Nicotine Dependence and Depression, What is the Future for Therapeutics?

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There is a complex relationship between nicotine use, subsequent nicotine dependence, and depression. Nicotine delivered by patch reportedly has antidepressant properties, even in non smokers [1], but the incidence of depression in smokers is high, and higher still in people attempting to quit smoking. Sorting out cause and effect with such observations is very difficult. One of the earliest theories on the etiology of depression was the cholinergic hypothesis proposed by Janowsky [2], which was based largely on the effects of cholinesterases inhibitors on mood, suggesting a relationship between a hypercholinergic state and depression. Since the early work by Janowsky, the concept of a hypercholinergic state in depression has been extended to apply to CNS muscarinic, and more recently, nicotinic receptor function. Here, with the additional consideration of nicotinic Acetylcholine Receptors (nAChRs), we have the confounding conundrums of the mixed activating and desensitizing properties of nicotine [3] and the well-documented up-regulation of brain nAChR with chronic nicotine [4,5]. To what degree is the hypercholinergic state hypothesized by Janowsky related to increased acetylcholine, affecting both nicotinic and muscarinic tone, or to upregulated receptor function in one system or in both systems?

The current therapies for depression are generally thought to work through the modulation of the biogenic amines, primarily serotonin and, to a lesser degree, nor-epinephrine. However, many antidepressants have anticholinergic activities as well. The antimuscarnic effects of antidepressants, most notable for tricyclics, are generally considered adverse side effects. However, the original work of Janowsky, and more recent work by Drevets [6], would suggest that such activity would also be part of their therapeutic efficacy. Numerous studies have also implicated antinicotinic activity as part of the profile for specific antidepressants and the antidepressant bupropion is approved for smoking cessation. Likewise, the smoking cessation drug varenicline has been shown to have antidepressant activity in animal models [7], with suggestive data for humans as well [8]. These two compounds hypothetically use different pharmacologic approaches for down-regulating the activity of select brain nAChR, noncompetitive antagonism for bupropion and partial agonism for varenicline.

The efficacy of bupropion, both as an antidepressant and as a smoking cessation aid, may be at the heart of the mysterious connection linking nicotine dependence and depression, since bupropion is both a modulator of biogenic amines [9] and a nAChR antagonist [10]. It was initially assumed that bupropion’s efficacy as a smoking cessation agent was due to the management of depression associated with nicotine withdrawal and therefore related to its blockade of biogenic amine reuptake [11]. Ironically, it might now be hypothesized that its antidepressant activity is also associated with its block of nAChRs. This leaves an unresolved paradox that might only be resolved when we can better appreciate the underlying, and likely heterogeneous, causes for major depressive disorder and why individual patients vary so greatly in their responsiveness to specific agents. For particular patients responding to bupropion therapy for depression, the relative importance of the two aspects of the drug’s action on biogenic amines or on nAChR may differ.

Is there a future for antidepressant therapies that rely exclusively on a nicotinic mechanism, and if so, will they be useful as monotherapy or fill a gap for adjunct therapies to be combined with more conventional antidepressants for refractory patients? The latter possibility was just put to a test with the combination of two specific agents, TC-5214, a stereoisomer of the classic neuronal nAChR antagonist mecamylamine, and citalopram, a popular serotonin reuptake inhibitor. A series of Phase 3 trials with these two agents were recently reported to have failed to show positive effects on their primary treatment endpoints. Do these failed trials mean an end for the development of anti-nicotinic drugs for depression? Several points could be argued against that conclusion.

Was mecamylamine the right choice for a down-regulator of nAChR function? Was TC-5214, the s-isomer, the best choice compared to the r-isomer or the racemic drug? Was citalopram the best choice for the drug to pair with mecamylamine in a combination therapy? Mecamylamine is strictly a nAChR antagonist, and more effective at inhibiting putative off-target α3β4 receptor subtypes associated with the function of the autonomic nervous system [12] than for the most likely target receptors, high affinity α4β2 nAChR in the brain. This factor alone might have limited the usefulness of mecamylamine, forcing dosages to be kept low in order to avoid autonomic side effects. An initial characterization of the two mecamylamine stereoisomers showed little reason to commend one over the other as a nAChR antagonist [13]. However, a subsequent study presented data suggesting the s-isomer (TC-5214) might have mixed effects, both potentiating and then at higher concentrations inhibiting a specific high sensitivity α4β2 receptor subtype that is believed to be up-regulated by chronic nicotine [14]. Notwithstanding that the putative potentiating activity for high sensitivity α4β2 receptors is not reproducible in a standard expression system (Xenopus oocytes, R. Papke, unpublished), it is unclear why potentiating activity for a target receptor subtype would be a desirable feature when the intended therapeutic mechanism is to inhibit that receptor subtype. Nonetheless, the s-isomer appeared to have a better activity profile in a series of animal studies and believed to be predictive for antidepressant efficacy, as well as a better safety profile than the r-isomer [15].

Would it have been better to pursue mecamylamine as a monotherapy than as an augmentation to a Selective Serotonin Reuptake Inhibitor (SSRI)? A primary rationale for combination therapies is to use two drugs with different mechanisms and therefore hopefully additive effects. This would have been a good rationale for combining TC-5214 with citalopram and supported by other studies.
combining mecamylamine with SSRIs [16]. However, contradictory results have been reported for mecamylamine in combination with citalopram in animal studies [17,18].

Another rationale for combination therapies, one that has already been demonstrated to be applicable to mecamylamine, is to use a second drug to manage the side effects produced by a primary therapeutic agent. Mecamylamine was previously shown in small scale trials to have efficacy for the treatment of Tourette’s syndrome [19], an observation which led to its use in a larger trial as a monotherapy. The larger trial failed [20], and in retrospect the efficacy in the earlier trials was judged to be due to mecamylamine’s suppression of hypercholinergic side effects associated with concomitant antipsychotic medications. Citalopram is considered to have few cholinergic side effects, while older antidepressants, most notably the tricyclics, have significant cholinergic side effects, which are usually classified as anti muscarinic. It might be hypothesized that nicotinics and muscarinics may be doing complementary things under normal conditions, so that something with antimuscarinic effects might therefore have a pro-nicotinic activity that could have been targeted by the mecamylamine. Moreover, antimuscarinic activity might induce a neuro-adaptive upregulation of cholinergic tone, which would also have pronicotinic effects. Therefore, it might have been more useful to pair TC-5214 with a tricyclic antidepressant. Side effects often limit the therapeutic dosing of antidepressants, and therefore better management of side effects might permit better therapeutic effects for the primary agent. As noted above, partial agonists present an alternative approach for managing hyperactivity of a neurotransmitter system. Partial agonists may be designed for significant selectivity for specific receptor subtypes. Such profiles can be highly variable and potentially very effectively tuned to function as agonists for some receptor subtypes and effectively as competitive antagonists of other subtypes. For example, varenicline and cytosine, two agents currently in use as smoking cessation aids, are often characterized as α4β2 partial agonists [21,22]. The α4β2 nAChR of the brain are generally accepted as a primary target for both smoking behavior and hypercholinergic activity in depression. However, the characterization of varenicline and cytosine as selective α4β2 partial agonists is not really correct, since both of these agents have significant activity for probable off-target receptors, such as ganglionic α3β4 receptors and the low affinity α7 receptors of the brain that are associated with cognition and neuropsychiatric disorders [22-24]. Additionally, as we are guided by evaluations of efficacy in animal models, we must also account for differences that may exist between the activity profiles of select agents for the receptors in the study animal and in humans. In fact, it has recently reported that the activity of varenicline and cytosine differ significantly for the ganglionic receptor analogs of rodents and humans [25].

In summary, the disappointing clinical results with TC-5214 should serve primarily to guide, rather than to discourage, future drug development in this area, especially since such work may lead to improved therapies for smoking cessation as well as for the potential management of major depressive disorders. It is possible that new nAChR antagonists with improved on-target activity for CNS receptors may be developed and paired with more appropriate primary agents in order to lead to positive outcomes for the treatment of depression. Additionally, it seems likely that the future of anti-nicotinic therapies, both as smoking cessation aids and as potential therapies for depression, will come from the development of new, truly selective, partial agonists that will produce a down-regulation of α4β2* receptor function with little or no activity for other nAChR subtypes. Recent publications indicate that such drugs are likely to become available [26,27], and the tools are available to confirm that agents that are active in animal models will be likely to have similar activity profiles for human receptors with therapeutically relevant experimental protocols [28]. However, the challenges for the development of therapeutics in these areas are great. While the majority of patients suffering from major depressive disorder will respond to one of the available pharmacotherapies, until we achieve a better understanding of the heterogeneity likely to exist in the causes of depression, it is probable that we will have to continue to rely on slow empirical determinations of whether each patient is matched to an effective therapy. Likewise, in order to design smoking cessation therapies with more than the marginal 15–20% efficacy of existing therapeutics, such as bupropion, varenicline, and cytosine, we need to improve our understanding of the root causes for nicotine dependence and smoking relapse.

References


