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Review Article

Neural mechanisms underlying nicotine addiction: acute positive reinforcement and withdrawal

Shelly S. Watkins, George F. Koob, Athina Markou

The neurobiology of nicotine addiction is reviewed within the context of neurobiological and behavioral theories postulated for other drugs of abuse. The roles of various neurotransmitter systems, including acetylcholine, dopamine, serotonin, glutamate, gamma-aminobutyric acid, and opioid peptides in acute nicotine reinforcement and withdrawal from chronic administration are examined followed by a discussion of potential neuroadaptations within these neurochemical systems that may lead to the development of nicotine dependence. The link between nicotine administration, depression and schizophrenia are also discussed. Finally, a theoretical model of the neurobiological mechanisms underlying acute nicotine withdrawal and protracted abstinence involves alterations within dopaminergic, serotonergic, and stress systems that are hypothesized to contribute to the negative affective state associated with nicotine abstinence.

Introduction

Evidence indicates that people smoke primarily to experience the psychopharmacological properties of nicotine and that the majority of smokers eventually become dependent upon nicotine (Balfour, 1984; Stolerman, 1991). The high addictive potential of nicotine is indicated by the vast number of people who habitually smoke, an estimated 25% of the US population (Substance Abuse and Mental Health Services Administration, 1993). Tobacco smoking is the leading, *avoidable* cause of disease and premature death in the US, responsible for over 500,000 deaths annually and contributing to about 40 diseases (United States Department of Health and Human Services, 1988). In view of the pervasiveness of tobacco use and the far-reaching costs to smokers and society, there has been increased interest in elucidating the actions of nicotine within the central nervous system that lead to acute positive reinforcement and potential neuroadaptations which mediate the development of dependence and withdrawal symptoms.

In humans, nicotine produces positive reinforcing effects including mild euphoria (Pomerleau & Pomerleau, 1992), increased energy, heightened arousal, reduced stress and anxiety, and appetite suppression (Benowitz, 1996; Stolerman & Jarvis, 1995). Cigarette smokers report that smoking produces arousal, particularly with the first cigarette of the day, and relaxation when under stress (Benowitz, 1988). A nicotine abstinence syndrome after chronic nicotine exposure has been characterized in both humans (Hughes, Gust, Skoog, Kennan, & Fenwick, 1991; Shiffman & Jarvik, 1976) and rats (Epping-Jordan, Watkins, Koob, & Markou, 1998b; Hildebrand, Nomikos, Bondjers, Nisell, & Svensson, 1997; Malin *et al.*, 1992; Malin, Lake, Carter, Cunningham, & Wilson, 1993; Malin *et al.*, 1994; Watkins, Stinus, Koob, & Markou, 2000), and has both somatic and affective components. In humans,

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acute nicotine withdrawal is characterized by somatic symptoms, such as bradycardia, gastrointestinal discomfort, and increased appetite leading to weight gain, as well as affective symptoms including depressed mood, dysphoria, irritability, anxiety, frustration, increased reactivity to environmental stimuli, and difficulty concentrating (American Psychiatric Association, 1994; Hughes *et al.*, 1991). The enduring symptoms of nicotine withdrawal (protracted abstinence) include continued affective changes, such as depressed mood (Hughes *et al.*, 1991), with abstinent smokers often reporting powerful cravings for tobacco (Hughes, Hatsukami, Pickens, Krahn, Malin, & Luknic, 1984). While the somatic symptoms of drugs of abuse are unpleasant and annoying, it has been hypothesized that avoidance of the affective components of drug withdrawal, including those associated with nicotine withdrawal, plays a more important role in the maintenance of nicotine dependence than the somatic symptoms of withdrawal (Koob, Markou, Weiss, & Schulteis, 1993; Markou, Kosten, & Koob, 1998).

The acute positive reinforcing effects of drugs are critically important in establishing self-administration behavior, but the mechanisms underlying the transition from initial drug use to drug dependence are not clear. It has been hypothesized that the transition to drug dependence involves neuroadaptations within brain circuitries that produce positive reinforcement (Koob & Bloom, 1988). These neuroadaptations may contribute to a negative affective state upon drug termination. One mechanism of perpetuating drug dependence would be continued drug use to avoid a negative affective state through negative reinforcement processes (Koob, 1996). Accordingly, the perpetuation of nicotine dependence is hypothesized to be facilitated by the avoidance of certain withdrawal symptoms through further nicotine administration. Thus, investigation of the neurobiology of nicotine withdrawal may be critical to our understanding of the development and maintenance of nicotine dependence.

The present review will first focus on the neurobiology of acute nicotine reinforcement, followed by a discussion of alterations in systems that may modulate symptoms of nicotine withdrawal, and then present a theoretical model of the neurobiological mechanisms that may underlie acute nicotine withdrawal and vulnerability to relapse. The intent of this review is to provide a bridge between psychology and neuroscience by examining the neurobiological substrates for the behavioral phenomena associated with nicotine reinforcement and withdrawal within the context of neurobiological and behavioral theories postulated for addiction to other major drugs of abuse.

Neurobiology of the acute rewarding effects of nicotine

Animal studies of the neurobiological bases of nicotine reinforcement using intravenous self-administration have yielded information about the neurochemical systems likely to be involved in mediating the acute positive reinforcing effects of nicotine. Nicotine activates nicotinic acetylcholine receptors in the mesocorticolimbic dopaminergic system that projects from the ventral tegmental area (VTA) to the nucleus accumbens and the prefrontal cortex (Corrigall, Coen, & Adamson, 1994; Corrigall, Franklin, Coen, & Clarke, 1992; Nisell, Nomikos, & Svensson, 1995; Pontieri, Tanka, Orzi, & Di Chiara, 1996). Non-dopamine neurochemical pathways also may modulate nicotine reinforcement processes. Nevertheless, the preponderance of data to date indicates that other neurochemical systems involved in nicotine reinforcement interact with the midbrain dopamine system. These systems include the cholinergic, glutamatergic, gamma-aminobutyric acid (GABA), and opioid peptide systems. Dopamine-independent positive reinforcing effects of nicotine remain to be demonstrated.

Acetylcholine

Nicotine produces its central and peripheral actions by binding to the nicotinic acetylcholine receptor (nAChR) complex. Sixteen nAChR subunits have been identified based on molecular composition ($\alpha1-\alpha9$; $\beta1-\beta4$; Arneric, Sullivan, & Williams, 1995; Wonnacott, 1997) with the neuronal nicotinic subunits including $\alpha2-\alpha8$ and $\beta2-\beta4$. It has been shown that all high affinity binding sites for nicotine include the $\beta2$ subunit (Picciotto *et al.*, 1995), and that nicotine-induced dopamine release is dependent on the $\beta2$ subunit (Picciotto *et al.*, 1998). For example, mutant mice lacking the $\beta2$ subunit will not self-administer nicotine (Picciotto *et al.*, 1998), indicating that the $\beta2$ subunit is critically involved in nicotine reinforcement. The most widely expressed subtypes of the nAChR in the brain contain $\alpha4$, $\beta2$, or $\alpha7$ subunits (Flores, Rogers, Pabreza, Wolfe, & Kellar, 1992; Wada *et al.*, 1989; Zoli, Lena, Picciotto, & Changeux, 1998). Various nAChR α and β subunit combinations, including the $\alpha4\beta2$ subtype, are present throughout the mesolimbic pathway including the VTA, prefrontal cortex, amygdala, septal area, and nucleus accumbens (Marks *et al.*, 1992; Sargent, 1993; Wada *et al.*, 1989). These nAChRs provide potential binding sites through which nicotine may activate neurons within these structures to stimulate the release of several neurotransmitters.

Evidence suggests that cholinergic input to the mesolimbic dopamine pathway may provide a system through which nicotine may increase dopamine release. Administration of the non-competitive nAChR antagonist, mecamylamine, or the competitive nAChR antagonist, dihydro-β-erythroidine (DHβE) blocked nicotine self-administration in the rat, indicating that activation of nAChRs is involved in the reinforcing actions of nicotine (Corrigall & Coen, 1989; Corrigall *et al.*, 1994; Watkins, Epping-Jordan, Koob, & Markou, 1999). Further, immuno-cytochemical studies indicated that the VTA receives cholinergic innervation from the pedunculopontine nucleus, with nAChRs found in both

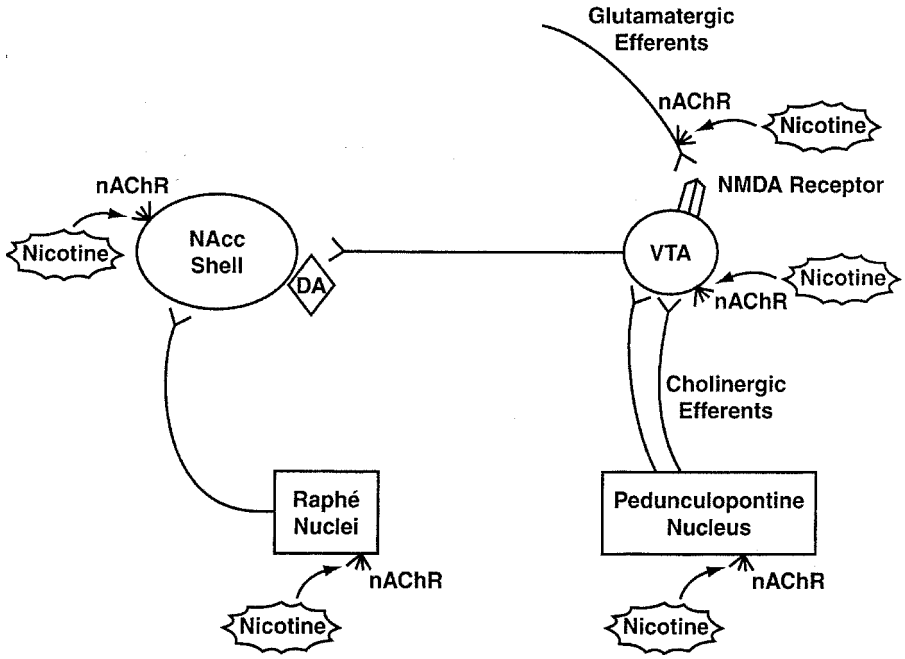

Figure 1. Schematic drawing of pathways partly mediating nicotine-induced positive reinforcement. Nicotine binding sites (nAChRs) are represented in the pedunculopontine nucleus, raphe nuclei, ventral tegmental area, and the nucleus accumbens. Depicted projections to the mesolimbic dopamine system include glutamatergic and GABAergic input, serotonergic afferents from the raphe nuclei, and cholinergic afferents from the pedunculopontine nucleus. Abbreviations: DA, dopamine; nAChR, nicotinic acetylcholine receptor; NMDA, *N*-methyl-D-aspartate; NAcc, nucleus accumbens; VTA, ventral tegmental area.

the VTA and the pedunculopontine nucleus (Bolam, Francis, & Henderson, 1991). Stimulation of cholinergic neurons within the pedunculopontine tegmental nucleus by exogenously administered nicotine leads to release of endogenous acetylcholine which excites dopamine neurons in the substantia nigra and VTA, and this activation is blocked by mecamylamine (Clarke, Hommer, Pert, & Skirboll, 1987). The finding that partial lesions of the pedunculopontine nucleus failed to block nicotine self-administration (Corrigall *et al.*, 1994) indicates that cholinergic input may not be required for the reinforcing actions of nicotine because exogenously administered nicotine may directly stimulate nAChRs within the VTA. Nevertheless, complete lesions of the pedunculopontine nucleus may be required to determine the functional role of the pedunculopontine nucleus to the VTA connection in acute nicotine reinforcement (Figure 1).

Dopamine

Stimulation of dopamine systems appears to be of critical importance for the acute positive reinforcing properties of nicotine. Experimental evidence indicates that nicotine induces dopamine release partly by binding directly to nAChRs located within the mesolimbic system, specifically within the VTA (Nisell, Nomikos, & Svensson, 1994). In the rat brain, nAChRs have been identified on the cell bodies and dendrites of dopamine neurons in the ventral tegmental area, as well as their terminal fields in the nucleus accumbens (Clarke & Pert, 1985; Schwartz, Lehmann, & Kellar, 1984; Swanson, Simmons, Whiting, & Lindstrom, 1987; Wada *et al.*, 1989). The presence of nAChRs throughout the dopamine neuron suggests that any of these sites could mediate the effect of nicotine on the mesolimbic dopamine system. It has been hypothesized, however, that nAChRs in the VTA play a more important role than those in the nucleus accumbens in mediating the effects of nicotine on dopamine release (Nisell *et al.*, 1994). Systemic administration of nicotine has been shown to produce a dose-dependent increase in extracellular dopamine levels in the shell of the nucleus accumbens, a neurochemical effect shared by other drugs that also serve as positive reinforcers (Nisell, Marcus, Nomikos, & Svensson, 1997; Pontieri *et al.*, 1996; Pontieri, Passarelli, Calo, & Caronti, 1998). Nevertheless, direct continuous infusion of nicotine in the VTA produced a longer lasting increase in dopamine release in the nucleus accumbens than nicotine infused into the nucleus accumbens (Nisell *et al.*, 1994). In addition, infusion of mecamylamine into the VTA blocked the systemically administered nicotine-induced dopamine release in the nucleus accumbens, while infusion of mecamylamine directly into the nucleus accumbens failed to block dopamine release (Nisell *et al.*, 1994). Further, nicotine-induced dopamine release from terminals in the nucleus accumbens is not affected by tetrodotoxin, a compound that prevents the generation of action potentials by blocking sodium channels (Giorguieff-Chesselet, Kemel, Wandscheer, & Glowinski, 1979; Rapier, Lunt, &

Wonnacott, 1990) suggesting that nAChRs on dopamine terminals do not significantly contribute to nicotine-induced dopamine release (Benwell, Balfour, & Lucchi, 1993).

The role of nAChRs in the VTA in the positive reinforcing effects of nicotine is further suggested by the finding that infusions of the competitive nAChR antagonist dihydro-β-erythroidine, directly into the VTA, but not the nucleus accumbens, produced a significant decrease in nicotine self-administration behavior (Corrigall *et al.*, 1994). Further, 6-hydroxydopamine lesions of the nucleus accumbens, or systemic administration of selective D1 (SCH23390) or D2 (spiperone) dopamine receptor antagonists attenuated nicotine self-administration (Corrigall & Coen, 1991; Corrigall *et al.*, 1992). Taken together, the results of the above neurochemical and behavioral studies offer support for the hypothesis that nicotine exerts its primary reinforcing action by activating dopamine neurons along the mesolimbic dopamine pathway.

In the context of nAChR activation and nicotine reinforcement, it is important to consider that nAChR activation in the VTA is followed by receptor desensitization (Pidoplichko, DeBiasi, Williams, & Dani, 1997). Receptor desensitization and recovery occurred at different rates, suggesting that within the VTA, there are multiple types of nAChRs with different activation and desensitization profiles (Pidoplichko *et al.*, 1997). Smokers report the first cigarette of the day as the most pleasurable (Russell, 1989), possibly because of nicotine-induced activation of recovered nAChRs in the VTA leading to greater dopamine release than later in the day. Throughout the day smokers maintain a steady blood nicotine level (Benowitz, 1996), and are exposed to nicotine concentrations which cause nAChR desensitization in the VTA (Pidoplichko *et al.*, 1997). If different nAChRs in the VTA have different sensitivities to nicotine, as suggested above, it may be that once a steady-state of nicotine is reached, periodic re-administration of nicotine engages nAChRs only activated by a high nicotine doses (Dani & Heinemann, 1996). Activation of these receptors would also cause dopamine release, thus contributing to the maintenance of cigarette smoking throughout waking hours. Nonetheless, the maintenance of smoking behavior in dependent organisms, despite the development of nAChR desensitization within the VTA, may indicate the involvement of parallel reward systems in the positive reinforcing actions of nicotine which extend beyond the mesolimbic dopamine pathway. Few, if any, studies to date have explored the neurobiology of the positive reinforcing actions of nicotine in dependent animals.

Glutamate–dopamine interactions

Increasing evidence supports a role for excitatory amino acids in the effects of drugs of abuse (for a review, see Trujillo & Akil, 1995). Most relevant to the present review are the indications of an excitatory role of *N*-methyl-D-aspartate (NMDA) receptors in the VTA on nicotine-induced increases in nucleus accumbens dopamine. Acute administration of nicotine activates nAChRs located pre-synaptically on glutamatergic terminals, leading to increased evoked glutamate release (Gray, Rajan, Radcliffe, Yakehiro, & Dani, 1996; McGehee, Heath, Gelber, Devay, & Role, 1995). In turn, through excitatory actions at NMDA receptors on VTA dopaminergic neurons, glutamate increases the burst firing of these neurons and subsequent dopamine release in the nucleus accumbens (Chergui *et al.*, 1993; Hu & White, 1996; Kalivas, Churchill, & Klitenick, 1993). Most importantly, blockade of NMDA receptors with 2-amino-5-phosphonopentanoic acid injected directly into the VTA dose-dependently attenuated the nicotine-induced dopamine release in the nucleus accumbens (Schilstrom, Nomikos, Nisell, Hertel, & Svensson, 1998). Systemic administration of another NMDA antagonist, MK-801 (dizocilpine), also blocked nicotine-induced dopamine release in the nucleus accumbens (Sziraki, Sershen, Benuck, Hashim, & Lajtha, 1998). These data indicate that activation of excitatory nAChRs on glutamatergic terminals also may contribute to the acute reinforcing properties of nicotine.

Gamma-aminobutyric acid (GABA)–dopamine interactions

GABAergic neurotransmission significantly modulates dopaminergic neurotransmission at the level of both the VTA and the nucleus accumbens (Churchill, Dilts, & Kalivas, 1992; Heimer, Zahm, Churchill, Kalivas, & Wahltmann, 1991; Kalivas *et al.*, 1993). There are GABAergic inhibitory afferents to dopaminergic ventral tegmental neurons (Walaas & Fonnum, 1980; Yim & Mogenson, 1980), inhibitory GABAergic interneurons within the VTA, and medium spiny GABAergic neurons in the nucleus accumbens that also inhibit mesolimbic dopamine release (Kalivas *et al.*, 1993). In addition, enhancement of GABAergic neurotransmission through administration of gamma-vinyl GABA (GVG), an indirect GABA agonist (an irreversible inhibitor of GABA transaminase), abolished nicotine-induced dopamine increases in the nucleus accumbens and the reinforcing effects of nicotine as reflected in the conditioned place preference paradigm (Dewey, Brodie, Gerasimov, Horan, Gardner, & Ashby, 1999). Taken together, these findings provide support for the hypothesis that GABAergic mechanisms may be involved in modulating nicotine reinforcement.

Opioid peptide–dopamine interactions

Nicotine also affects the release of endogenous opioid peptides (Boyadjieva & Sarkar, 1997; Pomerleau & Pomerleau, 1984; Pomerleau & Rosecrans, 1989). Within the mesolimbic dopamine system, systemic

nicotine administration increases tissue levels of opioid peptides in the nucleus accumbens (Houdi, Pierzchala, Marson, Palkovits, & VanLoon, 1991; Pierzchala, Houdi, VanLoon, 1987). A high density of μ-opioid receptors has been identified in the nucleus accumbens and it has been suggested that these receptors are occupied by endogenous opioid ligands released by nicotine (Davenport, Houdi, & VanLoon, 1990; Tempel & Zukin, 1987). Outside the mesolimbic dopamine system, nicotine stimulates nAChRs within the hypothalamus and induces the release of the pro-opiomelanocortin peptide group that includes the precursor to β-endorphin (Pomerleau, 1998). The β-endorphin system has been hypothesized to be involved in mood regulation, psychomotor stimulation, analgesia, reproduction, and temperature regulation (Cesselin, 1995; Terenius, 1992). Further, increased β-endorphin release is thought to decrease the response to stress, conserve energy, and facilitate relaxation (for reviews, see Cesselin, 1995; Henry, 1986; Herz, 1997; Terenius, 1992). It remains to be determined if activation of the hypothalamic β-endorphin system is involved in mediating the positive reinforcing effects of nicotine. Thus, the positive reinforcing properties of nicotine could be hypothesized to be modulated by activation of enkephalin neurons along parallel reward systems to the dopamine system (i.e., dopamine-independent systems) (Houdi *et al.*, 1991; Pomerleau & Pomerleau, 1984). Nevertheless, pharmacological studies in humans investigating the effects of naloxone, an opioid receptor antagonist on smoking behavior, have yielded inconsistent results (Karras & Kane, 1980; Nemeth-Coslett & Griffiths, 1986).

Serotonin

Evidence for the involvement of the serotonergic system in the positive reinforcing effects of nicotine is limited. Various subtypes of high-affinity nicotinic acetylcholine receptors which are activated by a low dose of nicotine have been identified in both the median raphe nucleus and the hippocampus (Alkondon & Albuquerque, 1993; Benwell, Balfour, & Anderson, 1988; Li, Rainnie, McCarley, & Greene, 1998; Marks *et al.*, 1992). These receptors may provide a potential site of action for nicotine within the serotonergic system. Acute systemic administration of a high nicotine dose increased the release of serotonin in the frontal cortex of rats (Ribeiro, Bettiker, Bogdanov, & Wurtman, 1993); however, it is not known whether this effect is involved in the positive reinforcing effects of nicotine because this dose was significantly higher than that normally experienced by smokers. Subsequent studies using doses of nicotine that more closely approximate those of cigarette smokers provide little support for a role of the serotonin system in acute nicotine reinforcement. For example, administration of either ICS 205–930 or MDL 72222, two selective 5-HT_3 receptor antagonists, had no effect on intravenous nicotine self-administration in the rat (Corrigall & Coen, 1994). Furthermore, in a rat model of oral nicotine self-administration, administration of ipsapirone, a 5-HT_{1A} agonist, had no effect on nicotine intake (Mosner, Kuhlman, Roehm, & Vogel, 1997). Nonetheless, neuroanatomical data suggest that both the VTA and the nucleus accumbens receive inputs from serotonergic neurons originating in the raphe nuclei (Steinbusch, 1981), thus providing a potential substrate for interactions between the serotonergic and dopaminergic systems. The functional role of serotonin in mediating the positive reinforcing or rewarding effects of nicotine is unclear and thus, further research is needed to explore this issue.

The extended amygdala

Structures and connections

It has been hypothesized that the reinforcing and withdrawal effects of various drugs of abuse may be modulated by neurochemical processes in specific basal forebrain areas that interface classical limbic structures with the extrapyramidal motor system (Koob, 1996; Koob *et al.*, 1993). Recent anatomical and functional analyses suggest that the reinforcing action of drugs may involve neuroanatomical substrates which extend beyond the pathway from the VTA to the nucleus accumbens (Alheid & Heimer, 1988; Koob *et al.*, 1993). The central nucleus of the amygdala, the bed nucleus of the stria terminalis, and a transition area in the posterior part of the shell of the nucleus accumbens are components of a large forebrain structure termed the 'extended amygdala' (de Olmos *et al.*, 1985; Heimer, Alheid, & Zabaorszky, 1985; Heimer & Alheid, 1991). The anatomical concept of the extended amygdala is based upon observations that the components of these brain regions have similar cell morphology, immunohistochemistry, and common afferent and efferent projections (Heimer & Alheid, 1991). Components of the extended amygdala receive afferent connections from limbic areas, the hippocampus, basolateral amygdala, midbrain, and lateral hypothalamus. The efferent connections include the ventral pallidum, VTA, and projections to the brainstem and lateral hypothalamus (Heimer & Alheid, 1991). These projections to and from the extended amygdala provide the necessary connections to modulate drug reward as well as neuroadaptive changes proposed to occur with chronic drug exposure (Koob, Sanna, & Bloom, 1998; Figure 2).

The extended amygdala and reinforcement

While little is known about the role of the extended amygdala in nicotine reinforcement, several studies have investigated the role of these structures in reinforcement associated with another psychomotor stimulant drug, cocaine. Lesions of dopamine neurons in the VTA or nucleus accumbens or administration of dopamine recep-

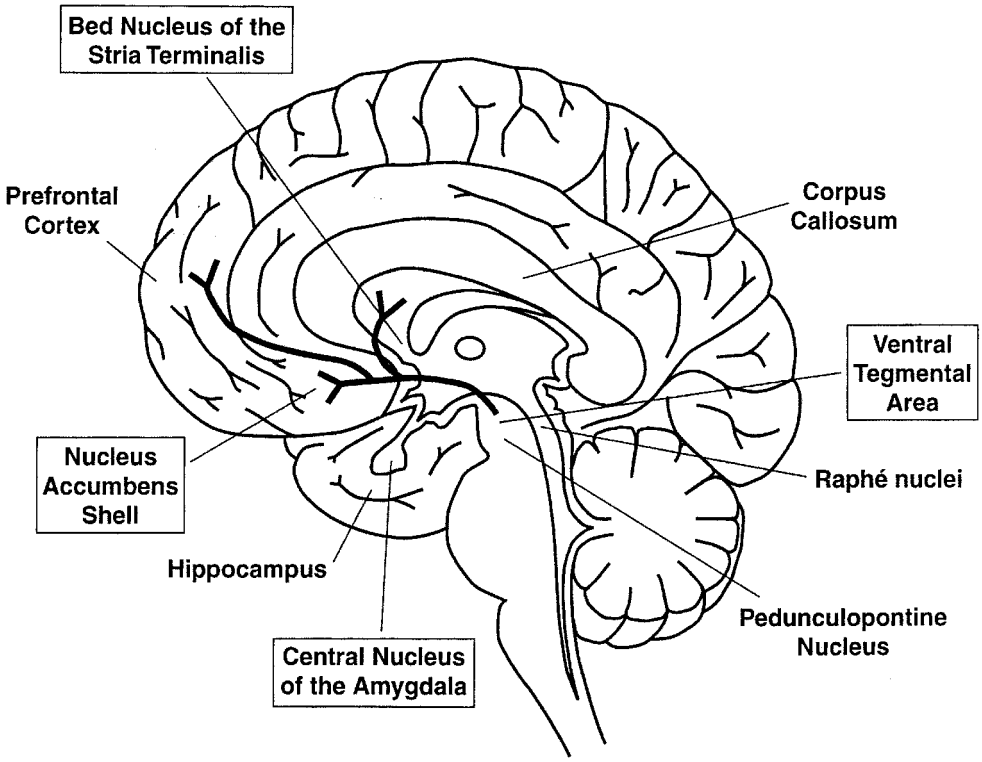

Figure 2. Schematic drawing of a midsagittal view of the human brain. Boxed terms indicate the components of the extended amygdala (shell of the nucleus accumbens, bed nucleus of the stria terminalis, central nucleus of the amygdala). Darkened lines indicate the mesolimbic dopamine projection from the ventral tegmental area to the nucleus accumbens and prefrontal cortex.

tor antagonists into areas associated with the extended amygdala, such as the shell of the nucleus accumbens, the central nucleus of the amygdala, or the bed nucleus of the stria terminalis, decreased the reinforcing efficacy of self-administered cocaine (Caine, Heinrichs, Coffin, & Koob, 1995; Caine & Koob, 1994; Epping-Jordan, Markou, & Koob, 1998a; Roberts & Koob, 1982; Roberts, Koob, Klonoff, & Fibiger, 1980). Like cocaine, nicotine may exert similar effects on specific components of the extended amygdala. Nicotinic acetylcholine receptor genes have been located in neurons throughout the rat amygdala, including the central nucleus of the amygdala (Wada *et al.*, 1989), indicating potential functional nAChRs within these areas. Further, activation of the immediate early gene *c-fos*, a marker of neuronal activation, and decreased dopamine release have been measured in the central nucleus of the amygdala during precipitated nicotine withdrawal (Panagis *et al.*, 1998), suggesting that alterations occur within the extended amygdala during chronic nicotine exposure. Taken together, the ability of both cocaine and nicotine to increase dopamine release specifically in the shell and not the core of the nucleus accumbens (Nisell *et al.*, 1994; Pontieri *et al.*, 1996), and the expression of nicotinic receptor genes in the central nucleus of the amygdala (Wada *et al.*, 1989) leave open the possibility of a potential role of the extended amygdala in the reinforcing effects of nicotine.

Nicotine withdrawal: theoretical framework for neurochemical adaptations

Solomon and Corbit (1974) elaborated on an opponent process theory of motivation wherein affective, emotional, or hedonic states are neutralized by changes within brain systems that modulate these emotional processes. It is hypothesized that specific brain systems are automatically recruited whenever significant departures from normal affect occur as a consequence of stimulation, and act to decrease the intensity of the subjective experience. The opponent process is hypothesized to be indirectly activated by stimulation of positive affective or positive hedonic states and acts to oppose the initial effect (Solomon & Corbit, 1974). Application of this theory to the development of drug dependence may involve postulated changes in neurochemical systems that oppose the initial reinforcing effects of a drug leading to a dependent state. Specifically, the same neuronal substrates involved in the acute, positive reinforcing properties of a drug are hypothesized to be compromised during chronic exposure as well as recruitment of neuronal substrates not involved in the acute reinforcing effects of drugs. These alterations are hypothesized to contribute to the negative motivational and affective states during withdrawal (Koob & Bloom, 1988; Koob & LeMoal, 1997).

Nicotine withdrawal phenomena

The nicotine withdrawal syndrome in both human and non-human animals includes somatic and affective symptomatology (see introduction). The somatic syndrome associated with nicotine withdrawal has been modeled in rats (Epping-Jordan *et al.*, 1998b; Hildebrand *et al.*, 1997; Malin *et al.*, 1992; 1993; 1994; Watkins *et al.*, 2000), but overt somatic withdrawal signs may not reflect the affective or motivational state of the animal. Affective changes are difficult to assess in animals; nevertheless, intracranial self-stimulation has been shown to be a valid and reliable measure of changes in reward associated with acute drug exposure (Baldo, Jain, Veraldi, Koob, & Markou, 1999; Bauco & Wise, 1994; Huston-Lyons & Kornetsky, 1992; Kornetsky & Esposito, 1981; Moolten & Kornetsky, 1990; Stellar & Rice, 1989) and withdrawal from several drugs of abuse, including cocaine, amphetamine, morphine, ethanol, and most recently, nicotine (Epping-Jordan *et al.*, 1998b; Leith & Barrett, 1976; Lin, Koob, & Markou, 1999; Markou & Koob, 1991; Schulteis, Markou, Cole, & Koob, 1995; Schulteis, Markou, Gold, Stinus, & Koob, 1994). Another common effect of withdrawal from many drugs of abuse is reduced dopamine output in the nucleus accumbens (Rossetti, Hmaidan, & Gessa, 1992). In studies employing *in vivo* microdialysis, extracellular dopamine levels in the nucleus accumbens decreased 30–40% during spontaneous cocaine withdrawal (Weiss, Markou, Lorang, & Koob, 1992), approximately 50% during spontaneous morphine withdrawal (Crippens & Robinson, 1994), 25% during precipitated morphine withdrawal (Spanagel, Almeida, Bartl, & Shippenberg, 1994), and 64% during spontaneous ethanol withdrawal (Weiss *et al.*, 1996). Recently, a decrease of 25% in extracellular dopamine levels in the nucleus accumbens was measured during mecamylamine-precipitated nicotine withdrawal in rats chronically exposed to nicotine (Hildebrand, Panagis, Svensson, & Nomikos, 1999). Microdialysis measures of dopamine levels during spontaneous nicotine withdrawal have not been reported, although tissue levels of dopamine in the nucleus accumbens were reduced approximately 32% compared to saline controls (Fung, Schmid, Anderson, & Lau, 1996).

Molecular adaptations during chronic nicotine exposure

The effects of nicotine on central nAChRs are complex and have been described as 'paradoxical' in that chronic nicotine exposure leads to receptor desensitization and inactivation which is followed by an upregulation in nicotinic receptors (Bhat, Marks, & Collins, 1994; Marks *et al.*, 1992; Wonnacott, 1990). Acute administration of nicotine stimulates the nAChR which leads to a brief opening of the ion channel (receptor activation), but then transiently becomes unresponsive to further exposure to agonists (receptor inactivation and desensitization; Corringer, Bertrand, Bohler, Edelstein, Changeux, & Bertrand, 1998). Consequently, chronic exposure to nicotine leads to an increase in the number of nAChRs (receptor upregulation; Collins, Bhat, Pauly, & Marks, 1990; Perry, Davila-Garcia, Stockmeier, & Kellar, 1999; Wonnacott, 1990). Even though this nicotinic receptor activation, desensitization, and upregulation can be viewed as a neuronal response to maintain the baseline level of synaptic activity within cholinergic and other neurotransmitter systems during chronic nicotine exposure (Dani & Heinemann, 1996; Reitstetter, Lukas, & Gruener, 1999), it is not clear if upregulation reflects an increase in functional receptors (Wonnacott, 1997). Moreover, nAChRs may exist in many different functional states within the brain (Changeux, Devillers-Thiery, & Chemouilli, 1984; Reitstetter *et al.*, 1999), thus maximizing function. The $\alpha 2$, $\alpha 4$, and $\alpha 7$ subunits become inactive and desensitized in the chronic presence of nicotine, while the $\alpha 3$ and $\alpha 6$ subunits do not show inactivation (Olale, Gerzanich, Kuryatov, Wang, & Lindstrom, 1997), suggesting that some subunits show a greater sensitivity to nicotine than others. Injection of $\alpha 3\beta 2$ or $\alpha 4\beta 2$ subunit RNAs in oocytes followed by subsequent nicotine administration indicated that $\alpha 4\beta 2$ nicotinic receptors desensitize more quickly and recover more slowly than $\alpha 3\beta 2$ receptors (Hsu, Amin, Weiss, & Wecker, 1996). Thus, a differential effect of chronic nicotine exposure on release of various neurotransmitter systems may be explained by the balance of receptor density, desensitization, and functionality.

During nicotine abstinence, such changes in nAChR function may mediate some of the negative affective states and somatic symptoms associated with nicotine withdrawal. For example, during nicotine abstinence that leads to decreased plasma nicotine levels, the previously desensitized or inactive nAChRs may begin to recover to functional states at different rates depending on the brain region or receptor subtype. During chronic nicotine exposure, upregulation of nAChRs also may occur along non-reward-related cholinergic pathways such that during abstinence, the recovery of nAChRs in reward and non-reward circuits may contribute to negative affective or somatic withdrawal symptoms (Dani & Heinemann, 1996). Thus, the development and perpetuation of nicotine addiction may involve self-medication to effectively control the number of functional nAChRs along pathways affected by nicotine (Dani & Heinemann, 1996; Koob *et al.*, 1998).

Neurochemical adaptations

Dopamine

Recent evidence supports the hypothesis that neuroadaptations in the dopaminergic system occur with chronic nicotine exposure. For example, after chronic exposure to nicotine, decreases in extracellular dopamine

levels in the nucleus accumbens and the central nucleus of the amygdala have been measured during mecamylamine-precipitated nicotine withdrawal (Hildebrand, Nomikos, Hertel, Schilstrom, & Svensson, 1998; Hildebrand *et al.*, 1999; Panagis *et al.*, 1998). Further, during spontaneous nicotine withdrawal, decreased tissue levels of dopamine in the nucleus accumbens have been reported (Fung *et al.*, 1996).

A possible explanation for the reduction in dopamine release during chronic nicotine exposure involves putative nicotinic receptor desensitization leading to decreased neuronal firing.

Decreased neuronal firing in the VTA has been reported during continuous chronic nicotine infusion (6 mg/kg/day, nicotine base, for 12 days; Rasmussen & Czachura, 1995). During spontaneous nicotine withdrawal, neuronal firing in the VTA returned to baseline levels 2 days after termination of chronic nicotine, while the firing of substantia nigra neurons, unaffected during chronic nicotine exposure, increased over baseline levels on days 2, 3, and 4 after termination of chronic nicotine (Rasmussen & Czachura, 1995). The differing effects of chronic nicotine and withdrawal on the firing rate of VTA and substantia nigra neurons may indicate distinct nAChR subtypes in these brain regions. It also has been reported that after chronic nicotine infusion (4 mg/kg/day, nicotine base, for 7 days), a subsequent acute nicotine challenge potentiated the increase in nicotine-induced dopamine release compared to the increase measured after an acute nicotine challenge without previous nicotine exposure (Marshall, Redfern, & Wonnacott, 1997). The acute challenge, however, was given approximately 20 h after termination of chronic nicotine exposure, potentially allowing the recovery of desensitized nAChRs. Taken together, these findings indicate that alterations within dopaminergic systems occur during chronic nicotine exposure. Nevertheless, the putative role of nAChR desensitization remains to be determined.

Further evidence indicates that intracranial self-stimulation reward thresholds are elevated in rats during spontaneous or precipitated nicotine withdrawal (Epping-Jordan *et al.*, 1998b; Watkins *et al.*, 2000). This alteration in brain reward function also may reflect alterations in dopaminergic systems. Brain stimulation reward has been shown to depend on continued activation of pedunculopontine cholinergic neurons that terminate on dopamine neurons in the VTA (Yeomans & Baptista, 1997; Yeomans, Mathur, & Tampakeras, 1993). It has been proposed that myelinated axons of the medial forebrain bundle (an area supporting high rates of self-stimulation behavior) projecting from the lateral hypothalamus to the pedunculopontine nucleus activate cholinergic neurons which then activate dopamine neurons in the VTA by stimulating both nicotinic and muscarinic receptors (Yeomans & Baptista, 1997). It may be that after nAChR desensitization and upregulation in the absence of sufficient agonist to stimulate the receptors, there is reduced cholinergic activation of dopamine neurons. Thus, a reduction in cholinergic input to dopamine neurons along the reward pathway may result in decreased brain reward function. Nevertheless, these proposed neuroadaptations involving dopamine may only partly contribute to nicotine withdrawal symptomatology. Alterations in glutamatergic, GABAergic, opioid peptide and serotonin systems also may contribute to the negative affective aspects of nicotine withdrawal.

Glutamate–dopamine interactions

Recent evidence indicates a role of a subset of glutamatergic receptors in the increases in the acoustic startle response, a measure of reactivity to environmental stimuli, associated with nicotine withdrawal (Helton, Tizzano, Monn, Schoepp, & Kallman, 1997; Wiley, 1998). Metabotropic glutamate receptors include Group I, II, and III receptor families, which modulate synaptic function through second messenger systems (Pin & Duvoisin, 1995). Group II receptors are most likely pre-synaptic, based on the finding that activation of these receptors leads to decreased glutamatergic neurotransmission in limbic areas, such as the hippocampus and the amygdala (Battaglia, Bruno, Ngomba, Di Grezia, Copani, & Nicoletti, 1998; Pin & Duvoisin, 1995). The pre-synaptic Group II metabotropic glutamate receptor agonist LY354740 completely blocked the increased startle response induced by nicotine withdrawal (Helton *et al.*, 1997). This attenuation of a nicotine-withdrawal symptom is presumably mediated by reversing an over-excitation of the glutamatergic system resulting from chronic nicotine administration. This hypothesis is supported by evidence indicating the Group II metabotropic glutamate receptor agonist DCG-IV protected against glutamate over-excitation (Bruno *et al.*, 1995; Buisson, Yu, & Choi, 1996; Miyamoto, Ishida, & Shinozaki, 1997). Taken together, these findings indicate that glutamate systems are involved in neuroadaptations to chronic nicotine exposure. Nevertheless, the above results may not accurately predict what the effects of the same glutamate receptor agonist would be on other measures of nicotine withdrawal, such as threshold elevations. If decreased mesolimbic dopamine neurotransmission during nicotine withdrawal (Hildebrand *et al.*, 1998, 1999; Panagis *et al.*, 1998) partly mediates the threshold elevations associated with withdrawal (Epping-Jordan *et al.*, 1998b), and glutamate positively modulates mesolimbic dopaminergic neurotransmission in the VTA and nucleus accumbens, then it would be predicted that decreased glutamatergic neurotransmission would exacerbate rather than reverse nicotine withdrawal symptoms.

There is also evidence that glutamate is involved in some behavioral changes and neuroadaptations occurring with chronic nicotine administration, although these phenomena may not be directly related to withdrawal symptomatology. Examples of neuroadaptations to chronic nicotine exposure include the development of

sensitization and tolerance to nicotine. Sensitization to a drug has been defined as a long-lasting increment in response occurring upon repeated presentation of a stimulus (Segal & Mandell, 1974). In rats, locomotor activity has been used as a behavioral measure of sensitization to nicotine. In nicotine-naive rats, acute administration of nicotine decreased exploratory locomotor activity, whereas repeated administration of nicotine produced a rapid tolerance to the locomotor-depressant effects, followed by an increase in locomotor activity (Clarke & Kumar, 1983; Stolerman, Bunker, & Jarvik, 1974; Stolerman, Fink, & Jarvik, 1973). Moreover, sensitization to the locomotor activating effects of nicotine develops after repeated administration (Clarke & Kumar, 1983; Benwell & Balfour, 1992). Co-administration of NMDA receptor antagonists, such as the non-competitive antagonist MK-801 (dizocilpine) or the competitive antagonist D-CPPene, with nicotine reduced the development of tolerance to the locomotor depressant effect of nicotine, attenuated the development of tolerance to the aversive stimulus effects of nicotine as measured by conditioned taste aversion, and prevented sensitization to the locomotor activating effects of nicotine (Shoaib, Benwell, Akbar, Stolerman, & Balfour, 1994; Shoaib, Schindler, Goldberg, & Pauly, 1997; Shoaib & Stolerman, 1996). Furthermore, pretreatment with the non-competitive NMDA receptor antagonist MK-801 reduced nicotinic receptor upregulation during chronic exposure suggesting a neuroadaptation that may account for the lack of development of the behavioral adaptations (Shoaib *et al.*, 1997).

Gamma-aminobutyric acid (GABA)–dopamine interactions

Although there is some evidence for the role of GABA neurotransmission in the acute neurochemical and behavioral effects of nicotine (see above), there is little evidence indicating a potential role of GABAergic neurotransmission in nicotine withdrawal. Based on the finding that activation of GABA receptors in the VTA has an inhibitory effect on mesolimbic dopamine neurotransmission, it may be hypothesized that enhancement of GABAergic neurotransmission during nicotine withdrawal may facilitate withdrawal symptoms.

Opioid peptides

Another proposed neuroadaptation to chronic nicotine administration involves opioid peptide systems. Recent examination of the nicotine withdrawal syndrome in rats suggests that opioid systems may play a role in nicotine dependence, although the findings are inconsistent. In rats, the somatic signs of nicotine withdrawal resemble those seen in opiate withdrawal, including the symptoms of abdominal constrictions, facial fasciculation, and ptosis. This syndrome has been observed after spontaneous nicotine withdrawal, as well as withdrawal precipitated by the nicotinic acetylcholine receptor antagonists mecamylamine or chlorisondamine (Epping-Jordan *et al.*, 1998b; Hildebrand *et al.*, 1997, Malin *et al.*, 1992, 1993, 1994; Watkins *et al.*, 2000) and dihydro-β-erythroidine (Malin, Lake, Upchurch, Shenoi, Rajan, & Schweinle, 1998; however, see Epping-Jordan *et al.*, 1998b). Interestingly, the somatic signs of nicotine withdrawal also have been precipitated by the opiate antagonist naloxone in nicotine-dependent rats (Malin *et al.*, 1993; however, see Watkins *et al.*, 2000), or dansyl-RFamide, an analog of neuropeptide FF, an anti-opiate peptide (Malin *et al.*, 1996). Moreover, acute injections of morphine, an opiate agonist, reversed the somatic signs of nicotine withdrawal (Malin *et al.*, 1993). A recent study has failed to replicate these findings and indicated that doses of naloxone as high as 8 mg/kg did not induce a differential number of somatic signs of nicotine withdrawal or threshold elevations in nicotine-dependent and control subjects (Watkins *et al.*, 2000). The reason for this discrepancy is unclear at this point. Nevertheless, administration of a low naloxone dose (0.12 mg/kg), but not low nAChR antagonist doses, induced conditioned place aversions in nicotine-treated rats suggesting that conditioned place aversions are mediated by reduced opioid neurotransmission, and not reduced cholinergic neurotransmission (Watkins *et al.*, 2000). Human studies of the effects of naloxone on smoking behavior have yielded inconsistent results (Karras & Kane, 1980; Nemeth-Coslett & Griffiths, 1986). In terms of withdrawal in humans, administration of naloxone to nicotine-dependent humans produced dose-dependent increases in self-reported affective and somatic signs of nicotine withdrawal, suggesting that long-term exposure to nicotine is associated with alterations in endogenous opioid peptide systems (Krishnan-Sarin, Rosen, & O'Malley, 1999). Thus, it may be hypothesized that during chronic nicotine exposure there is a release of opioid peptides (Boyadjieva & Sarkar, 1997; Pomerleau & Pomerleau, 1984; Pomerleau & Rosecrans, 1989) which leads to a downregulation of μ-opioid receptors or opioid receptor transduction mechanisms. During nicotine abstinence (i.e., in the absence of an agonist), this downregulation of μ-opioid receptors or opioid receptor transduction mechanisms may contribute to some, but not all, aspects of nicotine withdrawal.

Serotonin (5-HT$_{1A}$) receptor function

As discussed above, the acute effects of nicotine on the serotonin system are unclear. Nevertheless, evidence suggests a role of altered serotonin neurotransmission in nicotine withdrawal. Chronic nicotine treatment produced a selective decrease in the concentration of 5-HT in the hippocampus (Benwell & Balfour, 1979), providing evidence for a neuroadaptation to nicotine. The site of action for these alterations in serotonin processes may include the median raphe nucleus, the hippocampus, and potentially the amygdala. Increases in the number of hippocampal 5-HT$_{1A}$ receptors have been measured in

chronic smokers. This receptor upregulation may reflect a reduction in the activity of serotonergic neurons within the median raphe nucleus which innervates the hippocampus, the amygdala and several other forebrain structures (Benwell, Balfour, & Anderson, 1990). The behavioral or affective consequences of this neuroadaptation are unclear, but considering the findings that serotonin deficits have been implicated in depression and anxiety (Coppen, 1967; Delgado, Charney, Price, Aghajanian, Landis, & Heninger, 1990; Delgado *et al.*, 1991; Markou *et al.*, 1998; Young, Smith, Pihl, & Ervin, 1985), it may be hypothesized that during chronic nicotine exposure and nicotine withdrawal, the decreases in serotonin function play a role in the onset of negative affective symptoms, such as depressed mood, impulsivity and irritability.

A hypothesized mechanism of action for the nicotinic-serotonergic interaction begins with nicotine stimulating nAChRs located in the somatodendritic region in the median raphe nucleus and the terminal fields in the forebrain to facilitate serotonin release. The released serotonin would then stimulate post-synaptic 5-HT_{1A} receptors located throughout the hippocampus, amygdala, and other sites to modulate some of its positive effects on mood. With chronic nicotine treatment, the nicotinic receptor desensitization would lead to an upregulation in both pre-synaptic nicotinic and post-synaptic 5-HT_{1A} receptors to maintain baseline functional activity within the terminal regions. During nicotine abstinence, as the previously desensitized nicotinic receptors begin to recover to the pre-nicotine functional state, the absence of nicotine to stimulate these receptors combined with the upregulated post-synaptic 5-HT_{1A} serotonergic receptors may be hypothesized to contribute to decreased serotonergic function leading to the depressed mood often reported during nicotine withdrawal (Hughes *et al.*, 1991). An additional hypothesis involves an effect of nicotine on 5-HT_{1A} raphe autoreceptors.

Other brain sites where alterations in serotonin function could modulate the depressed mood associated with nicotine withdrawal include serotonin projections to the hypothalamus. The hypothalamus also contains post-synaptic 5-HT_{1A} receptors, as well as nAChRs located on pre-synaptic 5-HT terminals (Schwartz *et al.*, 1984). The lateral hypothalamus has significant projections to and from components of the extended amygdala (Heimer *et al.*, 1991; Usuda, Tanaka, & Chiba, 1998). Thus, alterations in serotonin function within the hypothalamus could also be hypothesized to modulate some of the changes in reward processes measured by intracranial self-stimulation of the lateral hypothalamus.

A different type of alteration in serotonin function may underlie the increased reactivity to environmental stimuli observed during nicotine withdrawal. Increased startle reactivity has been measured in rats during nicotine withdrawal (Helton, Modlin, Tizzano, & Rasmussen, 1993; Rasmussen, Czachura, Kallman, & Helton, 1996). In rats withdrawing from nicotine, pre-treatment with the 5-HT_{1A} antagonists NAN-190, LY206130, or WAY-100635 significantly reduced the withdrawal-induced increase in the startle response (Rasmussen, Kallman, & Helton, 1997). The exact mechanism and site of action for this reduction in startle reactivity is unknown. Nevertheless, it is hypothesized that the increased startle response observed during nicotine withdrawal is due to a decrease in the availability of synaptic serotonin because serotonin has an inhibitory influence on startle (Geyer, Peterson, & Rose, 1980; Geyer, Puerto, Menkes, Segal, & Mandell, 1976). Antagonism of 5-HT_{1A} autoreceptors in the raphe nuclei then would lead to an increase in serotonin release, effectively attenuating nicotine withdrawal, reflected in decreased startle reactivity. Interestingly, however, administration of p-MPPI, a 5-HT_{1A} receptor antagonist, did not reverse either threshold elevations or the somatic signs of nicotine withdrawal (Harrison *et al.*, 1999). These results, taken together, indicate that different symptoms of nicotine withdrawal may be mediated by different neurobiological alterations within the serotonergic system.

Corticotropin-releasing factor (CRF)

Alterations in brain stress systems also may contribute to the negative affective symptoms associated with nicotine withdrawal. Specifically, overactivity of the stress hormone corticotropin-releasing factor (CRF) may underlie the symptoms of anxiety, increased stress, and irritability often reported by abstinent smokers. The hypothesis that CRF is activated during nicotine withdrawal is based on the observation that acute withdrawal from nicotine can produce an increase in circulating corticosterone (Benwell & Balfour, 1979) and that CRF has been shown to be increased during withdrawal from chronic administration of other major drugs of abuse, including cocaine, ethanol, and cannabinoids (Baldwin, Rassnick, Rivier, Koob, & Britton, 1991; Rodriguez de Fonseca, Carrera, Navarro, Koob, & Weiss, 1997; Sarnyai, Biro, Gardi, Vecsernyes, Julesz, & Telegdy., 1995).

Nicotine and depression

During the last 20 years, an association has been observed between withdrawal from smoking and negative affect, including anxiety, frustration, anger, and depressed mood (Pomerleau, Adkins, & Pertschuk, 1978; Waal-Manning & de Hamel, 1978). The relationship between depressed mood and smoking is suggested by estimates indicating that up to 60% of smokers have a history of clinical depression (Glassman, Stetner, & Walsh, 1988; Hughes, Hatsukami, Mitchell, & Dahlgren, 1986). Epidemiological results from a sample of 3213 respondents demonstrated that the incidence of Major Depressive Disorder among smokers was twice that of non-smokers (Glassman *et al.*, 1990). Moreover, smokers who had a history of clinical depression were half as

likely to succeed in quitting smoking than smokers without depressive histories (14% versus 28%) (Glassman *et al.*, 1990). Prospective studies also showed that non-smokers scoring high on a depression inventory were more likely to be smokers 14 months later than individuals who scored low on this inventory (Breslau, Kilbey, & Andreski, 1993). From most of the studies reviewed above, it is unclear whether individuals who suffer from depressive symptomatology are more likely to initiate smoking or whether depressive symptoms are induced or exacerbated by long-term smoking (Markou *et al.*, 1998). As discussed above, nicotine has been hypothesized to produce an initial increase in serotonergic function, an effect that may be particularly reinforcing for individuals who suffer from chronically low levels of serotonin contributing to depressed mood. This effect on serotonin, however, is transient and nicotine's antidepressant actions may involve the recruitment of other neurochemical systems to alleviate depression, such as suppression of corticotropin-releasing factor, increased opioid activity, or increased dopaminergic function. Whatever the mechanism for the antidepressant actions of nicotine, smokers who report 'negative affect' as a reason for smoking are likely to fail at smoking cessation (Pomerleau *et al.*, 1978).

Recognition of the role of negative affect in smoking behavior has led to the use of antidepressant drugs to aid in smoking cessation programs. Early studies with the tricyclic antidepressant doxepin, which inhibits the reuptake of serotonin, norepinephrine, and to a lesser extent, dopamine (Stahl, 1997), showed promise as an aid to smoking cessation (Edwards, Murphy, Downs, Ackerman, & Rosenthal, 1989), but no further studies on doxepin have been reported. Investigation of another tricyclic antidepressant, nortriptyline, as an adjunct to smoking cessation indicated some effectiveness in promoting cessation. Results from a double-blind, placebo-controlled study showed that 14% of patients who received 75 mg of nortriptyline per day for 2 months were still abstinent after 6 months (Prochazka, Weaver, Keller, Fryer, Licari, & Lofaso, 1998). Self-reported withdrawal symptoms including irritability, anxiety, and difficulty concentrating were significantly reduced by day 8 of treatment in patients who received nortriptyline compared to placebo (Prochazka *et al.*, 1998). Interestingly, selective serotonin reuptake inhibitors appear not to affect smoking behavior in heavy smokers (Sellers, Naranjo, & Kadlec, 1987), suggesting that serotonin is probably only one of several neurotransmitters involved in nicotine dependence. Most recently, the effects of a sustained-release form of buproprion on smoking cessation have been investigated. Buproprion is a weak inhibitor of norepinephrine and dopamine uptake but does not affect serotonin reuptake (Ascher *et al.*, 1995). Results from two double-blind, placebo-controlled studies indicated that 23–30% of subjects who received 300 mg of buproprion per day for approximately 2 months were still abstinent after 1 year, values almost twice that of subjects receiving placebo (Hurt *et al.*, 1997; Jorenby *et al.*, 1999). Thus, preliminary results from clinical trials using antidepressants as an adjunct to smoking cessation suggest that dopamine and norepinephrine function, perhaps more so than serotonin, modulate some of the negative affective changes associated with nicotine withdrawal.

Nicotine and schizophrenia

Schizophrenia presents another promising area of research into the complex action of nicotinic receptor function in affective abnormalities seen in psychiatric populations. Patients with schizophrenia have the highest incidence of smoking, with some estimates exceeding 90%, compared to 25% of the general population (Glassman, 1993; Hughes *et al.*, 1986). Individuals with schizophrenia commonly smoke high-tar cigarettes and extract more nicotine from cigarettes than smokers without schizophrenia (Hughes *et al.*, 1986; Olincy, Young, & Freedman, 1997). The high rate of cigarette smoking among schizophrenia patients has been suggested to reflect an attempt to reduce neuroleptic-induced side-effects (Jarvik, 1991). Results from studies on smoking and the side-effects of antipsychotics have been mixed, with a few reports of diminished neuroleptic-induced dyskinesias among schizophrenia patients who smoke (Decina, Caracci, Sandik, Berman, Mukherjee, & Scapicchio, 1990; Goff, Henderson, & Amico, 1992; Sandyk, 1993), with other reports of increased tardive dyskinesia among smokers (Wirshing, Engle, Levin, Cummings, & Rose, 1989; Yassa, Lal, Korpassy, & Ally, 1987), and still other findings indicating no difference between smokers and non-smokers (Menza, Grossman, Van Horn, Cody, & Forman, 1991). From anecdotal reports, only a small percentage of schizophrenia patients report smoking to reduce the side-effects of antipsychotic medications (Dalack & Meador-Woodruff, 1996).

Another hypothesis involves the negative symptoms of schizophrenia, symptoms which include anhedonia (i.e., diminished interest or pleasure), avolition (i.e., lack of motivation), and affective flattening (American Psychiatric Association, 1994). It may be hypothesized that schizophrenia patients attempt to self-medicate their negative symptoms by smoking, symptoms which tend to be most resistant to currently available antipsychotic treatments (Jibson & Tandon, 1998; Krystal, D'Souza, Madonick, & Petrakis, 1999; Marder, Wirshing, & Van Putten, 1991; Moller, 1998; Wirshing *et al.*, 1989). As noted above, nicotine increases burst firing of dopamine neurons along the mesocorticolimbic pathway resulting in a net increase in extracellular dopamine in both the nucleus accumbens and the prefrontal cortex (Grenhoff, Aston-Jones, & Svensson, 1986; Nisell *et al.*, 1995; Pich, Pagliusi, Tessari, Talabot-Ayer, Hooft van Huijsduijnen, & Chiamulera, 1997; Svensson, Grenhoff, & Engberg, 1990). Schizophrenia patients exhibit a reduction in

metabolic activity in the prefrontal cortex, known as hypofrontality, which has been hypothesized to be associated with the negative symptoms of schizophrenia (Weinberger, Berman, & Ilowsky, 1988). The increased dopamine release in the prefrontal cortex may be hypothesized to lead to a reduction in the negative symptoms of schizophrenia and as such, the high incidence of smoking among schizophrenia patients may reflect an attempt at self-medication (Markou *et al.*, 1998; Svensson *et al.*, 1990).

Deficits in inhibitory mechanisms which regulate the processing of sensory information are also characteristic of patients with schizophrenia. Individuals with schizophrenia exhibit disrupted prepulse inhibition of the acoustic startle reflex that reflects a sensorimotor gating deficit (Geyer & Braff, 1987). Such sensory gating deficits may be reversed by nicotine administration through tobacco smoking. It has been shown that acute or chronic administration of nicotine improves prepulse inhibition of the acoustic startle response under baseline conditions in rats (Acri, Brown, Saah, & Grunberg, 1995; Curzon, Kim, & Decker, 1994). Further, animal models of the sensorimotor gating response indicate that alterations in dopamine neurotransmission may modulate sensory processing deficits (Swerdlow, Braff, & Geyer, 1990; Swerdlow, Braff, Geyer, & Koob, 1986; Swerdlow, Caine, & Geyer, 1992; Swerdlow & Geyer, 1993). In rats, depletion of dopamine in the prefrontal cortex or the nucleus accumbens reduced prepulse inhibition of the acoustic startle response, an effect similar to the sensorimotor gating deficit seen in patients with schizophrenia (Bubser & Koch, 1994; Geyer & Braff, 1987; Swerdlow & Geyer, 1998). While the above studies suggest that a reduction in dopamine mediates some alterations in sensorimotor gating, evidence indicates that alterations in nicotinic receptor function also may contribute to sensory gating deficits (see below).

Another measure of sensory gating is the P50 or N40 auditory event-related potential in humans and rats, respectively (Freedman, Adler, Myles-Worsley, Nagamoto, Miller, Kisley, McRae, Cawthra, & Waldo, 1996). Rats raised in social isolation showed abnormal sensory gating, as reflected in both prepulse inhibition and N40 event-related potentials, similar to deficits exhibited by patients with schizophrenia (Geyer, Wilkinson, Humby, & Robbins, 1993; Stevens, Johnson, & Rose, 1997). The abnormal N40 auditory gating in socially isolated rats was temporarily reversed by acute administration of nicotine (Stevens *et al.*, 1997), suggesting that activation of nAChRs by nicotine transiently normalizes sensory gating. Similarly, patients with schizophrenia fail to suppress the P50 auditory event-related potential to repeated stimuli, which appears to be correlated with decreased vigilance and distractibility (Adler, Pachtman, Franks, Pecevich, Waldo, & Freedman, 1982; Clementz, Geyer, & Braff, 1997; Cullum *et al.*, 1993; Griffith, O'Neill, Petty, Garver, Young, & Freedman, 1998). Similar to studies in rats, nicotine administration also transiently reversed the P50 deficits seen in patients with schizophrenia (Adler, Hoffer, Wiser, & Freedman, 1993). The failure to suppress the P50 response in patients with schizophrenia may be related to alterations in nAChR function, specifically activity of $\alpha 7$ nicotinic receptors in the hippocampus. Post-mortem brain analyses revealed that schizophrenics have reduced numbers of $\alpha 7$ nicotinic receptors in the hippocampus (Freedman, Hall, Adler, & Leonard, 1995). Within the hippocampus, nicotine has been shown to induce glutamate release through activation of $\alpha 7$ nicotinic receptors (Gray *et al.*, 1996), thus leading to the hypothesis that enhanced hippocampal glutamate release modulates sensory gating (Dalack, Healy, & Meador-Woodruff, 1998). It has been postulated that initial auditory stimulation activates $\alpha 7$ nicotinic receptors in the hippocampus to release glutamate (Leonard *et al.*, 1996). Glutamate then would activate receptors on GABA interneurons to release GABA and inhibit hippocampal neurons, thus reducing activation by further auditory stimulation (Leonard *et al.*, 1996). Accordingly, it has been suggested that smoking facilitates activation of $\alpha 7$ nicotinic receptors to effectively normalize attentional processing in patients with schizophrenia (Dalack *et al.*, 1998). Similar to all other nAChRs, $\alpha 7$ receptors are activated by nicotine or acetylcholine and then become desensitized to further stimulation (Seguela, Wadiche, Dineley-Miller, Dani, & Patrick, 1993). Interestingly, the finding of decreased $\alpha 7$ receptor expression in the hippocampus of schizophrenia smokers suggests that the $\alpha 7$ receptor may not upregulate in the presence of chronic nicotine. Thus, the neuropharmacological basis of increased smoking among schizophrenic patients may be hypothesized to also involve stimulation of nAChRs composed of α and β subunits in addition to $\alpha 7$ receptor activation.

Neurobiology of acute and protracted nicotine abstinence–synthesis

A large proportion of smokers, at some point in their smoking career, have tried to quit, albeit unsuccessfully. Only 10–20% of those who attempt to quit are still abstinent after 1 year. The determining factors for relapse include craving for nicotine and negative emotional states including depressed mood and psychosocial stress (Doherty, Kinnunen, Militello, & Garvey, 1995; Swan, Ward, & Jack, 1996). Interestingly, the best predictor of relapse between 4 and 12 months of abstinence was smoking at least one cigarette between the quitting day and 4 months (Nides *et al.*, 1995). This finding suggests that a heightened sensitivity to the reinforcing value of nicotine persists into periods of protracted abstinence. These powerful reinforcing effects could be especially detrimental for anyone attempting to quit smoking, in that a single relapse episode may progress rapidly to a full relapse.

From the data reviewed above, it is possible to develop a preliminary hypothesis of the neurobiological mechanisms underlying acute nicotine withdrawal. Based on the evidence of decreased dopamine in both the nucleus accumbens and the central nucleus of the amygdala during precipitated nicotine withdrawal (Hildebrand *et al.*, 1998; Panagis, Hildebrand, Svensson, & Nomikos, 1998), it may be hypothesized that adaptations of dopamine function in components of the extended amygdala partly modulate the depressed mood and dysphoria associated with acute nicotine withdrawal. These affective changes may be the best predictors of relapse to cigarette smoking. Alterations in serotonin function also are proposed to be involved in affective as well as sleep- and appetite-related changes during acute nicotine withdrawal.

It has been suggested that long-term drug exposure contributes to a change in hedonic set point which may increase the positive reinforcing efficacy of the drug (Koob & LeMoal, 1997). Thus, the neuroadaptations proposed to occur with long-term, chronic nicotine exposure would be hypothesized to play a role in protracted abstinence from nicotine by contributing to a heightened sensitivity to the positive reinforcing effects of nicotine. As discussed above, one of the effects of nicotine withdrawal is decreased dopamine neurotransmission within the mesolimbic dopamine system. The initial decrease in dopamine is hypothesized to modulate some of the negative affective symptoms associated with acute nicotine withdrawal; however, the role of adaptive mechanisms within the mesolimbic dopamine system during protracted abstinence is unknown.

While the proposed long-term alterations in the dopaminergic reward system may contribute to an increased sensitivity to nicotine during protracted abstinence, the effects, even during acute withdrawal, are not dramatic. Other neuropharmacological mechanisms such as alterations in opioid peptide function, serotonin, and even glutamate may be speculated to have a role. Evidence suggests that stress systems in the brain also may play a major role in vulnerability to relapse. Potential recruitment of systems such as corticotropin-releasing factor have been hypothesized to extend into periods of protracted abstinence, thus contributing to an increased stress response and anxiety during abstinence (Kreek & Koob, 1998). Increased corticotropin-releasing factor function has been measured in the amygdala during withdrawal from opiates, cocaine, ethanol, and cannabinoids and may modulate the stress response during abstinence (Heinrichs, Menzaghi, Schulteis, Koob, & Stinus, 1995; Koob, Heinrichs, Menzaghi, Merlo Pich, & Britton, 1994; Pich *et al.*, 1996; Richter & Weiss, 1999). As such, activation of brain stress systems may contribute to negative symptoms of withdrawal. It also has been suggested that an overactive stress response may make an individual vulnerable to relapse (Kreek & Koob, 1998). While the effects of acute nicotine and withdrawal on corticotropin-releasing factor function are unclear, one can speculate that acute nicotine decreases corticotropin-releasing factor, contributing to a sense of relaxation and calm, whereas nicotine withdrawal is characterized by increased corticotropin-releasing factor function, contributing to an increased stress response during abstinence. It is further hypothesized that increased corticotropin-releasing factor function persists into protracted nicotine abstinence, thus contributing to an increased vulnerability for relapse. An individual with a heightened corticotropin-releasing factor-induced stress response may be more likely to revert to previously learned coping patterns (i.e., smoking to facilitate relaxation).

To summarize, the transition from occasional or recreational drug use to dependence may involve 'affective habituation' or a change in hedonic set point, such that abstinence leads to negative affective consequences, thus contributing to the maintenance of drug dependence through negative reinforcement processes (Koob, 1996; Koob & Le Moal, 1997). Furthermore, the change in hedonic set point may be reflected in an increase in drug taking behavior (Ahmed & Koob, 1998). For nicotine, the transition from occasional cigarette smoking to chronic, dependent use in humans may involve an increase in hedonic set point requiring increased nicotine intake to reach the desired level of stimulation. The underlying mechanisms for alterations in hedonic processes that occur with chronic nicotine exposure are hypothesized to involve decreased dopamine, serotonin, and opioid peptide function, and activation of corticotropin-releasing factor function within the extended amygdala. These neurochemical alterations would require increased nicotine intake to reach and maintain a certain level of hedonic function within the midbrain reward pathways while concurrently avoiding the onset of affective withdrawal symptoms. During abstinence, the increase in hedonic set point is hypothesized to persist, and with the experience of the negative affective symptoms of withdrawal, the abstinent smoker would be especially vulnerable to relapse.

Based on the current knowledge of the neurobiology of nicotine withdrawal and the proposed neuroadaptations occurring in the presence of chronic nicotine, several avenues of pharmacological treatment of nicotine dependence warrant consideration. As discussed above, a negative affective state may be the best predictor of relapse to cigarette smoking and pharmacological therapies designed to alleviate negative affect induced by nicotine withdrawal should be explored. Serotonergic dysfunction has been hypothesized to partially modulate negative affect during withdrawal, but additional studies are needed to fully explore the role of serotonin in nicotine withdrawal. It also has been suggested that decreased dopamine function may underlie some of the negative affective symptoms of nicotine withdrawal. Therefore, the development of therapeutic compounds that target the mesolimbic dopamine system as an aid to smoking cessation should be

examined. Another promising treatment approach to aid in smoking cessation is regulation of stress systems involving corticotropin-releasing factor. Antagonists of corticotropin-releasing factor receptors may help reduce the symptoms of anxiety, frustration, and irritability associated with nicotine withdrawal which would likely contribute to significantly higher success rates of abstinence. Finally, further exploration into glutamate pathways involved in nicotine withdrawal symptoms could serve as the basis for the development of NMDA or metabotropic glutamate receptor compounds which may help to alleviate some of the impairment in cognitive abilities associated with nicotine withdrawal. Overall, from the above review and hypotheses, the focus of neuropharmacological research for the development of novel pharmacotherapies for nicotine addiction should involve manipulations of central serotonergic, dopaminergic, corticotropin-releasing factor, and glutamatergic systems.

Conclusions

In conclusion, the positive reinforcing effects of nicotine appear to be modulated through direct and indirect stimulatory actions on the mesolimbic dopamine system via actions on glutamatergic, GABAergic, opioid peptide, and serotonergic systems. In the presence of chronic nicotine, neurochemical adaptations occur to mediate the symptoms of nicotine withdrawal. The neurobiology of acute nicotine withdrawal and protracted abstinence is proposed to involve alterations within dopaminergic, serotonergic, opioid peptide, and possibly corticotropin-releasing factor systems, which are hypothesized to contribute to the negative affective state associated with nicotine abstinence. While the hypothesized underlying neurobiological mechanisms mediating the negative affective aspects of nicotine withdrawal are mostly speculative, these hypotheses have heuristic value. Future experiments exploring these hypotheses will yield important information about the central actions of nicotine and advance our knowledge of the neural mechanisms involved in nicotine dependence and withdrawal, and the role of cholinergic neurotransmission in depression and schizophrenia. Thus, such investigations may aid the development of new pharmacological agents for smoking cessation, depression, and schizophrenia.

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