ELSEVIER

Pharmacology, Biochemistry and Behavior 71 (2002) 757–771

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Involvement of serotonin in nicotine dependence: Processes relevant to positive and negative regulation of drug intake

Peter Olausson[a,*], Jörgen A. Engel[b], Bo Söderpalm[c]

[a]*Department of Psychiatry, Laboratory of Molecular Psychiatry, Yale University, 34 Park Street, New Haven, CT 06508, USA*
[b]*Department of Pharmacology, Göteborg University, Box 431, 405 30, Göteborg, Sweden*
[c]*Department of Clinical Neuroscience, Göteborg University, Blå stråket 7, 405 30, Göteborg, Sweden*

Received 18 April 2001; received in revised form 30 August 2001; accepted 6 September 2001

Abstract

The neurobiological substrate of nicotine dependence has been the subject of extensive preclinical and clinical research. Many experimental reports have implicated the brain serotonin (5-HT) systems in processes relevant to nicotine dependence, but the specific role of this neurotransmitter system largely remains to be elucidated. This review will focus on the role of 5-HT in the acute and chronic effects of nicotine. In particular, the evidence for a role of 5-HT neurotransmission in brain processes thought to be involved in positive and negative control of nicotine use will be examined, and potential clinical implications discussed.

Keywords: Serotonin; Dopamine; Smoking; Nicotine; Incentive motivation; Craving; Impulsivity; Inhibitory control

1. Background

Nicotine is for many individuals the first dependence-producing drug that is used habitually, and several epidemiological surveys have indicated that most drug addicts were smokers before they began to abuse alcohol or illicit drugs. This relationship can also be observed later in the addictive career, and a majority of drug abusers use multiple drugs of which nicotine almost always is one. Needless to say, the facts that nicotine is legal and the availability of nicotine in society is high, features shared with alcohol, can to a large extent explain the widespread use of nicotine. But whereas repeated exposure to large amounts of alcohol over extended periods of time appears to be required for the development of alcoholism, a much more limited exposure to nicotine seems sufficient to initiate nicotine dependence. Interestingly, a number of scientific investigations have demonstrated that chronic administration of nicotine to experimental animals also increases self-administration of other classes of drugs of abuse, e.g., alcohol and cocaine (Blomqvist et al., 1996; Horger et al., 1992; Pothoff et al., 1983). These observations could indicate that nicotine predisposes future intake of other dependence-producing drugs, and therefore it may be of particular interest to investigate the neurobiological alterations produced by repeated intake of nicotine as well as behavioral consequences of this exposure.

Drug abuse is a pathological state characterized by compulsive drug-seeking and drug-taking associated with a profound risk for relapse even after extended drug-free periods. This compulsive drug use takes place at the expense of more appropriate and beneficial normal activities, often resulting in an inability to pursue a normal life. The use of nicotine per se is, however, different in this respect, since serious social consequences rarely are observed in smokers. This may partly be explained by the fact that the acute pharmacological consequences of nicotine do not impair normal functions in the smoking individual and, in contrast to those of, e.g., ethanol, may actually enhance rather than decrease cognitive function (Rezvani and Levin, 2001).

2. Positive and negative control over drug-taking behavior

Drugs of abuse produce a wide variety of pharmacological effects in the human body. Besides their rewarding effects, repeated exposure to these substances causes neuroadaptive alterations that result in adverse physical and

* Corresponding author. Tel.: +1-203-974-7752; fax: +1-203-974-7897.
E-mail address: peter.olausson@yale.edu (P. Olausson).

0091-3057/02/$ – see front matter
PII: S0091-3057(01)00673-6

psychological effects. These effects are emphasized in the diagnostic criteria for drug dependence according to the widely used Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association) and include items related to drug tolerance and withdrawal reactions, drug craving (i.e., the urge or desire to use the drug) and compulsion to take the drug. Other criteria are related to the loss of control both over the drug intake and the social situation often observed in drug addicts.

Interestingly, nicotine and other addictive drugs produce similar pharmacodynamic effects in neuronal circuits involved in enhancing and reducing the incentive motivation to use the drug, i.e., neural systems involved in "positive" and "negative" control of behavior. Below follows a brief outline of the available support for an involvement of brain dopamine (DA) and serotonin (5-HT) systems in such positive and negative behavioral control followed by a review of our own and others' studies on the acute and chronic effects of nicotine on these systems, as well as some associated behavioral consequences that may potentially be important for the expression of addictive behaviors.

3. Mechanisms involved in positive control of addictive behaviors

Craving was early recognized as an important element in alcohol dependence (Jellinek et al., 1955), and today drug craving is often considered to be an important incentive motivational factor for obtaining and consuming drugs. Craving can be elicited both by internal or external cues, and the subjective quality and intensity of craving varies with personal characteristics as well as environmental circumstances. The incentive-sensitization theory of addiction, advanced by Robinson and Berridge (1993), hypothesizes that long-lasting neuroadaptive processes induced by repeated drug exposure, that are implicated in behavioral and neurochemical sensitization (see below), are involved in transforming the wanting of a drug into craving, and that the incentive motivational value of drug-associated (conditioned) enviromental stimuli is augmented and provides strong impulses for obtaining and consuming the drug. In support of this theory, animal experiments have demonstrated that previous drug experience increases subsequent self-administration both of alcohol (Blomqvist et al., 1996; Fahlke et al., 1994), amphetamine (Piazza et al., 1990; Pierre and Vezina, 1997) and cocaine (Horger et al., 1990, 1992). Moreover, preexposure to drugs enhances the rewarding and incentive motivational effects of nicotine, psychostimulants and opiates in the conditioned place preference paradigm (Lett, 1989; Shippenberg and Heidbreder, 1995; Shoaib et al., 1994). Other theories have implicated the adverse withdrawal state (Dackis and Gold, 1985) or dysregulation of hedonic homeostasis (Koob and Le Moal, 2001) as important mechanisms underlying incentive motivation for drug intake.

Associative learning (Pavlovian conditioning) is a central component of the incentive-sensitization theory. During conditioning, associative memories between the subjective effects of certain events (e.g., drug effects) and environmental cues or actions are formed. Thus, environmental stimuli (e.g., money, a place or a person) that repeatedly have been associated with the subjective drug effects eventually become conditioned cues that predict the availability of the drug and elicit both craving and drug-seeking behavior. Experimental observations in humans support this notion since cocaine addicts report elevated craving when watching drug-related movies (Childress et al., 1999).

Taken together, the incentive-sensitization theory proposes that the development of drug dependence and abuse is the result of abnormal motivational and/or associative stimulus-response learning processes. The general loss of behavioral control in drug abuse may not, however, be completely explained by this hypothesis. Therefore, a combination of this theory with other pathological mechanisms may more appropriately explain the multifaceted nature of drug abuse.

4. Systems involved in negative control of inappropriate behavior

The lack of control over drug intake and the social situation observed in drug abuse suggest impaired function in the brain inhibitory control systems that normally are involved in negative control of maladaptive behaviors. These systems counterbalance potentially inappropriate behaviors by transiently suppressing unconditioned or conditioned responses allowing slower cognitive processes to subsequently direct behavior (Jentsch and Taylor, 1999). Inhibitory control has also been implicated in the decision-making process, in which inhibitory control is given an important role in the functional output of making good decisions and plans (Damasio, 1996). The brain inhibitory control systems and executive function have also been proposed to constitute a behavioral monitoring system (Shallice and Burgess, 1996), which can suppress the expression of behaviors elicited via unconscious mechanisms that are inappropriate for the situation, implicating conscious mechanisms in inhibitory control. However, while a lack of inhibitory control is a core feature of impulsivity, other factors, like decision time, persistence and sensation seeking are also important for the expression of impulsive behavior in man (Evenden, 1998a).

Since several items of the DSM-IV diagnostic criteria both for substance dependence and abuse contain elements of impulsivity, drug addiction could be considered an impulse control disorder. The notion that inhibitory control is impaired in drug addicts is supported by several clinical observations. For example, drug addicts primarily using alcohol (Hallman et al., 1991; Lejoyeux et al., 1998; von Knorring et al., 1984), nicotine (Bickel et al., 1999; Mitchell, 1999; von Knorring et al., 1987), cocaine (Moeller et al.,

1994; Rosenthal et al., 1990), amphetamine (Williamson et al., 1997), methylenedioxy-methamphetamine (MDMA "ecstasy," McCann et al., 1994; Morgan, 1998) and phencyclidine (PCP, Rawson et al., 1981) display impulsive behavior when tested on neuropsychological tasks, as well as a disinhibited personality (e.g., extrovert, impulsive and risk-taking) when assessed using personality questionnaires (Mitchell, 1999; von Knorring and Oreland, 1985; von Knorring et al., 1987).

A large number of experimental findings have implicated the brain 5-HT systems in the neuronal circuits that mediate inhibitory control of behavior. In experimental animals, 5-HT depletion consistently produces an impulsive behavioral pattern, including inability to withhold responding for small immediate in favor of large delayed rewards, anticipatory responses in various animal models and aggressivity (Davidson et al., 2000; Hollander and Rosen, 2000; Soubrie, 1986). 5-HT has also been implicated in inhibitory control of incentive motivational impulses associated with appetitive stimuli in the absence of a conflict situation. Thus, a brain 5-HT depletion that reduces 5-HT neurotransmission increases responding for conditioned reward, whereas manipulations that facilitate brain 5-HT neurotransmission decreases responding for conditioned reinforcers as well as the amphetamine-induced enhancement of this behavior (Fletcher, 1996; Fletcher and Korth, 1999; Fletcher et al., 1999). A direct link to 5-HT involvement in the regulation of drug intake is provided by findings showing that manipulations which decrease brain 5-HT neurotransmission (e.g., a neurotoxic 5-HT depletion or a lasting 5-HT synthesis inhibition) elevate self-administration of several different drugs in rats (Engel et al., 1992; LeMarquand et al., 1994b; Roberts et al., 1994) and compounds that facilitate 5-HT neurotransmission, like selective 5-HT reuptake inhibitors, decrease voluntary ethanol consumption in rats (for review, see LeMarquand et al., 1994b). Similar effects of 5-HT enhancing drugs have been reported on the intake of nicotine (Opitz and Weischer, 1988), opiates (Higgins et al., 1994) and psychostimulants (Porrino et al., 1989; Walsh and Cunningham, 1997) as well as on intracranial self-stimulation (Olds, 1994; Redgrave, 1978). Since drugs that augment brain 5-HT neurotransmission also reduce the intake of natural rewards (food and fluids), Amit et al. (1991) suggested that the effects of these serotonergic agents are global in nature and not specific to any single consummatory behavior. However, these observations suggest that an increase in 5-HT neurotransmission could reduce drug consumption by means of strengthening inhibitory control.

The involvement of 5-HT in inhibitory control is also supported by clinical observations showing that individuals suffering from impulsive behavior or impulse control disorders display signs of decreased 5-HT neurotransmission (i.e., low concentrations of 5-HIAA in the cerebrospinal fluid or low platelet MAO; af Klinteberg et al., 1987; Åsberg et al., 1976; Linnoila et al., 1983). A reduced number of brain 5-HT reuptake transporters, indicative of a low number of 5-HT neurons, as also been demonstrated in impulsive, violent humans (Tiihonen et al., 1997). Conversely, drugs that facilitate brain 5-HT neurotransmission, like selective 5-HT reuptake inhibitors, are effective in the treatment of some of these psychiatric disorders (Hollander and Rosen, 2000).

A key question regarding the relationship between impulsive personality traits, signs of deficient inhibitory control in experimental settings, and low 5-HT neurotransmission on one hand and drug dependence on the other is whether these behavioral and neurochemical features are a cause and/or a result of drug abuse. Some of the studies discussed below have tried to shed light on this issue using experimental animals.

5. The involvement of DA and 5-HT in positive control of drug-taking behavior

In 1954, Olds and Milner (Olds and Milner, 1954) were the first to report that experimental animals operantly respond for electrical self-stimulation of certain neuronal pathways via electrodes implanted in distinct regions of the brain. Most brain sites in which ICSS can be established are located in the diencephalic medial forebrain bundle, the ventral tegmental area (VTA), the ventral striatum (i.e., the nucleus accumbens), the prefrontal cortex, the hippocampus and the amygdala (Fibiger et al., 1987; Wise and Rompre, 1989; Wise et al., 1992), regions that are innervated by the mesocorticolimbic DA neurons, which originate in the VTA. Experimental animals also self-administer drugs abused by humans systemically or directly into the mesocorticolimbic DA system and several studies have demonstrated that, as a common denominator, drugs of abuse increase the extracellular DA levels in the ventral striatum (Koob, 1992; Wise and Rompre, 1989; Wise et al., 1992). Furthermore, lesioning or pharmacological impairment of mesolimbic DA neurotransmission prevents the acquisition of self-administrating behavior and/or disrupts established drug self-administration. Thus, mesocorticolimbic DA neurons have frequently been implicated in positive control of drug-seeking/consummatory behavior, and the involvement of this neural pathway in the neurobiological substrate of drug addiction and nicotine dependence has been the subject of a large number of comprehensive reviews (Balfour et al., 1998, 2000; Di Chara 2000a,b; Di Chiara et al., 1999; Koob, 1992; Koob and Le Moal, 1997; Everitt et al., 1999; Spanagel and Weiss, 1999).

5.1. Acute effects of nicotine on DA and 5-HT neurotransmission

Acute systemic administration of drugs of abuse produces a variety of neurochemical effects which are specific for each drug, but, as mentioned above, a shared feature of these substances is their ability to increase DA neurotransmission

in the rodent brain (Engel, 1977; Koob, 1992). Thus, nicotine elevates both the firing frequency and the burst firing of mesolimbic DA neurons (Grenhoff and Svensson, 1988; Grenhoff et al., 1986) and this activation increases the extracellular DA levels in the ventral striatum (Benwell and Balfour, 1992; Di Chiara and Imperato, 1988; Imperato et al., 1986; Mifsud et al., 1989; Nisell et al., 1994), most likely reflecting enhanced synaptic DA release. Recent data indicate that stimulation of nicotinic acetylcholine receptors of the $\alpha4\beta2$ subtype located on DA neurons in the VTA is mediating some of the effects of nicotine on neurochemistry (Schilström, 2000). However, processes mediated via other nicotine receptor subtypes may also be involved in the DA activation produced by nicotine. A behavioral consequence of the drug-induced activation of mesolimbic DA neurons is stimulation of locomotor activity (Wise and Bozarth, 1987), resulting from activation of postsynaptic DA receptors in the ventral striatum (Jackson et al., 1975; Kelly et al., 1975; Pijnenburg and van Rossum, 1973). Nicotine increases locomotor activity in animals that have been habituated to the testing environment. This activation is reduced by administration of DA receptor antagonists systemically or locally in the ventral striatum, or by lesions of the mesolimbic DA neurons (Clarke, 1990; Clarke et al., 1988). However, nicotine has also been reported to decrease exploratory locomotor activity in nonhabituated animals suggesting a state-dependent effect of nicotine on this behavior (Stolerman, 1999). Finally, the mesolimbic DA activating effect of nicotine has been linked to its reinforcing effects (Corrigall et al., 1992; Pich et al., 1997) and, thus, to positive control of reward-directed behavior.

Besides the midbrain DA systems, drugs of abuse also interact with other neurotransmitter systems. For example, in addition to their stimulatory effects on DA neurotransmission, ethanol (Yoshimoto et al., 1991), amphetamine (Kuczenski and Segal, 1989; Kuczenski et al., 1995), cocaine (Parsons and Justice, 1993), opiates (Grauer et al., 1992) and PCP (Martin, 1998) also elevate the extracellular concentrations of 5-HT in different brain regions. Nicotine increases the release of 5-HT from striatal synaptosomes in vitro (Reuben and Clarke, 2000) and administration of a high dose of nicotine elevates extracellular frontocortical 5-HT levels in vivo (Ribeiro et al., 1993). In contrast, acute nicotine decreases 5-HT biosynthesis as well as the extracellular 5-HT levels in the hippocampus (Balfour and Ridley, 2000; Benwell and Balfour, 1982). Since 5-HT has been given a role in the modulation of mesocorticolimbic DA activity (for review, see Kelland and Chiodo, 1996), the nicotine-induced effects on 5-HT neurotransmission in the frontal cortex, and other brain regions influencing mesocorticolimbic DA activity, could modulate the nicotine-induced stimulation of DA neurotransmission and locomotor activity. It should be noted, however, that also nondopaminergic mechanisms, including some mediated by 5-HT, could be more directly involved in brain reward processes (Rocha et al., 1998). Nevertheless, acute pretreatment with the selective 5-HT reuptake inhibitor (SSRI) citalopram, at a dose that increases extracellular levels of 5-HT in some brain regions (Hjorth and Auerbach, 1994), did not alter the acute locomotor stimulation produced by nicotine (Olausson et al., 1999). Administration of the 5-HT_2 receptor agonist DOI also failed to influence acute nicotine-induced locomotor stimulation (Olausson et al., 2001b). In line with these observations, repeated treatment with citalopram or DOI did not alter the increase in extracellular DA levels in the ventral striatum observed after acute nicotine administration (Olausson et al., 2001b, unpublished).

A pharmacological manipulation which decreases brain 5-HT neurotransmission (i.e. a pronounced, selective depletion of brain 5-HT using the neurotoxin 5,7-dihydroxytryptamine) also did not alter the elevation of the extracellular DA levels in the ventral striatum or the locomotor stimulation produced by acute nicotine (Olausson et al., 2000). Depletion of 5-HT in the hippocampus also failed to influence nicotine-induced locomotor behavior (Balfour et al., 1986), and a lack of effect on nicotine-induced locomotor stimulation has been observed after antagonists at 5-HT_2 (i.e., ritanserin), 5-HT_3 (i.e., MDL, 72222 and ICS 205-930) and 5-HT_4 (i.e., SB-204070-A) receptors (Arnold et al., 1995; Corrigall and Coen, 1994; Reavill et al., 1998; Olausson et al., unpublished). Thus, serotonergic manipulations, either aimed at increasing or decreasing 5-HT neurotransmission, appear not to influence acute nicotine-induced activation of mesolimbic DA neurotransmission or locomotor stimulation.

One exception appears to be pretreatment with the $5\text{-HT}_{1A/7}$ receptor agonist 8-OH-DPAT This compound markedly potentiates the locomotor stimulation produced by acute nicotine administration (Olausson et al., 2001c), an effect that can not be explained by an enhancement of the nicotine-induced elevation of extracellular DA levels in the ventral striatum (Olausson et al., 2001c). The mechanisms underlying this potentiation are unknown but could involve a complex change in the balance between 5-HT receptor subtypes being activated, since 8-OH-DPAT both reduces 5-HT release, due to activation of somatodendritic autoinhibitory 5-HT_{1A} receptors (Chaput et al., 1991; Sprouse and Aghajanian, 1988), and stimulates postsynaptic $5\text{-HT}_{1A/7}$ receptors.

The lack of effect observed after number of pharmacological manipulations of brain 5-HT neurotransmission on acute nicotine-induced effects is in contrast to those observed on the effects of psychostimulants and opiates. For example, depletion of brain 5-HT increases the acute locomotor stimulatory effects of amphetamine and cocaine (Breese et al., 1974; Carter and Pycock, 1979; Morrow and Roth, 1996). Moreover, pretreatment with the SSRI citalopram decreased the locomotor stimulation produced by acute amphetamine (Olausson et al., 2000), and the locomotor stimulation produced by acute morphine is blocked by the SSRI fluoxetine (Sills and Fletcher, 1997). These

observations are supported by experimental findings demonstrating that infusion of 5-HT in the ventral striatum counteracts the potentiation of responding for conditioned reward induced by acute amphetamine (Fletcher, 1996), and that chronic treatment with the SSRI fluoxetine blocks the facilitatory effects of acute amphetamine treatment on ICSS (Lin et al., 1999). The acute neurochemical, electrophysiological and behavioral effects of various other drugs of abuse have also been reported to be attenuated or blocked by 5-HT_2 (Ichikawa and Meltzer, 1992; Layer et al., 1992; Olausson et al., 1998; Palfreyman et al., 1993) and 5-HT_3 receptor antagonists (Carboni et al., 1989a,b; Yoshimoto et al., 1991), as well as by 5-HT_{1A} receptor agonists (Blomqvist et al., 1994; De la Garza and Cunningham, 2000; Engberg, 1992; Ichikawa et al., 1995; Przegalinski and Filip, 1997) and antagonists (De la Garza and Cunningham, 1996).

5.2. Chronic effects of nicotine on DA and 5-HT neurotransmission

Repeated exposure to drugs of abuse progressively enhances the locomotor stimulatory properties of these substances (Clarke and Kumar, 1983; Kalivas et al., 1993; Pierce and Kalivas, 1997; Post and Rose, 1976; Segal and Mandell, 1974). This phenomenon is generally referred to as behavioral sensitization and can be defined as an increased effect of a fixed drug dose, or a maintained effect even after dose reduction, occurring after recurrent drug exposures. Once drug-induced sensitization has developed, it persists even after long periods of drug abstinence (Robinson and Berridge, 1993, 2000). Moreover, the expression of nicotine sensitization is rapidly restored after extended drug abstinence (Söderpalm, 1999).

Behavioral sensitization appears to be associated with drug-induced neural alterations that make the mesolimbic DA projection hypersensitive. These alterations occur both pre- and postsynaptically, and include augmented drug-induced elevation of the DA output in the ventral striatum and enhanced postsynaptic DA receptor function (Balfour et al., 1998, 2000; Henry and White, 1991; Pierce and Kalivas, 1997; Robinson and Berridge, 2000). In addition, upregulated intracellular signal transduction pathways in the postsynaptic neurons is observed in sensitized animals, and drug-induced effects on certain gene transcription factors and protein synthesis are essential in the development of sensitization (Nestler and Aghajanian, 1997).

The effects of repeated nicotine treatment on nicotine-induced stimulation of mesolimbic DA neurotransmission have recently been reviewed in great detail by Balfour and colleagues (1998, 2000). In short, repeated treatment with nicotine augments DA output and turnover in the ventral striatum in response to a subsequent injection of nicotine, a finding described in a large number of reports (e.g., Benwell and Balfour, 1992; Cadoni and Di Chiara, 2000; Shoaib et al., 1994). Given the parallel development of sensitization to the stimulatory effects of nicotine on mesolimbic DA neurotransmission and locomotor activity, this neurochemical sensitization has been implicated in the expression of nicotine-induced locomotor sensitization. Recent findings suggest that nicotine-induced elevation of the extracellular DA levels is sensitized in the core region of the nucleus accumbens, but not in the shell (Cadoni and Di Chiara, 2000). This observation may strengthen the hypothesis that sensitization to the nicotine-induced mesolimbic DA activation is involved in the neural processes underlying the expression of locomotor sensitization since the nucleus accumbens core is implicated in motor functions (Deutch et al., 1993).

When administered in combination with nicotine, subchronic repeated treatment with the SSRI citalopram or the 5-HT_2 receptor agonist DOI, but not the 5-$HT_{1A/7}$ receptor agonist 8-OH-DPAT, counteract the expression of nicotine-induced locomotor sensitization (Olausson et al., 1999, 2001b). These findings are in line with the observation that repeated treatment with the SSRI fluoxetine also counteracts the expression of locomotor sensitization to morphine (Sills and Fletcher, 1997). Pharmacological manipulations of brain 5-HT neurotransmission do, however, not influence the processes underlying induction of nicotine-induced locomotor sensitization (Olausson et al., 1999, 2001a,b). Other experiments have indicated that the 5-HT_{1A} receptor antagonist WAY 100,635 reduces the expression of behavioral sensitization to cocaine, without affecting the processes underlying induction (De la Garza and Cunningham, 1996). Thus, the effect of WAY 100,635 on cocaine sensitization resembles that of citalopram and DOI on nicotine sensitization. Since WAY 100,635 enhances the electrophysiological activity in brain 5-HT neurons (Fornal et al., 1996), the effects produced by the SSRI's and WAY 100,635 on expression of drug-induced locomotor sensitization could be related to facilitation of brain 5-HT neurotransmission. However, in our studies, neither subchronic citalopram nor acute 5-HTP treatment modified the expression of amphetamine sensitization (Olausson et al., 2000). This observation indicates a qualitative difference between the mechanisms underlying expression of locomotor sensitization to nicotine and amphetamine. These drugs activate the mesolimbic DA system via separate mechanisms, and whereas nicotine stimulates the electrophysiological activity of the mesolimbic DA neurons, amphetamine increases the extracellular DA levels in the ventral striatum via actions at DA transporters independent of neuronal activity. Experimental evidence suggest that 5-HT tonically inhibits electrophysiological activity in VTA DA neurons via stimulation of 5-HT_2 receptors (North and Uchimura, 1989; Ugedo et al., 1989). Thus, citalopram and DOI may attenuate expression of nicotine-induced locomotor sensitization via counteraction of nicotine-induced excitation of mesolimbic DA neurons via a 5-HT_2 receptor-mediated mechanism, leaving the firing-independent amphetamine-induced locomotor sens-

itization unaffected. In contrast to the potential inhibitory effect of 5-HT_2 receptor stimulation on mesolimbic DA neurotransmission, administration of 5-HT_3 receptor agonists elevate the extracellular DA levels in the ventral striatum (Benloucif et al., 1993; Jiang et al., 1990). Interestingly, the expression of locomotor sensitization to cocaine was counteracted by antagonism of 5-HT_3 receptors (King et al., 1997, 1998), possibly indicating that the expression of cocaine sensitization involves stimulation of mesolimbic DA activity via these receptors.

The proposed relationship between sensitization of the nicotine-induced mesolimbic DA activating effects and expression of nicotine-induced locomotor sensitization is partly supported by the consequences of serotonergic manipulations on these drug-induced effects. Thus, we found that repeated daily treatment with the 5-HT_2 agonist DOI antagonizes the expression of both locomotor and neurochemical sensitization to nicotine, whereas the 5-HT_{1A} receptor agonist 8-OH-DPAT has no effect on either of these nicotine-induced effects (Olausson et al., 2001b). By contrast, repeated nicotine treatment failed to produce neurochemical sensitization in 5-HT depleted animals even though the expression of locomotor sensitization tended to be enhanced in these animals (Olausson et al., 2001a). A similar discrepancy was also observed after chronic treatment with the SSRI citalopram, which has no effect on neurochemical sensitization to nicotine (Olausson et al., unpublished) and yet counteracts the expression of nicotine-induced locomotor sensitization (Olausson et al., 1999).

Whereas the chronic effects of dependence-producing drugs on mesocorticolimbic DA neurotransmission have been the focus of numerous experiments, their long-term effects on brain 5-HT neurotransmission are not as well investigated. Available data suggest that chronic cocaine exposure produces sensitization not only to the drug-induced elevation of DA, but also to the elevation of 5-HT output in the ventral striatum, the VTA and the dorsal raphe nucleus (Parsons and Justice, 1993). Interestingly, distinct patterns of 5-HT and DA sensitization were observed, and the 5-HT sensitization was more pronounced in the dorsal raphe nucleus (i.e., the 5-HT cell-body region; DRN) than in the terminal regions in the ventral striatum and the VTA. On the other hand, sensitization of the cocaine-induced elevation of the extracellular DA levels was observed in the ventral striatum and DRN (i.e. the terminal regions) but not in the VTA. These findings may indicate that repeated exposure to at least psychostimulants produces an imbalance between DA and 5-HT in the terminal regions of the mesocorticolimbic DA system, an alteration that may be involved in the altered behavioral output after these treatments. The enhanced autoinhibition of the DRN 5-HT neurons expected as a consequence of the augmented cocaine-induced elevation of 5-HT levels mentioned above is likely to result in decreased 5-HT neurotransmission within forebrain and cortical regions. This effect could thus be a consequence of the drug exposure that contributes to the expression of behaviors aimed at acquiring and consuming drugs of abuse. However, whether repeated treatment with nicotine or other drugs also produce a similar imbalance between DA and 5-HT neurotransmission in these brain regions has yet to be examined.

Since manipulations which decrease 5-HT neurotransmission enhance the locomotor stimulatory effects of DA activating drugs, like psychostimulants (see above), the enhanced locomotor activity observed after repeated drug treatment could in part derive from reduced 5-HT neurotransmission. Arguing against this hypothesis is, however, the fact that subchronic citalopram treatment did not modify the expression of amphetamine sensitization (Olausson et al., 2000), whereas the opposite was observed in animals sensitized to nicotine and morphine (Sills and Fletcher, 1997; Olausson et al., 1999). An interesting pharmacokinetic interaction between some SSRI's and amphetamine has been described in the literature, and pretreatment with fluoxetine, sertraline and citalopram appear to increase the brain levels of amphetamine after systemic injection (Arnt et al., 1984, Sills et al., 1999, 2000). Thus, pharmacokinetic interactions could prevent tentative antagonistic effects of SSRI's on the expression of amphetamine-induced locomotor sensitization. However, acute pretreatment with the 5-HT synthesis precursor 5-HTP, which is unlikely to interfere with amphetamine pharmacokinetics, did not influence the expression of amphetamine sensitization (Olausson et al., 2000).

6. Involvement of inhibitory control deficits in functional consequences of repeated exposure to nicotine

Apart from the sensitized nicotine-induced stimulation of locomotor activity that is observed after repeated nicotine treatment, at least two other behavioral phenomena that may be relevant to processes involved in nicotine dependence have been observed to develop upon intermittent, subchronic exposure to nicotine in the rat, i.e., nicotine-induced behavioral disinhibition in the elevated plus-maze and enhancement of voluntary ethanol preference and intake.

6.1. Behavioral disinhibition in the elevated plus-maze

The elevated plus-maze is a simple, widely used experimental rodent model in which an animal is allowed to freely explore an elevated plus-formed maze consisting of two arms with and two arms without walls. The contrast between arms with and without walls inhibits the exploration of the open arms. A number of reports have consistently demonstrated that anxiolytics that are positive modulators of γ-aminobutyric acid type A ($GABA_A$) receptor function, e.g. benzodiazepines, increase the proportion of the time and entries spent on open arms, and hence disinhibits exploratory behavior in the plus-maze. Based largely on this pharmacological evidence, such disinhibition has been proposed to reflect anxiolysis (Pellow, 1986;

Pellow et al., 1985). However, other known anxiolytic compounds, like chronic treatment with SSRI's or tricyclic antidepressants fail to influence behavior in the elevated plus-maze (Cole and Rodgers, 1995; Griebel et al., 1994, 1999; Harro et al., 1997; Olausson et al., 1999, 2000; Silva and Brandao, 2000).

In addition to benzodiazepines, depletion of brain 5-HT consistently produces behavioral disinhibition in animal conflict models, including the elevated plus-maze (Briley et al., 1990; Engel et al., 1984; Söderpalm, 1990; Soubrie, 1986). However, manipulations which reduce brain 5-HT levels do not reduce anxiety in humans (Evenden, 1999), and, thus, as argued by Soubrie (1986), 5-HT deficient animals may be exactly as anxious as non-deficient animals, but unable to inhibit the behavioral response. Therefore, anticonflict effects in these experimental models could be related to a disruption of inhibitory control of behavior rather than alleviation of anxiety, a notion supported by the observations that individuals with disinhibited or impulsive personalities display signs of low 5-HT neurotransmission (see above). Based on these reports, and in concert with the views put forward by Soubrie, we believe that increased exploration of open arms in the elevated plus-maze (i.e., behavioral disinhibition) could be interpreted as reduced inhibitory control of behavior. As mentioned above, decreased inhibitory control is a core feature of impulsivity (Evenden, 1998a), and behavioral disinhibition in the elevated plus-maze may therefore be relevant to impulsivity-like behaviors. This view is also supported by findings demonstrating that benzodiazepines increase impulsive behaviors in rodents (Evenden, 1998b,c; Thiebot et al., 1985).

6.2. Effects of nicotine on behavior in the elevated plus-maze

Even though some studies have indicated that acute nicotine produces behavioral disinhibition in the elevated plus-maze in mice (Brioni et al., 1993; Decker et al., 1995), in rats acute nicotine produces highly variable effects in this model (Balfour et al., 1986; Benwell et al., 1994; Olausson et al., 1999, 2001b; Ouagazzal et al., 1999). A lack of effect of nicotine in the elevated plus-maze has also been reported after repeated (6 days) and continuous nicotine exposure in rats (Balfour et al., 1986; Benwell et al., 1994). However, after an extended period of intermittent nicotine treatment (15 days), rats display nicotine-induced behavioral disinhibition in the elevated plus-maze (Olausson et al., 1999, 2001b,c). In addition, Irvine and colleagues (2001) recently reported that nicotine increases the time and entries spent on open arms after 7 days of treatment with a lower dose of nicotine, but observed no effects of nicotine after 14 days of treatment.

These observations may indicate that chronic intermittent exposure to nicotine impairs neural mechanisms involved in inhibitory control of behavior. Clinical observations support this view since cigarette smokers display impulsive behavior when assessed in neuropsychological test paradigms (Bickel et al., 1999; Mitchell, 1999) and have higher scores in questionnaires that measure impulsivity (Mitchell,1999; von Knorring and Oreland, 1985). Taken together, both preclinical and clinical findings thus suggest that intermittent exposure to nicotine impairs brain processes involved in inhibitory control.

As mentioned above, impulsivity may be an important factor contributing to the expression of addictive behaviors. In addition to the experimental data suggesting that repeated intake of nicotine and other drugs of abuse lowers inhibitory control per se, the possibility remains that the impulsive behavior observed in some smokers could reflect a premorbid personality trait since individuals with impulsive and risk-taking (i.e., disinhibited) personality are markedly overrepresented among cigarette smokers and drug using individuals (von Knorring and Oreland, 1985; von Knorring et al., 1987). A third possibility is that repeated nicotine exposure further reduces inhibitory control in individuals with such a predisposing personality trait, making them more vulnerable to the effects of repeated nicotine intake. Interestingly, both individuals with a disinhibited personality and cigarette smokers display reduced platelet MAO-B activity (Garpenstrand, 2000), a possible genetic marker for the functional capacity of the central 5-HT system (af Klinteberg et al., 1990; Garpenstrand, 2000). The reduced MAO activity observed in smokers has, however, also been related to the ability of cigarette smoke to inhibit platelet MAO (Norman et al., 1987; Oreland et al., 1981; Yu and Boulton, 1987), and low platelet MAO activity has been proposed to be a potential state marker for smoking (Anthenelli et al., 1998). Interestingly, neither the low platelet MAO activity nor the disinhibited personality is observed in former smokers (Bickel et al., 1999; von Knorring and Oreland, 1985), possibly supporting the relationship between these measures and active smoking. The lack of disinhibited personality and low platelet MAO in ex-smokers has, however, also been proposed to be an important factor underlying their ability to quit smoking (von Knorring and Oreland, 1985), suggesting that disinhibited personality trait is not a predisposing factor for initiating drug use but rather for inability to quit. Unfortunately, to our knowledge no longitudinal studies are available in which personality and platelet MAO activity have been evaluated both before and after quitting smoking. Such a study would most likely resolve this issue.

Subchronic treatment with the SSRI citalopram or the 5-$HT_{1A/7}$ agonist 8-OH-DPAT, but not the 5-HT_2 agonist DOI, counteracts the expression of behavioral disinhibition in nicotine-treated animals (Olausson et al., 1999, 2001b). These findings suggest that the restoration of inhibitory control produced by citalopram and 8-OH-DPAT involves stimulation of postsynaptic 5-$HT_{1A/7}$, but not 5-HT_2, receptors, that is exactly the opposite to what was found regarding expression of nicotine-induced locomotor sensitization. Repeated exposures to psychostimulants have also been demonstrated to reduce inhibitory control in rats and pri-

mates (Jentsch and Taylor, 1999; Taylor and Jentsch, 2001; Jentsch et al., 1997a,b; Olausson et al., 2000). Acute pretreatment with the 5-HT synthesis precursor 5-HTP or chronic treatment with the SSRI citalopram counteracts amphetamine-induced disinhibition (Olausson et al., 2000). Since inhibitory control deficits may be associated with low 5-HT activity these findings could indicate that the loss of inhibitory control observed after repeated nicotine or amphetamine treatment is compatible with induction of a low-serotonergic state, at least in relation to the activity of other neurotransmitters implicated in incentive motivation and inhibitory control, such as DA. Thus, the inhibitory control deficits produced by repeated drug exposure could be a behavioral consequence of an altered balance between brain 5-HT and DA neurotransmission. Possibly supporting this notion, repeated treatment with nicotine reduces the 5-HT tissue levels in the limbic region (Olausson et al., 2001a), the frontal cortex (Kirch et al., 1987) and the hippocampus (Benwell and Balfour, 1982; Benwell et al., 1990), although the hypothalamic 5-HT levels are increased (Kirch et al., 1987). Repeated treatment with non-neurotoxic doses of amphetamine also reduces 5-HT levels in the striatum and the cerebral cortex of the vervet monkey (Ridley et al., 1982), and prenatal cocaine exposure decreases the levels of 5-HT in several brain regions in rats, including the frontal cortex (Cabrera-Vera et al., 2000). In addition, drug abusing humans have low levels of the 5-HT metabolite 5-HIAA in the cerebrospinal fluid (Virkkunen and Rawlings, 1994), and reduced brain 5-HT levels have been reported in ecstacy (McCann et al., 1994, 1998; Woolverton et al., 1989), and methamphetamine abusers post mortem (Wilson et al., 1996). Observations made in human smokers post mortem have indicated decreased levels of the main 5-HT metabolite in the MRN (Benwell et al., 1990).

Neurotoxic lesions of the DRN and the MRN differentially decrease the tissue levels of 5-HT in different brain regions (Harrison et al., 1997b), and, in animals, both repeated nicotine treatment and neurotoxic lesions of the DRN decrease tissue levels of 5-HT in limbic and frontocortical regions (see above; Harrison et al., 1997b), and it is thus possible that nicotine predominantly affects the 5-HT neurons originating in the DRN, at least in rats. Interestingly, the impulsive behaviors observed after depletion of 5-HT in the whole brain are also produced by lesion of the DRN, but not of the MRN (Harrison et al., 1997b). Thus, it is possible that repeated nicotine treatment decreases inhibitory control by specifically reducing 5-HT neurotransmission mediated by the DRN.

Pharmacological experiments have demonstrated that manipulations which decrease brain 5-HT neurotransmission (e.g., a neurotoxic 5-HT depletion or a lasting 5-HT synthesis inhibition) elevate self-administration of several different drugs in rats (Engel et al., 1992; LeMarquand et al., 1994b; Roberts et al., 1994), and compounds that facilitate 5-HT neurotransmission, like selective 5-HT reuptake inhibitors, decrease voluntary ethanol consumption in rats (for review, see LeMarquand et al., 1994b). Similar effects of 5-HT enhancing drugs have also been reported on the intake of nicotine (Opitz and Weischer, 1988), opiates (Higgins et al., 1994), psychostimulants (Porrino et al., 1989; Walsh and Cunningham, 1997) as well as intracranial self-stimulation (Olds, 1994; Redgrave, 1978) in experimental animals. These observations may suggest that increased 5-HT neurotransmission reduce drug consumption, at least in animals, and since an enhancement of 5-HT neurotransmission increases inhibitory control (Hollander and Rosen, 2000), these effects could partly be mediated via strengthening of inhibitory control of behavior.

6.3. Enhancement of ethanol preference and intake

The co-abuse of nicotine and ethanol is well described, and clinical studies have reported that as many as 90% of alcoholics are smokers. Interestingly, available evidence suggests a pharmacological interaction between ethanol and nicotinergic mechanisms. For example, ethanol stimulates mesolimbic DA activity at least partly via actions involving central nAChRs and repeated nicotine treatment increases voluntary ethanol intake in rats (Blomqvist, 1996; Ericson, 2000; Le et al., 2000; Pothoff et al., 1983; Söderpalm et al., 2000). An acute nicotine injection further elevates ethanol intake and preference in animals repeatedly treated with nicotine but not with saline (Olausson et al., 2001c). Interestingly, the effects of subchronic nicotine pretreatment on nicotine-induced behavioral disinhibition and ethanol consumption appear to be closely related, since the measures of behavioral disinhibition correlate to the increase in ethanol consumption produced by this treatment (Olausson et al., 2001c). This observation is supported by other investigators reporting a strong relationship between impulsivity/disinhibition and ethanol consumption (Johansson et al., 1999; Poulos et al., 1995, 1998). The observation that 5-HT1_A agonists (which decrease 5-HT neurotransmission via autoinhibitory mechanisms) infused into the DRN, but not into the MRN, increase voluntary ethanol intake in rats (Tomkins et al., 1994) may further support this idea since the DRN 5-HT neurons appear to be an important part of the neural circuits mediating inhibitory control of behavior (Harrison et al., 1997b). In contrast, we failed to observe any correlation between nicotine-induced locomotor sensitization and voluntary ethanol consumption (Olausson et al., 2001c). Similarly, no relationship was observed between spontaneous locomotor activity, nicotine-induced locomotor activity or sensitization to the latter effect and voluntary ethanol consumption in a previous study (Blomqvist et al., 1996). Thus, mechanisms related to the nicotine-induced behavioral disinhibition caused by subchronic nicotine exposure may also be involved in mediating the increased ethanol intake observed after this treatment, whereas the neuroadaptations underlying locomotor sensitization appear to be less important in this respect. Further support for this conclusion comes from evidence indicating that induction of

nicotine sensitization involves intermittent stimulation of central nicotinic acetylcholine receptors, whereas, surprisingly, the development of nicotine-induced behavioral disinhibition and the nicotine-induced elevation of voluntary ethanol consumption may also invoke intermittent blockade of peripheral nicotinic acetylcholine receptors (Ericson et al., 2000a,b).

As mentioned above, repeated psychostimulant treatment has also been demonstrated to reduce inhibitory control (Jentsch and Taylor, 1999; Taylor and Jentsch, 2001; Olausson et al., 2000), but also to increase ethanol intake in rats (Fahlke et al., 1994), possibly indicating a relationship between low inhibitory control and high ethanol consumption also after this treatment. Previous studies have indicated a strong relationship between high ethanol consumption and low impulse control in rats (Poulos et al., 1995). In addition, repeated treatment with nicotine or amphetamine has been demonstrated to increase self-administration of cocaine (Horger et al., 1992), and nicotine treatment during periadolescence reduces the rewarding effects of cocaine in mice, which may lead to increased drug self-administration (Kelley and Middaugh, 1999). Thus, repeated exposure to at least nicotine and amphetamine may predispose intake of other drugs of abuse partly by reducing the function of the inhibitory control systems. Taken together, these preclinical observations may indicate a component (i.e., loss of inhibitory control) of the neurobiological substrate by which repeated nicotine exposure can predispose abuse also of other dependence producing drugs, as suggested by epidemiological studies in human drug addicts.

7. Discussion

Both preclinical and clinical observations support the notion that repeated exposure to nicotine and several different classes of dependence-producing drugs concurrently results in at least two distinct behavioral consequences; increased drug-related incentive motivation (possibly via mechanisms similar to those underlying sensitization to the mesolimbic DA-activating/locomotor stimulatory properties of the drugs) and reduced inhibitory control of behavior. Combined, these drug-induced behavioral deficits could play an important role in the compulsive pattern of drug-taking behavior that characterizes drug addiction. Since these effects are caused by the drug intake alone, repeated use of addictive substances may drive the drug addict to further drug-seeking and drug-taking by maintaining or further impairing neuronal processes involved in both positive and negative regulation of addictive behaviors (see Jentsch and Taylor, 1999). These preclinical findings are supported by the impulsive personality observed in human drug abusers, and may indicate that both predisposing factors and drug-induced effects to various degrees contribute to impulsivity in drug abusers, including smokers.

Impaired function in the cortical processes involved in regulation of behaviors mediated by subcortical structures has been implicated in the inhibitory control deficits produced by repeated drug exposure (Jentsch and Taylor, 1999). The reversal of these deficits produced by treatment with serotonergic compounds could include actions on these corticostriatal circuits, direct actions of 5-HT on the subcortical structures or a combination of both mechanisms. The large number of clinical and preclinical findings that have identified the prefrontal cortex as an important brain region for inhibitory control of behavior may indeed indicate that the reduced inhibitory control observed after repeated nicotine or amphetamine exposure is related to drug-induced alterations in this brain region. Supporting this notion, chronic treatment with several different dependence-producing drugs alter frontocortical DA activity and produce deficits in inhibitory control and cognitive processes mediated by this brain region (Jentsch and Taylor, 1999; Taylor and Jentsch, 2001; Jentsch et al., 1997a,b). These observations are corroborated also by imaging studies in human cocaine addicts, who display reduced activity in the ventromedial (i.e., orbital) prefrontal cortex (Childress et al., 2000).

Repeated nicotine treatment increases frontocortical DA turnover (Vezina et al., 1992) and produces sensitization to the nicotine-induced DA release in this brain region (Nisell et al., 1996), but decreases frontocortical and limbic 5-HT levels (Kirch et al., 1987; Olausson et al., 2001a). Low levels of 5-HT have also been observed in the orbital prefrontal cortex of human methamphetamine abusers (Wilson et al., 1996), and amphetamine-abusers and tryptophan-depleted (i.e., 5-HT deficient) volunteers also display similar decision-making deficits as patients with damage to the orbital prefrontal cortex (Rogers et al., 2000). In experimental animals, the balance between DA and 5-HT within the frontal cortex appears crucial for the function of the brain inhibitory control systems (Harrison et al., 1997a). Thus, a drug-induced disruption of the balance between DA and 5-HT neurotransmission in forebrain and/or frontocortical brain regions may contribute to the inhibitory control deficits observed after repeated drug exposure and the reversal of the drug-induced inhibitory control impairment produced by 5-HT enhancing substances could primarily be mediated via restoration of this balance, or, alternatively, via a strengthening of brain 5-HT neurotransmisson to a point at which it outweighs the neuroadaptations produced by repeated drug exposure.

Further support for this theory comes from observations made by Rogers and colleagues (1999) in tryptophan-depleted human volunteers who displayed a selective deficit in reversal learning, a behavioral pattern similar to that observed in humans and primates with impaired function in the orbital prefrontal cortex (Dias et al., 1996; Rogers et al., 2000). Similarly, tryptophan-depleted young men with a family history of alcoholism made more commission errors in a go/no-go task than controls (LeMarquand et al., 1999), indicating impaired frontocortical function in individuals

with genetic predisposition for alcoholism after manipulation of 5-HT neurotransmission.

7.1. The role of 5-HT in the effects of nicotine: our hypothesis

Since manipulations that either increase or decrease brain 5-HT neurotransmission have no or only minor effects on the results of acute nicotine administration on several different neurochemical and behavioral measures relevant to dependence, the involvement of 5-HT in these acute effects should be minor. On the other hand, a number of independent observations have demonstrated that repeated nicotine exposure produces lasting alterations of brain 5-HT and DA neurotransmission in multiple brain regions (for references, see above). Therefore, based on the preclinical and clinical data reviewed above, we believe repeated treatment with nicotine produces neuroadaptive changes leading to an imbalance between DA and 5-HT neurotransmission within brain regions that are involved in positive and negative control of incentive motivational impulses and conditioned behaviors (e.g., the ventral striatum, the amygdala and the frontal cortex). These drug-induced neuroadaptive changes may functionally result in *enhanced* incentive motivation to consume nicotine and other drugs, as proposed by the incentive sensitization theory of addiction, combined with an inability to suppress such inappropriate motivational impulses due to *decreased* function in the brain inhibitory control systems (Robinson and Berridge, 1993; Jentsch and Taylor, 1999). Together, these drug-induced neuroadaptations may be important components involved in the compulsive drug-seeking and -taking behaviors that are observed in animals, but also in nicotine-using individuals.

7.2. Clinical relevance

The neuroadaptive alterations occurring in neural pathways involved in positive and negative control of drug-taking behavior following repeated drug exposure could influence the development and expression of addictive behaviors and predispose relapse. Indeed, both abnormal incentive motivation and loss of impulse control appear to be critical components in the development of drug dependence as well as in predicting relapse in human drug addicts (Ciccocioppo, 1999; Robinson and Berridge, 2000). However, relapse in human cocaine addicts has interestingly been reported to be related to impulsivity, rather than craving (Miller and Gold, 1994), and urges to drink have also been suggested to correlate poorly with relapse in alcoholics (Rohsenhow and Monti, 1999), possibly indicating a more important role of impulsivity.

Drugs that block the expression of these phenomena could prove helpful in a wider treatment program for drug abuse. Indeed, some studies indicate that citalopram may reduce ethanol intake in heavy drinkers (i.e., large-scale consumers; Balldin et al., 1994; Engel et al., 1992; LeMarquand et al., 1994a,b; Naranjo et al., 1987), and a few studies have reported some efficacy of SSRI's in treatment of cocaine abusers (Covi et al., 1995; Pollack and Rosenbaum, 1991). Some antidepressant agents (bupropion and nortriptyline) may also aid smoking cessation (Hughes et al., 2000). In contrast, treatment with citalopram alone failed to lower the number of cigarettes smoked in heavy drinkers not motivated to quit smoking (Sellers et al., 1987). This result is, however, not unexpected given the fact that recent studies have stressed the importance of motivation in smoking cessation. Instead, a multifactorial treatment program designed to address several of the critical components underlying smoking, including pharmacotherapies that reduce craving and impulsivity, may improve the success-rate in individuals motivated to quit smoking. Indeed, the SSRI paroxetine increases abstinence rates over placebo when used in combination with a transdermal nicotine substitution therapy (Killen et al., 2000). Similarly, the combination of naltrexone and sertraline was more efficient in treatment of alcoholism than naltrexone alone (Farren, 1998), and treatment with fluoxetine increased retention in treatment programs in crack-cocaine users (Batki et al., 1996).

We believe that increased understanding of the consequences of chronic exposure to drugs of abuse on mechanisms involved in positive and negative modulation of addictive behaviors could lead to development of novel research-based strategies for treatment of smoking and drug addiction. Experimental data presented to date suggest that further studies on the effects of 5-HT activity enhancing drugs as one component of a treatment program are warranted, and that such research could indicate beneficial clinical effects of these compounds in treatment strategies for smoking and, possibly, for drug abuse in general.

Acknowledgments

The authors want to express their sincere gratitude to Dr. David Jentsch for valuable comments on this manuscript. The preparation of this manuscript was supported by a Swedish Brain Foundation fellowship to PO. The authors' research is financially supported by the Swedish Medical Research Council (grants no. 11583 and 4247), NIDA (DA 10765) and the Swedish Match Foundation.

References

af Klinteberg B, Schalling D, Edman G, Oreland L, Åsberg M. Personality correlates of platelet monoamine oxidase (MAO) activity in female and male subjects. Neuropsychobiology 1987;18:89–96.

af Klinteberg B, Oreland L, Hallman J, Wirsen A, Levander SE, Schalling D. Exploring the connections between platelet monoamine oxidase ac-

tivity and behavior: relationships with performance in neuropsychological tasks. Neuropsychobiology 1990;23:188–96.
Amit Z, Smith BR, Gill K. Serotonin uptake inhibitors: effects on motivated consummatory behaviors. J Clin Psychiatry 1991;52:55–60 (Suppl.).
Anthenelli RM, Tipp J, Li TK, Magnes L, Schuckit MA, Rice J, Daw W, Nurnberger DJ. Platelet monoamine oxidase activity in subgroups of alcoholics and controls: results from the collaborative study on the genetics of alcoholism. Alcohol Clin Exp Res 1998;22:598–604.
Arnold B, Allison K, Ivanova S, Paetsch PR, Paslawski T, Greenshaw AJ. 5-HT_3 receptor antagonists do not block nicotine induced hyperactivity in rats. Psychopharmacology 1995;119:213–21.
Arnt J, Hyttel J, Overo KF. Prolonged treatment with the specific 5-HT-uptake inhibitor citalopram: effect on dopaminergic and serotonergic functions. Pol J Pharmacol Pharm 1984;36:221–30.
Åsberg M, Träskman L, Thorén P. 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor. Arch Gen Psychiatry 1976;33:1193–7.
Balfour DJ, Ridley DL. The effects of nicotine on neural pathways implicated in depression: a factor in nicotine addiction? Pharmacol, Biochem Behav 2000;66:79–85.
Balfour DJ, Graham CA, Vale AL. Studies on the possible role of brain 5-HT systems and adrenocortical activity in behavioural responses to nicotine and diazepam in an elevated X-maze. Psychopharmacology 1986;90:528–32.
Balfour DJ, Benwell ME, Birrell CE, Kelly RJ, Al-Aloul M. Sensitization of the mesoaccumbens dopamine response to nicotine. Pharmacol, Biochem Behav 1998;59:1021–30.
Balfour DJ, Wright AE, Benwell ME, Birrell CE. The putative role of extrasynaptic mesolimbic dopamine in the neurobiology of nicotine dependence. Behav Brain Res 2000;113:73–83.
Balldin J, Berggren U, Engel J, Eriksson M, Hård E, Söderpalm B. Effect of citalopram on alcohol intake in heavy drinkers. Alcohol Clin Exp Res 1994;18:1133–6.
Batki SL, Washburn AM, Delucchi K, Jones RT. A controlled trial of fluoxetine in crack cocaine dependence. Drug Alcohol Depend 1996; 41:137–42.
Benloucif S, Keegan MJ, Galloway MP. Serotonin-facilitated dopamine release in vivo: pharmacological characterization. J Pharmacol Exp Ther 1993;265:373–7.
Benwell ME, Balfour DJ. The effects of nicotine administration on 5-HT uptake and biosynthesis in rat brain. Eur J Pharmacol 1982;84:71–7.
Benwell ME, Balfour DJ. The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol 1992;105:849–56.
Benwell ME, Balfour DJ, Anderson JM. Smoking-associated changes in the serotonergic systems of discrete regions of human brain. Psychopharmacology 1990;102:68–72.
Benwell ME, Balfour DJ, Khadra LF. Studies on the influence of nicotine infusions on mesolimbic dopamine and locomotor responses to nicotine. Clin Invest 1994;72:233–9.
Bickel WK, Odum AL, Madden GJ. Impulsivity and cigarrette smoking: delay discounting in current, never, and ex-smokers. Psychopharmacology 1999;146:447–54.
Blomqvist O. Ethanol and central nicotinic acetylcholine receptors. Thesis, Dept of Pharmacol, Göteborg University, 1996. pp. 1–61.
Blomqvist O, Söderpalm B, Engel JA. 5-HT_{1A} receptor agonists reduce ethanol-induced locomotor activity in mice. Alcohol 1994;11:157–61.
Blomqvist O, Ericson M, Johnson DH, Engel JA, Söderpalm B. Voluntary ethanol intake in the rat: effects of nicotinic acetylcholine receptor blockade or subchronic nicotine treatment. Eur J Pharmacol 1996; 314:257–67.
Breese GR, Cooper BR, Mueller RA. Evidence for the involvement of 5-hydroxytryptamine in the actions of amphetamine. Br J Pharmacol 1974;52:307–14.
Briley M, Chopin P, Moret C. Effect of serotonergic lesion on "anxious" behaviour measured in the elevated plus-maze test in the rat. Psychopharmacology 1990;101:187–9.
Brioni JD, O'Neill AB, Kim DJ, Decker MW. Nicotinic receptor agonists exhibit anxiolytic-like effects on the elevated plus-maze test. Eur J Pharmacol 1993;238:1–8.
Cabrera-Vera TM, Garcia F, Pinto W, Battaglia G. Neurochemical changes in brain serotonin neurons in immature and adult offspring prenatally exposed to cocaine. Brain Res 2000;7:1–9.
Cadoni C, Di Chiara G. Differential changes in accumbens shell and core dopamine in behavioral sensitization to nicotine. Eur J Pharmacol 2000;387:R23–5.
Carboni E, Acquas E, Frau R, Di Chiara G. Differential inhibitory effects of a 5-HT_3 antagonist on drug-induced stimulation of dopamine release. Eur J Pharmacol 1989a;164:515–9.
Carboni E, Acquas E, Leone P, Di Chiara G. 5HT_3 receptor antagonists block morphine—and nicotine—but not amphetamine-induced reward. Psychopharmacology 1989b;97:175–8.
Carter CJ, Pycock CJ. The effects of 5,7-dihydroxytryptamine lesions of extrapyramidal and mesolimbic sites on spontaneous motor behaviour, and amphetamine-induced stereotype. Naunyn Schmiedebergs Arch Pharmacol 1979;308:51–4.
Chaput Y, de Montigny C, Blier P. Presynaptic and postsynaptic modifications of the serotonin system by long-term administration of antidepressant treatments. An in vivo electrophysiologic study in the rat. Neuropsychopharmacology 1991;5:219–29.
Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. Am J Psychiatry 1999;156:11–8.
Childress AR, Franklin TR, Monterosso JR, Mozley PD, O'Brien CP. Orbitofrontal hypofunction in cocaine patients compared to controls. Soc Neurosci Abstr 2000;26:1314.
Ciccocioppo R. The role of serotonin in craving: from basic research to human studies. Alcohol Alcohol 1999;34:244–53.
Clarke PB. Dopaminergic mechanisms in the locomotor stimulant effects of nicotine. Biochem Pharmacol 1990;40:1427–32.
Clarke PB, Kumar R. The effects of nicotine on locomotor activity in non-tolerant and tolerant rats. Br J Pharmacol 1983;78:329–37.
Clarke PB, Fu DS, Jakubovic A, Fibiger HC. Evidence that mesolimbic dopaminergic activation underlies the locomotor stimulant action of nicotine in rats. J Pharmacol Exp Ther 1988;246:701–8.
Cole JC, Rodgers RJ. Ethological comparison of the effects of diazepam and acute/chronic imipramine on the behaviour of mice in the elevated plus-maze. Pharmacol, Biochem Behav 1995;52:473–8.
Corrigall WA, Coen KM. Nicotine self-administration and locomotor activity are not modified by the 5-HT_3 antagonists ICS 205-930 and MDL 72222. Pharmacol, Biochem Behav 1994;49:67–71.
Corrigall WA, Franklin KB, Coen KM, Clarke PB. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology 1992;107:285–9.
Covi L, Hess JM, Kreiter NA, Haertzen CA. Effects of combined fluoxetine and counseling in outpatient treatment of cocaine abusers. Am J Drug Alcohol Abuse 1995;21:327–44.
Dackis CA, Gold MS. New concepts in cocaine addiction: the dopamine depletion hypothesis. Neurosci Biobehav Rev 1985;9:469.
Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans R Soc Lond, Ser. B 1996;351: 1413–20.
Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation—a possible prelude to violence. Science 2000; 289:591–4.
Decker MW, Anderson DJ, Brioni JD, Donnelly RD, Kang CH, O'Neill AB, Piattoni KM, Swanson S, Sullivan JP. Erysodine, a competitive antagonist at neuronal nicotinic acetylcholine receptors. Eur J Pharmacol 1995;280:79–89.
De la Garza R, Cunningham KA. The 5-HT_{1A} antagonist WAY 100635 attenuates cocaine-induced hyperactivity, but not behavioral sensitization. Soc Neurosci Abstr 1996;22:931.
De la Garza R, Cunningham KA. The effects of the 5-hydroxytryptamine(1A) agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin on spontaneous activity, cocaine-induced hyperactivity and behavioral sensitization:

a microanalysis of locomotor activity. J Pharmacol Exp Ther 2000;292: 610–7.
Deutch AY, Bourdelais AJ, Zahm DS. The nucleus accumbens core and shell: accumbal compartments and their functional attributes. In: Kalivas PW, Barnes CD, editors. Limbic motor circuits and neuropsychiatry. Boca Raton: CRC Press, 1993. pp. 45–88.
Dias R, Robbins TW, Roberts AC. Dissociation in prefrontal cortex of affective and attentional shifts. Nature 1996;380:69–72.
Di Chiara G. Behavioural pharmacology and neurobiology of nicotine reward and dependence. In: Clementi F, Fornasari D, Gotti C, editors. Handbook of experimental pharmacology, vol. 144. Neuronal nicotine receptors. New York: Springer, 2000a. pp. 603–750.
Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. Eur J Pharmacol 2000b;393:295–314.
Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. PNAS 1988;85:5274–8.
Di Chiara G, Tanda G, Bassareo V, Pontieri F, Acquas E, Fenu S, Cadoni C, Carboni E. Drug addiction as a disorder of associative learning. Role of nucleus accumbens shell/extended amygdala dopamine. Ann NY Acad Sci 1999;877:461–85.
Engberg G. Citalopram and 8-OH-DPAT attenuate nicotine-induced excitation of central noradrenaline neurons. J Neural Transm: Gen Sect 1992;89:149–54.
Engel JA. Neurochemical aspects of the euphoria induced by dependence-producing drugs. In: Ideström CM, editor. Recent advances in the study of alcoholism, vol. 407. Amsterdam: Excerpta Medica, 1977. pp. 16–22.
Engel JA, Hjorth S, Svensson K, Carlsson A, Liljequist S. Anticonflict effect of the putative serotonin receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). Eur J Pharmacol 1984;105:365–8.
Engel JA, Enerbäck C, Fahlke C, Hulthe P, Hård E, Johannessen K, Svensson L, Söderpalm B. Serotonergic and dopaminergic involvement in ethanol intake. In: Naranjo CA, Sellers EM, editors. Novel pharmacological interventions for alcoholism. New York: Springer Verlag, 1992. pp. 68–82.
Ericson M. Nicotinic mechanisms in ethanol reinforcement. Thesis, Dept. of Pharmacol., Göteborg University, 2000. pp. 1–75.
Ericson M, Engel JA, Söderpalm B. Peripheral involvement in nicotine-induced enhancement of ethanol intake. Alcohol 2000a;21:37–47.
Ericson M, Olausson P, Engel JA, Söderpalm B. Nicotine induces disinhibitory behavior in the rat after subchronic peripheral nicotinic acetylcholine receptor blockade. Eur J Pharmacol 2000b;397:103–11.
Evenden JL. Serotonergic and steroidal influences on impulsive behaviour in rats. Thesis, Department of Neuroscience, Uppsala University, 1998. pp. 1–80.
Evenden JL. The pharmacology of impulsive behaviour in rats: III. The effects of amphetamine, haloperidol, imipramine, chlordiazepoxide and ethanol on a paced fixed consecutive number schedule. Psychopharmacology 1998b;138:295–304.
Evenden JL. The pharmacology of impulsive behaviour in rats: II. The effects of amphetamine, haloperidol, imipramine, chlordiazepoxide and other drugs on fixed consecutive number schedules (FCN 8 and FCN 32). Psychopharmacology 1998c;138:283–94.
Evenden JL. Varieties of impulsivity. Psychopharmacology 1999;146: 348–61.
Everitt BJ, Parkinson JA, Olmstead MC, Arroyo M, Robledo P, Robbins TW. Associative processes in addiction and reward. The role of amygdala-ventral striatal subsystems. Ann NY Acad Sci 1999;877:412–38.
Fahlke C, Hanssen S, Engel JA, Hård E. Effects of ventral striatal 6-OHDA lesions or amphetamine sensitization on ethanol consumption in the rat. Pharmacol, Biochem Behav 1994;47:345–9.
Farren CK. Sertraline with naltrexone versus naltrexone alone in the treatment of alcohol dependence. Alcohol: Clin Exp Res 1998;22:143 (suppl.).
Fibiger HC, LePiane FG, Jakubovic A, Phillips AG. The role of dopamine in intracranial self-stimulation of the ventral tegmental area. J Neurosci 1987;7:3888–96.
Fletcher PJ. Injection of 5-HT into the nucleus accumbens reduces the effects of D-amphetamine on responding for conditioned reward. Psychopharmacology 1996;126:62–9.
Fletcher PJ, Korth KM. Activation of 5-HT_{1B} receptors in the nucleus accumbens reduces amphetamine-induced enhancement of responding for conditioned reward. Psychopharmacology 1999;142:165–74.
Fletcher PJ, Korth KM, Chambers JW. Selective destruction of brain serotonin neurons by 5,7-dihydroxytryptamine increases responding for a conditioned reward. Psychopharmacology 1999;147:291–9.
Fornal CA, Metzler CW, Gallegos RA, Veasey SC, McCreary AC, Jacobs BL. WAY-100635, a potent and selective 5-hydroxytryptamine1A antagonist, increases serotonergic neuronal activity in behaving cats: comparison with (S)-WAY-100135. J Pharmacol Exp Ther 1996; 278:752–62.
Garpenstrand H. Platelet monoamine oxidase: from genetic regulation to behavior. Thesis, Section of Pharmacology, Uppsala University, 2000. pp. 1–60.
Grauer SM, Tao R, Auerbach SB. Morphine induces an increase in extracellular serotonin in the rat diencephalon. Brain Res 1992;599:277–82.
Grenhoff J, Svensson TH. Selective stimulation of limbic dopamine activity by nicotine. Acta Physiol Scand 1988;133:595–6.
Grenhoff J, Aston-Jones G, Svensson TH. Nicotinic effects on the firing pattern of midbrain dopamine neurons. Acta Physiol Scand 1986;128: 351–8.
Griebel G, Moreau JL, Jenck F, Misslin R, Martin JR. Acute and chronic treatment with 5-HT reuptake inhibitors differentially modulate emotional responses in anxiety models in rodents. Psychopharmacology 1994;113:463–70.
Griebel G, Cohen C, Perrault G, Sanger DJ. Behavioral effects of acute and chronic fluoxetine in Wistar–Kyoto rats. Physiol Behav 1999; 67:315–20.
Hallman J, von Knorring L, Edman G, Oreland L. Personality traits and platelet monoamine oxidase activity in alcoholic women. Addict Behav 1991;16:533–41.
Harrison AA, Everitt BJ, Robbins TW. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. Psychopharmacology 1997a;133:329–42.
Harrison AA, Everitt BJ, Robbins TW. Doubly dissociable effects of median- and dorsal-raphe lesions on the performance of the five-choice serial reaction time test of attention in rats. Behav Brain Res 1997b; 89:135–49.
Harro J, Lofberg C, Pahkla R, Matto V, Rago L, Oreland L, Allikmets L. Different molecular forms of cholecystokinin and CCKB receptor binding in the rat brain after chronic antidepressant treatment. Naunyn-Schmiedeberg's Arch Pharmacol 1997;355:57–63.
Henry DJ, White FJ. Repeated cocaine administration causes persistent enhancement of D1 dopamine receptor sensitivity within the rat nucleus accumbens. J Pharmacol Exp Ther 1991;258:882–90.
Higgins GA, Wang Y, Corrigall WA, Sellers EM. Influence of 5-HT_3 receptor antagonists and the indirect 5-HT agonist, dexfenfluramine, on heroin self-administration in rats. Psychopharmacology 1994;114:611–9.
Hjorth S, Auerbach SB. Lack of 5-HT_{1a} autoreceptor desensitization following chronic citalopram treatment, as determined by in vivo microdialysis. Neuropharmacology 1994;33:331–4.
Hollander E, Rosen J. Impulsivity. J Psychopharmacol 2000;14:S39–44.
Horger BA, Shelton K, Schenk S. Preexposure sensitizes rats to the rewarding effects of cocaine. Pharmacol, Biochem Behav 1990;37:707–11.
Horger BA, Giles MK, Schenk S. Preexposure to amphetamine and nicotine predisposes rats to self-administer a low dose of cocaine. Psychopharmacology 1992;107:271–6.
Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation (Cochrane review). The Cochrane library, vol. 4. Oxford: Update Software, 2000, ISSN, 1464-780X.
Ichikawa J, Meltzer HY. Amperozide, a novel antipsychotic drug, inhibits the ability to increase dopamine in vivo in rat striatum and nucleus accumbens. J Neurochem 1992;58:2285–91.

Ichikawa J, Kuroki T, Kitchen MT, Meltzer HY. *R*(+)-8-OH-DPAT, a 5-HT1A receptor agonist, inhibits amphetamine-induced dopamine release in rat striatum and nucleus accumbens. Eur J Pharmacol 1995; 287:179–84.

Imperato A, Mulas A, Di Chiara G. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. Eur J Pharmacol 1986;132:337–8.

Irvine EE, Cheeta S, File SE. Tolerance to nicotine's effects in the elevated plus-maze and increased anxiety during withdrawal. Pharmacol, Biochem Behav 2001;68:319–25.

Jackson DM, Andén N-E, Dahlström A. A functional effect of dopamine in the nucleus accumbens and in some other dopamine-rich parts of the brain. Psychopharmacologia 1975;45:139–49.

Jellinek EM, Isbell H, Lundquist G, Tiebout HM, Duchene H, Maredones J, Macleod LD. The "craving" for alcohol. Quat J Stud Alcohol 1955;16: 34–66.

Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology 1999;146:373–90.

Jentsch JD, Redmond DE, Elsworth JD, Taylor JR, Youngren KD, Roth RH. Enduring cognitive deficits and cortical dopamine dysfunction in monkeys after long-term administration of phencyclidine. Science 1997a;277:953–5.

Jentsch JD, Andrusiak E, Tran A, Bowers MB, Roth RH. Delta 9-tetrahydrocannabinol increases prefrontal cortical catecholaminergic utilization and impairs spatial working memory in the rat: blockade of dopaminergic effects with HA966. Neuropsychopharmacology 1997b;16:426–32.

Jiang LH, Ashby CJ, Kasser RJ, Wang RY. The effect of intraventricular administration of the 5-HT_3 receptor agonist 2-methylserotonin on the release of dopamine in the nucleus accumbens: an in vivo chronocoulometric study. Brain Res 1990;513:156–60.

Johansson ÅK, Bergvall AH, Hansen S. Behavioral disinhibition following basal forebrain excitotoxin lesions: alcohol consumption, defensive aggression and serotonin levels. Behav Brain Res 1999;102:17–29.

Kalivas PW, Sorg BA, Hooks MS. The pharmacology and neural circuitry of sensitization to psychostimulants. Behav Pharmacol 1993;4:315–34.

Kelland MC, Chiodo LA. Serotonergic modulation of midbrain dopamine systems. In: Ashby CR, editor. The modulation of dopaminergic neurotransmission by other neurotransmitters. Boca Raton: CRC Press, 1996. pp. 87–122.

Kelley BM, Middaugh LD. Periadolescent nicotine exposure reduces cocaine reward in adult mice. J Addict Dis 1999;18:27–39.

Kelly PH, Seviour PW, Iversen SD. Amphetamine and apomorphine responses in the rat following 6-OH-DA lesions of the nucleus accumbens and the corpus striatum. Brain Res 1975;94:507–22.

Killen JD, Fortmann SP, Schatzberg AF, Hayward C, Sussman L, Rothman M, Strausberg L, Varady A. Nicotine patch and paroxetine for smoking cessation. J Consult Clin Psychol 2000;68:883–9.

King GR, Xiong Z, Ellinwood EJ. Blockade of cocaine sensitization and tolerance by the co-administration of ondansetron, a 5-HT_3 receptor antagonist, and cocaine. Psychopharmacology 1997;130:159–65.

King GR, Xiong Z, Ellinwood EJ. Blockade of the expression of sensitization and tolerance by ondansetron, a 5-HT_3 receptor antagonist, administered during withdrawal from intermittent and continuous cocaine. Psychopharmacology 1998;135:263–9.

Kirch DG, Gerhardt GA, Shelton RC, Freedman R, Wyatt RJ. Effect of chronic nicotine administration on monoamine and monoamine metabolite concentrations in rat brain. Clin Neuropharmacol 1987;10:376–83.

Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 1992;13:177–84.

Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science 1997;278:52–8.

Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 2001;24:97–129.

Kuczenski R, Segal D. Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. J Neurosci 1989;9:2051–65.

Kuczenski R, Segal DS, Cho AK, Melega W. Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. J Neurosci 1995;15:1308–17.

Layer RT, Uretsky NJ, Wallace LJ. Effect of serotonergic agonists in the nucleus accumbens on d-amphetamine-stimulated locomotion. Life Sci 1992;50:813–20.

Le AD, Corrigall WA, Harding JW, Juzytsch W, Li TK. Involvement of nicotinic receptors in alcohol self-administration. Alcohol: Clin Exp Res 2000;24:155–63.

Lejoyeux M, Feuche N, Loi S, Solomon J, Ades J. Impulse-control disorders in alcoholics are related to sensation seeking and not to impulsivity. Psychiatry Res 1998;81:149–55

LeMarquand DG, Pihl RO, Benkelfat C. Serotonin and alcohol intake, abuse, and dependence: clinical evidence. Biol Psychiatry 1994a;36: 326–37.

LeMarquand DG, Pihl RO, Benkelfat C. Serotonin and alcohol intake, abuse, and dependence: findings of animal studies. Biol Psychiatry 1994b;36:395–421.

LeMarquand DG, Benkelfat C, Pihl RO, Palmour RM, Young SN. Behavioral disinhibition iduced by tryptophan depletion in nonalcoholic young men with multigenerational family histories of paternal alcoholism. Am J Psychiatry 1999;156:1771–9.

Lett BT. Repeated exposure intensify rather than diminish the rewarding effects of amphetamine, morphine and cocaine. Psychopharmacology 1989;98:357–62.

Lin D, Koob GF, Markou A. Differential effects of withdrawal from chronic amphetamine or fluoxetine administration on brain stimulation reward in the rat interactions between the two drugs. Psychopharmacology 1999;145:283–94.

Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. Low cerebrospinal fluid 5-hydroxyindolacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sci 1983; 33:2609–14.

Martin P. 5-HT_2 receptor antagonism and antipsychotic drugs; a behavioural and neurochemical study in a rodent hypoglutamatergia model. Thesis, Department of Pharmacology, Göteborg University, 1998. pp. 1–64.

McCann UD, Ridenour A, Shaham Y, Ricaurte GA. Serotonin neurotoxicity after (+/−)3,4-methylenedioxymethamphetamine (MDMA; "ecstasy"): a controlled study in humans. Neuropsychopharmacology 1994;10:129–38.

McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA (ecstasy) on brain serotonin neurons in human beings. Lancet 1998;352:1433–7.

Mifsud J-C, Hernandez L, Hoebel BG. Nicotine infused into the nucleus accumbens increases synaptic dopamine as measured by in vivo microdialysis. Brain Res 1989;478:365–7.

Miller NS, Gold MS. Dissociation of "conscious desire" (craving) from and relapse in alcohol and cocaine dependence. Ann Clin Psychiatry 1994;6:99–106.

Mitchell SH. Measures of impulsivity in cigarette smokers and non-smokers. Psychopharmacology 1999;146:455–64.

Moeller FG, Steinberg JL, Petty F, Fulton M, Cherek DR, Kramer G, Garver DL. Serotonin and impulsive/aggressive behavior in cocaine dependent subjects. Prog Neuropsychopharmacol Biol Psychiatry 1994; 18:1027–35.

Morgan M. Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 1998;19:252–64.

Morrow BA, Roth RH. Serotonergic lesions alter cocaine-induced locomotor behavior and stress-activation of the mesocorticolimbic dopamine system. Synapse 1996;23:174–81.

Naranjo CA, Sellers EM, Sullivan JT, Woodley DV, Kadlec K, Sykora K. The serotonin uptake inhibitor citalopram attenuates ethanol intake. Clin Pharmacol Ther 1987;41:266–74.

Nestler EJ, Aghajanian GK. Molecular and cellular basis of addiction. Science 1997;278:58–63.

Nisell M, Nomikos GG, Svensson TH. Systemic nicotine-induced dopa-

mine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. Synapse 1994;16:36–44.
Nisell M, Nomikos GG, Hertel P, Panagis G, Svensson TH. Condition-independent sensitization of locomotor stimulation and mesocortical dopamine release following chronic nicotine treatment in the rat. Synapse 1996;22:369–81.
Norman TR, Chamberlain KG, French MA, Burrows GD. Platelet monoamine oxidase: low activity in cigarette smokers. Psychiatry Res 1987; 20:199–205.
North RA, Uchimura N. 5-Hydroxytryptamine acts at 5-HT_2 receptors to decrease potassium conductance in rat nucleus accumbens neurones. J Physiol 1989;417:1–12.
Olausson P, Ericson M, Petersson A, Kosowski A, Söderpalm B, Engel JA. Nefazodone attenuates the behavioral and neurochemical effects of ethanol. Alcohol 1998;15:77–86.
Olausson P, Engel JA, Söderpalm B. Behavioral sensitization to nicotine is associated with behavioral disinhibition: counteraction by citalopram. Psychopharmacology 1999;142:111–9.
Olausson P, Engel JA, Söderpalm B. Effect of serotonergic manipulations on the behavioral sensitization and disinhibition associated with repeated amphetamine treatment. Pharmacol, Biochem Behav 2000;66: 211–20.
Olausson P, Petersson A, Engel JA, Söderpalm B. Behavioral and neurochemical consequences of repeated nicotine treatment in the serotonin depleted rat. Psychopharmacology 2001a;155:348–61.
Olausson P, Engel JA, Söderpalm B. The effect of 5-HT_{1A} and 5-HT_2 receptor agonists on the behavioral and neurochemical consequences of repeated nicotine treatment. Eur J Pharmacol 2001b;420:45–54.
Olausson P, Ericson M, Löf E, Engel JA, Söderpalm B. Nicotine-induced behavioral disinhibition and ethanol preference correlate after repeated nicotine treatment. Eur J Pharmacol 2001c;417:117–23.
Olds ME. Opposite effects of PCA and chlorimipramine on ICSS and on its facilitation by amphetamine. Pharmacol, Biochem Behav 1994;47: 803–17.
Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of the brain. J Comp Physiol Psychol 1954;47:419–23.
Opitz K, Weischer M-L. Volitional intake of nicotine in tupaias: drug-induced alterations. Drug Alcohol Depend 1988;21:99–104.
Oreland L, Fowler CJ, Schalling D. Low platelet monoamine oxidase activity in cigarette smokers. Life Sci 1981;29:2508–11.
Ouagazzal AM, Kenny PJ, File SE. Modulation of behaviour on trials 1 and 2 in the elevated plus-maze test of anxiety after systemic and hippocampal administration of nicotine. Psychopharmacology 1999;144:54–60.
Palfreyman MG, Schmidt CJ, Sorensen SM, Dudley MW, Kehne JH, Moser P, Gittos MW, Carr AA. Electrophysiological, biochemical and behavioural evidence for 5-HT_2 and 5-HT_3 mediated control of dopaminergic function. Psychopharmacology 1993;112:60–7.
Parsons LH, Justice JB. Serotonin and dopamine sensitization in the nucleus accumbens, ventral tegmental area, and dorsal raphe nucleus following repeated cocaine administration. J Neurochem 1993;61:1611–9.
Pellow S. Anxiolytic and anxiogenic drug effects in a novel test of anxiety: are exploratory models of anxiety in rodents valid? Methods Find Exp Clin Pharmacol 1986;8:557–65.
Pellow S, Chopin P, File SE, Briley M. Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J. Neurosci Methods 1985;14:149-67.
Piazza PV, Deminiere JM, le Moal M, Simon H. Stress-and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. Brain Res 1990;514:22–6.
Pich EM, Pagliusi SR, Tessari M, Talabot-Ayer D, Hooft van Huijsduijnen R, Chiamulera C. Common neural substrates for the addictive properties of nicotine and cocaine. Science 1997;275:83–6.
Pierce RC, Kalivas PW. A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. Brain Res Rev 1997;25:192–216.
Pierre PJ, Vezina P. Predisposition to self-administer amphetamine: the contribution of response to novelty and prior exposure to the drug. Psychopharmacology 1997;129:277–84.
Pijnenburg AJJ, van Rossum JM. Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens. J Pharm Pharmacol 1973;25:1003–5.
Pollack MH, Rosenbaum JF. Fluoxetine treatment of cocaine abuse in heroin addicts. J Clin Psychiatry 1991;52:31–3.
Porrino LJ, Ritz MC, Goodman NL, Sharpe LG, Kuhar MJ, Goldberg SR. Differential effects of the pharmacological manipulation of serotonin systems on cocaine and amphetamine self-administration in rats. Life Sci 1989;45:1529–35.
Post RM, Rose H. Increasing effects of repetitive cocaine administration in the rat. Nature 1976;260:731–2.
Pothoff AD, Ellison G, Nelson L. Ethanol intake increases during continuous administration of amphetamine and nicotine, but not several other drugs. Pharmacol, Biochem Behav 1983;18:489–93.
Poulos CX, Le DA, Parker JL. Impulsivity predicts individual susceptibility to high levels of alcohol self-administration. Behav Pharmacol 1995; 6:810–4.
Poulos CX, Parker JL, Le DA. Increased impulsivity after injected alcohol predicts later alcohol consumption in rats: evidence for ''loss-of-control drinking'' and marked individual differences. Behav Neurosci 1998; 112:1247–57.
Przegalinski E, Filip M. Stimulation of serotonin (5-HT)1A receptors attenuates the locomotor, but not the discriminative, effects of amphetamine and cocaine in rats. Behav Pharmacol 1997;8:699–706.
Rawson RA, Tennant FS, McCann MA. Characteristics of 68 chronic phencyclidine abusers who sought treatment. Drug Alcohol Depend 1981;8:223–7.
Reavill C, Hatcher JP, Lewis VA, Sanger GJ, Hagan J. 5-HT_4 receptor antagonism does not affect motor and reward mechanisms in the rat. Eur J Pharmacol 1998;357:115–20.
Redgrave P. Modulation of intracranial self-stimulation behaviour by local perfusions of dopamine, noradrenaline and serotonin within the caudate nucleus and nucleus accumbens. Brain Res 1978;155:277–95.
Reuben M, Clarke PB. Nicotine-evoked [^{3}H]-5-hydroxytryptamine release from rat striatal synaptosomes. Neuropharmacology 2000;39:290–9.
Rezvani AH, Levin ED. Cognitive effects of nicotine. Biol Psychiatry 2001; 49:258–67.
Ribeiro EB, Bettiker RL, Bogdanov M, Wurtman RJ. Effects of systemic nicotine on serotonin release in rat brain. Brain Res 1993;621:311–8.
Ridley RM, Baker HF, Owen F, Cross AJ, Crow TJ. Behavioural and biochemical effects of chronic amphetamine treatment in the vervet monkey. Psychopharmacology 1982;78:245–51.
Roberts DC, Loh EA, Baker GB, Vickers G. Lesions of central serotonin systems affect responding on a progressive ratio schedule reinforced either by intravenous cocaine or by food. Pharmacol, Biochem Behav 1994;49:177–82.
Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 1993;18: 247–91.
Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 2000;95:S91–S117.
Rocha BA, Fumagalli F, Gainetdinov RR, Jones SR, Ator R, Giros B, Miller GW, Caron MG. Cocaine self-administration in dopamine-transporter knockout mice. Nat Neurosci 1998;1(2):132–7.
Rogers RD, Blackshaw AJ, Middleton HC, Matthews K, Hawtin K, Crowley C, Hopwood A, Wallace C, Deakin JFW, Sahakian BJ, Robbins TW. Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: implications for the monoaminergic basis of impulsive behavior. Psychopharmacology 1999;146:482–91.
Rogers RD, Everitt BJ, Baldacchino A, Blackshaw AJ, Swainson R, Wynne K, Baker NB, Hunter J, Carthy T, Booker E, London M, Deakin JFW, Sahakian BJ, Robbins TW. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal vol-

unters: evidence for monoaminergic mechanisms. Neuropsychopharmacology 2000;20:322–39.
Rohsenhow DJ, Monti PM. Does urge to drink predict relapse after treatment? Alcohol Res Health 1999;23:225–32.
Rosenthal TL, Edwards NB, Ackerman BJ, Knott DH, Rosenthal RH. Substance abuse patterns reveal contrasting personal traits. J Subst Abuse 1990;2:255–63.
Schilström B. Nicotinic effects on midbrain dopamine neurons: a dual mechanism of action. Thesis, Department of Pharmacology, Karolinska Institute, 2000. ISBN 91-628-4309-5, pp. 1–73.
Segal DS, Mandell AJ. Long-term administration of d-amphetamine: progressive augmentation of motor activity and stereotypy. Pharmacol, Biochem Behav 1974;2:249–55.
Sellers EM, Naranjo CA, Kadlec K. Do seretonin uptake inhibitors decrease smoking? Observations in a group of heavy drinkers. J Clin Psychopharmacol 1987;7:417–20.
Shallice T, Burgess P. The domain of supervisory processes and temporal organization of behaviour. Philos Trans R Soc Lond, Ser B 1996;351: 1405–12.
Shippenberg TS, Heidbreder C. Sensitization to the conditioned rewarding effects of cocaine: pharmacological and temporal characteristics. J Pharmacol Exp Ther 1995;273:808–15.
Shoaib M, Stolerman IP, Kumar RC. Nicotine-induced place preferences following prior nicotine exposure in rats. Psychopharmacology 1994; 113:445–52.
Sills TL, Fletcher PJ. Fluoxetine attenuates morphine-induced locomotion and blocks morphine-sensitization. Eur J Pharmacol 1997;337:161–4.
Sills TL, Greenshaw AJ, Baker GB, Fletcher PJ. The potentiating effect of sertraline and fluoxetine on amphetamine-induced locomotor activity is not mediated by serotonin. Psychopharmacology 1999;143:426–32.
Sills TL, Greenshaw AJ, Baker GB, Fletcher PJ. Subchronic fluoxetine treatment induces a transient potentiation of amphetamine-induced hyperlocomotion: possible pharmacokinetic interaction. Behav Pharmacol 2000;11:109–16.
Silva RC, Brandao ML. Acute and chronic effects of gepirone and fluoxetine in rats tested in the elevated plus-maze: an ethological analysis. Pharmacol, Biochem Behav 2000;65:209–16.
Söderpalm B. On the neuropharmacology of conflict behaviour. Thesis, Department of Pharmacology, Göteborg University, 1990. pp. 1–94.
Söderpalm B. Sensitiseringsfenomen och beroendeframkallande droger-mekanismer och konsekvenser. Folkhälsoinstitutet ISBN 91-7257-048-2, 1999, 24. pp. 11–21.
Söderpalm B, Ericson M, Olausson P, Blomqvist O, Engel JA. Nicotinic mechanisms involved in the dopamine activating and reinforcing properties of ethanol. Behav Brain Res 2000;113:85–96.
Soubrie P. Reconsiling the role of central serotonin neurons in human and animal behavior. Behav Brain Sci 1986;9:319–64.
Spanagel R, Weiss F. The dopamine hypothesis of reward: past and current status. TINS 1999;22:521–7.
Sprouse JS, Aghajanian GK. Responses of hippocampal pyramidal cells to putative serotonin 5-HT_{1A} and 5-HT_{1B} agonists: a comparative study with dorsal raphe neurons. Neuropharmacology 1988;27:707–15.
Stolerman IP. Inter-species consistency in the behavioural pharmacology of nicotine dependence. Behav Pharmacol 1999;10:559–80.
Taylor JR, Jentsch JD. Repeated intermittent administration of psychomotor stimulant drugs alters the acquisition of pavlovian approach behavior in rats: differential effects of cocaine, D-amphetamine and 3,4-methylenedioxymethamphetamine ("ecstasy"). Biol Psychiatry 2001;50:137–43.
Thiebot MH, Le Bihan C, Soubrie P, Simon P. Benzodiazepines reduce the tolerance to reward delay in rats. Psychopharmacology 1985; 86: 147–52.
Tiihonen J, Kuikka JT, Bergström KA, Karhu J, Viinamaki H, Lehtonen J, Hallikainen T, Yang J, Hakola P. Single-photon emission tomography imaging of monoamine transporters in impulsive violent behaviour. Eur J Nucl Med 1997;24:1253–60.
Tomkins DM, Sellers EM, Fletcher PJ. Median and dorsal raphe injections of the 5-HT_{1A} agonist, 8-OH-DPAT, and the GABAA agonist, muscimol, increase voluntary ethanol intake in Wistar rats. Neuropharmacology 1994;33:349–58.
Ugedo L, Grenhoff J, Svensson TH. Ritanserin, a 5-HT_2 receptor antagonist, activates midbrain dopamine neurons by blocking serotonergic inhibition. Psychopharmacology 1989;98:45–50.
Vezina P, Blanc G, Glowinski J, Tassin J-P. Nicotine and morphine differentially activate brain dopamine in prefronttocortical and subcortical terminal fields: effects of acute and repeated injections. J Pharmacol Exp Ther 1992;261:484–90.
Virkkunen M, Rawlings R. CSF biochemistries, glucose metabolism, and diurnal activity rythms in alcoholic, violent offenders, fire setters and healthy volunters. Arch Gen Psychiatry 1994;51:20–7.
von Knorring L, Oreland L. Personality traits and platelet monoamine oxidase in tobacco smokers. Psychol Med 1985;15:327–34.
von Knorring L, Oreland L, Winblad B. Personality traits related to monoamine oxidase activity in platelets. Psychiatry Res 1984;12:11–26.
von Knorring L, Oreland L, von Knorring AL. Personality traits and platelet MAO activity in alcohol and drug abusing teenage boys. Acta Psychiatr Scand 1987;75:307–14.
Walsh SL, Cunningham KA. Serotonergic mechanisms involved in the discriminative stimulus, reinforcing and subjective effects of cocaine. Psychopharmacology 1997;130:41–58.
Williamson S, Gossop M, Powis B, Griffiths P, Fountain J, Strang J. Adverse effects of stimulant drugs in a community sample of drug users. Drug Alcohol Depend 1997;44:87–94.
Wilson JM, Kalasinsky KS, Levey AI, Bergeron C, Reiber G, Anthony RM, Schmunk GA, Shannak K, Haycock JW, Kish SJ. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. Nat Med 1996;2:699–703.
Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychol Rev 1987;94:469–92.
Wise RA, Rompre PP. Brain dopamine and reward. Ann Rev Psychol 1989;40:191–225.
Wise RA, Bauco P, Carlezon WA, Trojniar W. Self-stimulation and drug reward mechanisms. Ann NY Acad Sci 1992;654:193–8.
Woolverton WL, Ricaurte GA, Forno LS, Seiden LS. Long-term effects of chronic methamphetamine administration in rhesus monkeys. Brain Res 1989;486:73–8.
Yoshimoto K, McBride WJ, Lumeng L, Li T-K. Alcohol stimulates the release of dopamine and serotonin in the nucleus accumbens. Alcohol 1991;9:17–22.
Yu PH, Boulton AA. Irreversible inhibition of monoamine oxidase by some components of cigarette smoke. Life Sci 1987;41:675–82.