REVIEW  —Current Perspective—

Neuronal Nicotinic Receptor and Psychiatric Disorders: Functional and Behavioral Effects of Nicotine

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ABSTRACT—Both retrospective and prospective clinical studies have demonstrated positive associations of smoking with psychiatric disorders such as schizophrenia, depression and anxiety. Neuronal nicotinic acetylcholine receptors (nAChR) belong to a family of ligand-gated ion channels that are widely distributed in the brain. The pre-synaptically located nAChR, which are composed of α3 or α4 subunits in combination with β2 subunit on axon terminals, modulate the multiple transmission release. Several studies indicated which individual nicotinic receptor subtype is responsible for mediating each of the behavioral effects of nicotine. A reduced number of α7 nicotinic receptor subtypes in the hippocampus were reported in schizophrenic patients. In addition, it was assumed that nicotine provided useful therapeutic treatment for a variety of cognitive impairments including those found in Alzheimer’s disease, schizophrenia and attention deficit hyperactive disorder. Both α7 and α4β2 nicotinic receptors in the hippocampus are involved in these phenomena. In the genetic depressive rats, nicotine showed antidepressant-like effects in forced swim models of depression, suggesting the involvement of α4β2 nicotinic receptor in this phenomenon. Thus, it appears likely that pre-synaptic nAChR on monoaminergic fibers are composed of α3 or α4 subunits in combination with the β2 subunit, and these subunit compositions mediate dopaminergic and noradrenergic release, and glutamate is mainly controlled by the α7 subunit. All these findings suggest that nicotine and other nicotinic drugs warrant further study for possible clinical prescription to psychiatric disorders.

Keywords: Nicotine, Schizophrenia, Anxiety, Depression, Withdrawal syndrome

1. Introduction

Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring (Fig. 1), and it is a commonly used psychoactive drug that is orally self-administered. Tobacco, the most commonly used nicotine-containing substance, represents the most toxic and addictive form of nicotine delivery and it is well known that nicotine plays a major role in mediating the pharmacological, biochemical, psychological and other effects of tobacco-smoking (1). Nicotine affects many aspects of behavior including locomotion, nociception, anxiety, learning and memory as well those associated with drug abuse (2). Smoking is negatively correlated with the incidence of Parkinson’s disease and Alzheimer’s disease (3). Previous epidemiological studies have shown positive associations of smoking with psychiatric disorders. The rate of smoking is much higher in schizophrenics (up to 90%), depressed patients (up to 65%) and alcoholics (up to 90%) than in the general population (4). It appears that these effects of nicotine are mediated through selective activation of different subtypes of nicotine acetylcholine receptor (nAChR). Nicotine interacts with a variety of pre-synaptic nAChR to facilitate the release of a number of neurotransmitters including acetylcholine (ACh), dopamine (DA), noradrenaline (NA), serotonin (5-HT), γ-aminobutyric acid (GABA) and glutamate.

Fig. 1.  Structure of (−) nicotine.
many of which have been implicated in mediating/modulating a number of behavioral tasks (4). Thus, central nAChR are associated with a number of psychiatric disorders. This review will attempt to integrate psychiatric disorders and the pharmacological properties of nAChR subunits with behavioral and neurochemical findings.

2. Neuronal nicotine receptors

Neuronal nAChR is a family of ligand-gated ion channels that are widely distributed in the brain and are controlled by ACh and nicotine receptor agonists. nAChR has a pentameric structure consisting of five membrane spanning regions around a central ion-channel. A number of differential subtypes of neuronal nAChR exist, each with individual pharmacological and physiological profiles and distinct anatomical distribution in the brain. To date, eleven neuronal nAChR subunits, eight α (α2 – α9) and three β (β2 – β4), have been identified in mammals (5). However, these nAChR’s roles are not fully understood. Nicotine receptors do not only exist on neuronal cell bodies and dendrites but are also located on axon terminals and are involved in modulation of multiple transmission release. Local application of nicotine to the striatum produced an increase in the extracellular level of glutamate (6). Nicotine increased the release of DA in the rat striatum in vivo and it has been reported that the N-type Ca2+ channel and voltage dependent sodium channels are involved in the releasing effect of nAChR stimulation (7). The nAChR-induced DA release is inhibited by α3β2 subunit composition antagonists, but not α3β4 selective nAChR antagonists. On the other hand, the nicotine-induced DA release appears to be mediated via the glutaminergic system in vivo since kynurenic acid is able to almost completely prevent the effect of nicotine on glutamic acid release (6). Not only the α3β2 subunit, but also the α4(α5)β2 subunit composition appears to be the subtype on dopaminergic terminals in the striatum, because the α4(α5)β2 subunit causes the α-conotoxin MII-insensitive release of DA in the striatum (8). NMDA antagonists could modulate the effects of nicotine on dopaminergic neurons in the ventral tegmental area (VTA) (9). In the projecting mesolimbic dopaminergic neurons, nicotine can modulate the release of glutamate and exert an indirect excitatory effect on dopaminergic neurons. At least a part of the nicotinic effects in the mesolimbic dopaminergic system are similar to that seen in the striatum. The importance of the nAChR in psychiatric diseases such as schizophrenia and depression is described.

3. Schizophrenia

Previous epidemiological studies have shown that there is high percentage of smokers present in the schizophrenic population (90%) compared with the general population (33%) and a low rate of smoking cessation among individuals with schizophrenia (4). It has been suggested that the high rates of smoking arise from the ameliorating effects of nicotine on attentional abnormalities in schizophrenia or from patients trying to reduce antipsychotic medication-induced side effects. For example, nicotine has been shown to reduce akathisia and cognitive psychomotor impairment associated with treatment with haloperidol.

On the other hand, schizophrenics show auditory sensory gating deficit characterized as diminished suppression of an auditory-evoked response (P50) to repeated stimuli and nicotine normalizes the P50 deficit in schizophrenia (10). Another sensory deficit, abnormal smooth pursuit eye movements, is also normalized by nicotine. Interestingly, clozapine, but not typical antidopaminergic neuroleptic drugs, normalizes the P50 deficit in schizophrenics who show a favorable therapeutic response to clozapine (10). Smoking decreases when patients with schizophrenia switch treatments from typical antidopaminergic neuroleptic drugs to clozapine (11), and smokers show greater therapeutic responses to clozapine than nonsmokers (12). From these observations, it is suggested that nicotine may have “therapeutic” effects in the patients with schizophrenia.

Recently, we examined the effect of nicotine on the disruption of prepulse inhibition (PPI) of acoustic startle induced by apomorphine in rats. Haloperidol dose-dependently inhibited disruption of PPI induced by apomorphine. Nicotine also dose-dependently inhibited the disruption of PPI without changing PPI itself. The inhibitory effect of nicotine was abolished by the administration of mecamylamine, but not hexamethonium. In addition, the inhibitory effect of nicotine was antagonized by methyllycaconitine, the α7 nicotinic receptor antagonist, but not dihydro-beta-erythroidine, the α4β2 nicotinic receptor antagonist. The present findings suggest that nicotine blocks apomorphine-induced disruption of PPI, and central α7 nicotinic receptors are involved in this phenomenon (13).

Postmortem studies have shown that a reduced number of [125I]α-bungarotoxin-sensitive nAChR are selective for the α7 nicotinic receptor subtype in the hippocampus in schizophrenic patients (14). Animal studies have also suggested that nicotine can enhance PPI of the acoustic startle reflex in rodents. GTS-21, a selective α7 nicotinic receptor agonist, also normalizes the inhibition of the auditory response in DBA/2 mice, a strain that shows schizophrenia-like deficits in sensory inhibition (15). Furthermore, recent human and animal investigations have suggested an altered expression and function of the α7 nAChR may be responsible for the auditory sensory gating deficit characterized in schizophrenia patients (16).

4. Depression

Both retrospective and prospective clinical studies have
demonstrated a relation between smoking and major depression. The rate of smoking is much higher in depressed patients as well as schizophrenia and alcoholics than in the general population (4). These patients have greater difficulty in stopping smoking and are at increased risk of suffering mild to severe depression having succeeded in stopping. Epidemiological studies have demonstrated that the lifetime prevalence of depression in smokers is directly correlated with the prevalence of nicotine dependence (17, 18), and smokers with a history of major depression are less likely to quit smoking (19). Moreover, smoking cessation frequently precipitates depressive symptoms that can be reversed with the reintroduction of smoking (20). Thus, it has been postulated that smoking is a self-medication effort to alleviate some symptoms of depression using nicotine. However, it is difficult to evaluate the antidepressant properties of nicotine in smokers because it is difficult to separate the antidepressant effect per se from the alleviation of the depression that follows nicotine withdrawal.

Interestingly, clinical studies have observed that transdermal nicotine parches improve the mood of non-smoking depressed patients and increase the duration of REM sleep (21). In behavioral studies with rodents, chronic nicotine has been shown to have antidepressant-like effects in learned helplessness. In addition, behavioral studies using genetic depressive rats (Flinders Sensitive Line rats) have shown an antidepressant-like effect of nicotine in forced swim models of depression (22). The Flinders Sensitive Line rats have higher cytosine binding (selective for $\alpha_4\beta_2$ nicotinic receptor subtype) but not $[^{125}\text{I}]\alpha$-bungarotoxin-sensitive nAChR (selective for the $\alpha_7$ subtype) in the frontal cortex, striatum, midbrain and coliculi compared with their control Flinders Resistant Line rats (FRL).

5. Anxiety

Several studies have reported an association between anxiety disorders and smoking. Persons with nicotine dependence have higher rates of anxiety disorders, and patients with panic disorders have also elevated smoking rates (17). However, patients with obsessive-compulsive disorder (OCD) have been reported to have a low prevalence of smoking (23).

Although clinical evidence suggests that nicotine reduces anxiety in stressful situations, nicotine administration has been observed to have either anxiolytic or anxiogenic effects in some pre-clinical animal models of anxiety. The anxiolytic effects have been reported in the elevated plus-maze test, the mirrored chamber, the white/black box, the potentiated startle paradigm and the social interaction test. The anxiolytic action of nicotine in the elevated plus-maze test can be blocked by the nAChR antagonist mecamyllamine but not by hexamethonium, indicating involvement of central nicotinic receptors (24). In addition to this benzodiazepine inverse agonist, flumazenil also blocked the nicotine-induced anxiolytic effects in humans and in animal models of anxiety. This suggests that the nicotine-induced anxiolytic action is produced by enhanced release of the inhibitory neurotransmitter GABA, which acts on central benzodiazepine-GABAB receptor complex (25). On the other hand, File et al. (26) reported that systemic nicotine administration with low doses had anxiolytic effects, whereas higher doses had an anxiogenic effect in social interaction tests in rats. Administration of nicotine directly into the dorsal hippocampus and lateral septal produced anxiogenic effects in social interaction tests, but administration of nicotine into the dorsal hippocampus had anxiolytic effects in trial 2 in the elevated plus-maze (a model of specific phobia) in rats (27). Thus, the cholinergic septo-hippocampal system has been implicated in the control of anxiety, but little is known about the specific nAChR subtypes involved in the actions of nicotine. Recently, Ross et al. (28) reported that the behavior of homozygous mutant mice (an $\alpha_4$ nAChR subunit knock-out line) in the elevated plus-maze assay was consistent with increased basal levels of anxiety.

6. Nicotine withdrawal (smoking cessation)

Withdrawal from nicotine following chronic tobacco smoking results in withdrawal symptoms such as depressed mood, frustration, irritability, anxiety, difficulty of concentration and craving for tobacco. Although nicotine replacement therapies have been well established as smoking cessation aids, some antidepressants such as fluoxetine, moclobemide, nortriptyline and bupropion have been reported to have beneficial effects on nicotine withdrawal symptoms and in helping patients achieve smoking cessation (29). It is interesting to note that bupropion appears to work equally well in smokers with and without a past history of depression, suggesting the efficacy is not due to its antidepressant effect. The mechanism underlying this efficacy is postulated to be a non-competitive inhibition of nAChR by antidepressants.

In behavioral studies with experimental animals, cessation of continuous nicotine infusion via a subcutaneously implanted minipump and repeated subcutaneous administration of produces withdrawal symptoms that are like opiate withdrawal. In addition, these withdrawal signs can also be precipitated by the administration of mecamylamine, a nicotinic receptor antagonist, and dihydro-β-erythroidine, the $\alpha_4\beta_2$ nicotinic receptor antagonist, in the nicotine-dependent rats (30), suggesting an involvement of $\alpha_4\beta_2$ nicotinic receptor subtype in the withdrawal symptoms can also precipitate these withdrawal sighs. Furthermore, previous studies, which used these animal models of nicotine withdrawal, have shown that the reduced DA output in the nucleus accumbens is of critical
importance for the nicotine withdrawal syndrome (31). On the other hand, it has been reported that nicotine withdrawal leads to increased sensitivity of serotoninergic neurons in the dorsal raphe to the 5-HT$_{1A}$ agonists in rats and that 5-HT$_{1A}$ antagonists attenuate the nicotine-withdrawal-enhanced auditory response in rats (32, 33). Recently, we found that cessation of chronic nicotine administration enhances wet-dog shake responses to 5-HT$_{2A}$ receptor stimulation by DOI ((±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane), and mecamylamine precipitated enhancement of DOI-induced wet-dog shake responses in rats chronically treated with nicotine but not with saline (34).

In addition, the exposure to tobacco smoking for 21 days and cessation of it for 1 day also enhances wet-dog shake responses induced by DOI (Fig. 2). Mecamylamine, a non-competitive nicotine receptor antagonist, precipitated enhancement of the DOI-induced head twitch response in mice repeatedly treated with nicotine. A competitive $\alpha_4\beta_2$ nicotinic receptor antagonist, dihydroxy-$\beta$-erythroidine, but not $\alpha_7$ nicotinic receptor antagonist, methyllycaconitine, showed a similar phenomenon, an increase in DOI-induced head twitch response. These findings suggest the increased sensitivity of the 5-HT receptor systems may be related to the expression of nicotine withdrawal symptoms. Presynaptic $\alpha_4\beta_2$ nicotinic receptor may inhibit the release of 5-HT, and postsynaptic 5-HT$_{2A}$ receptor susceptibility may be consequentially changed to supersensitivity (Fig. 3).

7. Nicotine reinforcement

Nicotine, the active ingredient in tobacco that leads to addiction, is commonly self-administered by the inhalation of tobacco smoke. Although there are several thousands of substances present in tobacco smoke, accumulated evidence indicates that only one of them, nicotine, is the component of tobacco smoke that leads to addiction. Several behavioral studies have demonstrated the reinforcing properties of nicotine in animal models. The conditioned place preference paradigm, a main laboratory technique to characterize the conditioned reinforcing effects of drugs, has previously shown that nicotine produces addictive behaviors in rodents (35). Nicotine can maintain a self-administration behavior in rats, and lesion and discrete

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**Fig. 2.** Effects of chronic exposure to cigarette smoke and nicotine on DOI-induced wet-dog shakes in rats. DOI (1 mg/kg) was administered subcutaneously (s.c.) 24 h after the final exposure to cigarette smoke and nicotine (0.5 mg/kg per day, s.c.) for 21 days. Each column represents the mean ± S.E.M. of wet-dog shakes for 30 min (n = 6–8 for each).

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**Fig. 3.** Possible changes in serotonergic systems during nicotine and cigarette withdrawal. The increased sensitivity of the 5-HT$_{1A}$ receptor system may play some role in the nicotine and cigarette withdrawal symptoms. Serotonergic neurotransmission may be an important substrate for pharmacotherapeutic intervention in the treatment of nicotine withdrawal syndrome and for smoking cessation.
Table 1. Possible nAChR-subtype composition for the psychotic disorders and behavioral actions of nicotine

| Psychotic disorders & behavioral actions | Related nAChR subtypes |
|----------------------------------------|------------------------|
| 1. Schizophrenia                        | \( \alpha 7 (\alpha 4\beta 2) \) |
| auditory sensory gating deficit         |                        |
| pre-pulse inhibition                    |                        |
| 2. Depression                           | \( \alpha 4\beta 2 (\alpha 7 ?) \) |
| Flinders Sensitive Line rats            |                        |
| 3. Anxiety                              | \( \alpha 4 (\alpha 7 ?) \) |
| knockout mice                           |                        |
| 4. Nicotine withdrawal                  | \( \alpha 4\beta 2 \) |
| (Smoking cessation)                     |                        |
| withdrawal signs                        |                        |
| 5. Nicotine reinforcement               | \( \alpha 4\beta (\alpha 6/\beta 3) \) |

microinjection studies have demonstrated a critical role for the mesolimbic DA pathway in nicotine self-administration. Picciotto et al. (36) reported that mutant mice lacking the \( \beta 2 \) subunit of the nAChR do not self-administer nicotine and do not show a stimulatory DA. Systemically administered and direct VTA injection of dihydro-\( \beta \)-erythroidine, the \( \alpha 4\beta 2 \) nicotinic receptor antagonist, also reduces nicotine self-administration (37). These findings suggest an involvement of the \( \alpha 4\beta 2 \) receptor in the rewarding effects of nicotine.

8. Conclusions

Although it has been known that central nAChR is a target for a number of psychiatric and neurological illnesses, recent progress in neurochemical and pharmacological studies suggested that differential nAChR subtypes are involved in psychiatric disorders (Table 1). At the same time, it has been shown that the reinforcing properties of nicotine and the withdrawal symptoms are associated with psychiatric disorders complicatedly. And several effects of nicotine in psychiatric disorders may be mediated through neuromodulatory potentiation of the release of neurotransmitters including ACh, DA, NA, 5-HT, GABA and glutamate in different nervous system functions. It appears likely that pre-synaptic nAChR on monoaminergic fibers are composed of \( \alpha 3 \) or \( \alpha 4 \) subunits in combination with the \( \beta 2 \) subunit, and these subunit compositions mediate DA and NA release. In contrast, the release of glutamate is mainly controlled by \( \alpha 7 \)-nicotinic receptors. Therefore, research on the therapeutic potential of selective ligands for the various nAChR subtypes without addiction potential may have benefits as therapeutic agents.

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REFERENCES

1. Jaffe JH: Drug addiction and drugs abuse. In The Pharmacological Basis of Therapeutics, Edited by Gilman AC, Goodman LS, Rall TW and Murad F, pp 532 – 581, Macmillan, New York (1985)
2. Decker MW, Brioni JD, Bannon AW and Amberg SP: Diversity of neuronal nicotinic acetylcholine receptors: Lessons from behavior and implications for CNS therapeutics. Life Sci 56, 545 – 570 (1995)
3. James JR and Nordberg A: Genetic and environmental aspects of the role of nicotine receptors in neurodegenerative disorders: emphasis on Alzheimer’s disease and Parkinson’s disease. Behav Genet 25, 149 – 159 (1995)
4. Picciotto MR, Caldarone BJ, King SL and Zachariou V: Nicotinic receptors in the brain: links between molecular biology and behavior. Neuropsychopharmacology 22, 451 – 465, (2000)
5. Lloyd GK and Williams M: Neuronal nicotine acetylcholine receptors as novel drug targets. J Pharmacol Exp Ther 292, 461 – 467 (2000)
6. Toth E, Visi ES and Lajtha A: Effect of nicotine on levels of extracellular amino acids in regions of the rat brain in vivo. Neuropharmacology 32, 827 – 832 (1993)
7. Soliakov L and Wonnacott S: Voltage-sensitive Ca\(^{2+}\) channels involved in nicotinic receptor-mediated \([H]^2\)-dopamine release from rat striatal synaptosomes. J Neurochem 67, 163 – 170 (1996)
8. Schulz DW and Zigmond RE: Neuronal bungarotoxin blocks the nicotine stimulation of endogenous dopamine release from rat striatum. Neurosci Lett 108, 310 – 316 (1998)
9. Fu Y, Matta SG, Gao W, Brower VG and Sharp BM: Systemic nicotine stimulates dopamine release in nucleus accumbens: re-evaluation of the role of \(N\)-methyl-\(D\)-aspartate receptors in the ventral tegmental area. J Pharmacol Exp Ther 294, 458 – 465 (2000)
10. Adler LE, Hoffer LJ, Griffith J, Waldo MC and Freedman R: Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. Biol Psychiatry 32, 607 – 616 (1992)
11. McEvoy JP, Freudreich O, McGee M, VanderZwaag C, Levin E and Rose J: Clozapine decreases smoking in patients with chronic schizophrenia. Biol Psychiatry 37, 550 – 552 (1995)
12. McEvoy JP, Freudreich O and Wilson WH: Smoking and therapeutic response to clozapine in patients with schizophrenia. Biol Psychiatry 46, 125 – 129 (1999)
13. Yasuda K, Araki H, Suemaru K and Gomita Y: Nicotine blocks apomorphine-induced disruption of prepulse inhibition in rats; involvements of \(\alpha 7\)-nicotinic receptors. Jpn J Pharmacol 85, Suppl 1, 252P (2001)
14. Freedman R, Hall M, Adler LE and Leonard S: Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol Psychiatry 38, 22 – 33 (1995)
15. Stevens KE, Kem WR, Mahmood VM and Freedman R: Selective \(\alpha 7\)-nicotinic agonists normalize inhibition of auditory response
in DBA mice. Psychopharmacology (Berl) 136, 320 – 327 (1998)
16 Adler LE, Olincy A, Waldo M, Harris JG, Griffith J, Stevens K, Flach K, Nagamoto H, Bickford P, Leonard S and Freedman R: Schizophrenia, sensory gating, and nicotinic receptors. Schizophrenia Bull 24, 189 – 202 (1998)
17 Breslau N and Klein DF: Smoking and panic attacks: an epidemiologic investigation. Arch Gen Psychiatry 56, 1141 – 1147 (1999)
18 Breslau N, Kilbey M and Andreski P: Nicotine dependence, major depression, and anxiety in young adults. Arch Gen Psychiatry 48, 1069 – 1074 (1991)
19 Covey LS, Glassman AH and Stetner F: Cigarette smoking and major depression. J Addict Dis 17, 35 – 46 (1998)
20 Stage KB, Glassman AH and Covey LS: Depression after smoking cessation: case reports. J Clin Psychiatry 57, 467 – 469 (1996)
21 Salin-Pascual RJ, Rosas M, Jimenez-Genchi A, Rivera-Meza BL and Delgado-Parra V: Antidepressant effect of transdermal nicotine patches in nonsmoking patients with major depression. J Clin Psychiatry 57, 387 – 389 (1996)
22 Tizabi Y, Overstreet DH, Rezvani AH, Louis VA, Clark E Jr, Janowsky DS and Kling MA: Antidepressant effects of nicotine in an animal model of depression. Psychopharmacologia 142, 193 – 199 (1999)
23 Bejerot S and Humble M: Low prevalence of smoking among patients with obsessive-compulsive disorder. Compr Psychiatry 40, 268 – 272 (1999)
24 Brioni JD, O’Neill AB, Kim DJ and Decker MW: Nicotinic receptor agonists exhibit anxiolytic-like effects on the elevated plus-maze test. Eur J Pharmacol 238, 1 – 8 (1993)
25 Paterson D and Nordberg A: Neuronal nicotinic receptors in the human brain. Prog Neurobiol 61, 75 – 111 (2000)
26 File SE, Kenny PJ and Ouagazzal: Bimodal modulation by nicotine of anxiety in the social interaction test: role of the dorsal hippocampus. Behav Neurosci 112, 1423 – 1429 (1998)
27 File SE, Cheeta S and Kenny PJ: Neurobiological mechanisms by which nicotine mediates different types of anxiety. Eur J Pharmacol 393, 231 – 236 (2000)
28 Ross SA, Wong JY, Clifford JJ, Kinsella A, Massalas JS, Horne MK, Scheffer IE, Kola I, Waddington JL, Berkovic SF and Drago J: Phenotype characterization of an alpha 4 neuronal nicotinic acetylcholine receptor subunit knock-out mouse. J Neurosci 20, 6431 – 6441 (2000)
29 Hitsman B, Pingitore R, Spring B, Mahabeshwarkar A, Mizes JS, Segraves KA, Kristeller JL and Xu W: Antidepressant pharmacotherapy helps some cigarette smokers more than others. J Consult Clin Psychol 67, 547 – 554 (1999)
30 Malin DH, Lake JR, Upchurch TP, Shenoi M, Rajan N and Schweinle WE: Nicotine abstinence syndrome precipitated by the competitive nicotinic antagonist dihydro-beta-erythroidine. Pharmacol Biochem Behav 60, 609 – 613 (1998)
31 Hildebrand BE, Nomikos GG, Hertel P, Schilstrom B and Svensson TH: Reduced dopamine output in the nucleus accumbens but not in the medial prefrontal cortex in rats displaying a mecamylamine-precipitated nicotine withdrawal syndrome. Brain Res 779, 214 – 225 (1998)
32 Rasmussen K, Kallman MJ and Helton DR: Serotonin-1A antagonists attenuate the effects of nicotine withdrawal on the auditory startle response. Synapse 27, 145 – 152 (1997)
33 Rasmussen K and Czachura JF: Nicotine withdrawal leads to increased sensitivity of serotoninergic neurons to the 5-HT1A agonist 8-OH-DPAT. Psychopharmacology (Berl) 133, 343 – 346 (1997)
34 Suemaru K, Araki H, Kitamura Y, Yasuda K and Gomita Y: Withdrawal from chronic exposures of cigarette smoke and nicotine enhances wet-dog shake responses to 5-HT2 receptor stimulation in rats. Psychopharmacology (Berl) 159, 38 – 41 (2001)
35 Shoib M, Stolerman IP and Kumar RC: Nicotine-induced place preferences following prior nicotine exposure in rats. Psychopharmacology (Berl) 113, 445 – 452 (1994)
36 Picciotto MR, Zoil M, Rimondini R, Lena C, Marubio LM, Pich EN, Fuxe K and Changeux JP: Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature 391, 173 – 177 (1998)
37 Corrigall WA, Coen KM and Adamson KL: Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res 653, 278 – 284 (1994)