demonstrated that the deletion of $\beta 2^*$ nAChRs leads to an antidepressant-like phenotype in the forced swim and tail suspension tests (Caldarone et al., 2004). Moreover, the effect of the classical antidepressant amitriptyline is abolished in these knockout mice (Caldarone et al., 2004), strongly suggesting that blockade of $\beta 2^*$ nAChRs may result in antidepressant-like effects and could be necessary for efficacy of classical antidepressants. Similarly, the antidepressant-like effects of the nicotinic antagonist mecamylamine are also abolished in $\beta 2$ subunit knockout mice (Rabenstein et al., 2006). It should be noted that the absence of $\beta 2^*$ nAChRs throughout development in these knockout mice may result in long-term changes in other neurotransmitter systems that might be responsible for the lack of antidepressant-like effects in these animals, however the hypothesis that high affinity nAChRs are important for antidepressant response is consistent with these findings.

A number of pharmacological studies have also contributed to the hypothesis that nicotinic receptor blockade has antidepressant-like properties (Andreasen et al., 2008, Mineur et al., 2007, Rabenstein et al., 2006). In addition to studies of mecamylamine cited above, nicotinic partial agonists (that can decrease endogenous acetylcholine transmission at high affinity nAChRs) also induce an antidepressant-like response. For example, cytisine, a plant alkaloid that is a nicotinic partial agonist used in eastern Europe as an aid for smoking cessation, is a low efficacy partial agonist at $\alpha 4\beta 2^*$ nAChRs (Papke & Heinemann, 1994). In mice, cytisine has antidepressant-like properties in a number of behavioral paradigms including the tail suspension, forced swim and novelty-suppressed feeding tests (Mineur et al., 2007). These studies suggest that the nicotinic partial agonist varenicline that is currently in use as an aid to

smoking cessation might also result in antidepressant effects in human subjects. Similarly, highly selective partial agonists at $\alpha 4\beta 2^*$ nAChRs may be useful for treating depressive symptoms in people with mood disorders, either alone or in combination with more classical antidepressants such as SSRIs.

Conclusions

In summary, there is significant co-morbidity between smoking and mood disorders, suggesting that there is a common biological basis for tobacco dependence and depression. It seems likely that the relationship between smoking and depression is bidirectional, with nicotine and brain changes due to chronic nicotine intake leading to increases in depressed mood, and depressed mood promoting continued nicotine intake to maintain desensitization of nAChRs. These observations suggest that pharmacological treatments that modulate nicotinic receptor function could provide novel pharmacotherapeutic strategies for treating mood disorders. Furthermore, if smoking is used to self-medicate depression in a subset of smokers, then nicotinic antagonists and partial agonists could both limit depressive symptoms in those individuals while decreasing nicotine craving and withdrawal.

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Figure 1. Simplified representation of the relationship between genetic factors, depressive symptoms, and smoking behavior

Genetic factors contribute to susceptibility to smoking and depression and twin studies show that some of these genetic factors are shared (Kendler et al., 1993, McCaffery et al., 2003). Depression leads to an increased susceptibility to smoking. Inversely, smoking behavior improves mood and decreases depressive symptoms probably through nicotinic receptor desensitization. Concomitantly, nicotine withdrawal can precipitate depression-like symptoms. Several classes of antidepressants, particularly the atypical antidepressant bupropion, can decrease smoking and help smokers to quit in addition to their ability to improve mood and decrease depressive symptoms.