Abstract Rationale: Repeated exposure to addictive drugs causes neuroadaptive alterations that are proposed to increase the incentive motivation to consume drugs and to decrease the ability to inhibit such inappropriate motivational impulses and responses. Together, these behavioral consequences of drug intake may underlie the compulsive drug-seeking and-taking behaviors observed in drug abuse. Objective: Brain serotonin (5-HT) has been implicated in these mechanisms and this study therefore investigated the consequences of brain 5-HT depletion on the behavioral and neurochemical effects induced by repeated daily nicotine treatment (15 days) in male rats. Methods: The effects of the present pharmacological manipulations were evaluated behaviorally (locomotor activity, the elevated plus-maze) and neurochemically (microdialysis, brain biochemistry). Results: Depletion of brain 5-HT produced behavioral disinhibition in the elevated plus-maze. In 5-HT-depleted animals, nicotine-induced locomotor sensitization was observed on treatment days 5, 10, and 15, but only on day 15 in the sham-operated rats. Postsensitization, the locomotor stimulatory effects of amphetamine and the dopamine receptor agonists SKF 38,393, apomorphine, and quinpirole were decreased in 5-HT-depleted animals, an effect that appeared to be more pronounced in nicotine-treated rats. Repeated nicotine treatment sensitized the nicotine-induced elevation of the extracellular accumbal dopamine levels in sham-operated, but not in 5-HT-depleted rats, and was also associated with decreased D₃ autoreceptor function in both nicotine-treated experimental groups. Conclusions: Depletion of brain 5-HT, which produces behavioral disinhibition, may slightly facilitate the overall expression of locomotor sensitization to nicotine and differentially affect the pre- and postsynaptic neuroadaptive events involved in the expression of these phenomena.

Keywords 5,7-DHT · Behavioral sensitization · Behavioral disinhibition · Dopamine · Serotonin · Elevated plus-maze · Locomotor activity · Microdialysis · Nicotine

Introduction

Drugs of abuse, including nicotine, share the ability to activate the mesocorticolimbic dopamine (DA) system (Di Chiara and Imperato 1988; Koob 1992), which projects from the ventral tegmental area to the terminal regions in the nucleus accumbens (N Acc) and the prefrontal cortex (Björklund and Lindvall 1984). This neural pathway has been implicated in processes related to drug reward (Engel 1977; Koob 1992; Wise and Rompre 1989) as well as in mechanisms involved in motivational processes and innate drives (Mogenson et al. 1993). Drug abuse is a state characterized by compulsive behaviors focused on drug-seeking and intake, and by a marked liability for relapse after drug withdrawal. Since the mesocorticolimbic DA system has been implicated in these behaviors, as well as in the reward associated with the drug intake, preclinical research on drug abuse has mainly been focused on mechanisms involving this DA pathway.

The mesocorticolimbic DA activation produced by nicotine as well as other drugs of abuse is associated with increased extracellular DA levels in the N Acc (Di Chiara and Imperato 1988; Koob 1992; Nisell et al. 1994; Sharp et al. 1987). The subsequent activation of postsynaptic accumbal DA receptors generally stimulat-
Drug-induced sensitization has been suggested to progressively augment the incentive qualities of addictive drugs and drug-associated stimuli, and the neurobiological processes underlying the behavioral and neurochemical sensitization could thus contribute to the development of drug abuse. The incentive-sensitization theory of addiction (Robinson and Berridge 1993) hypothesizes that drug-induced sensitization is involved in transforming the wanting of a drug into craving, and that conditioned stimuli which activate the hypersensitive mesocorticolimbic DA system provide strong motivational impulses for obtaining and consuming the drug. Supporting this theory, experiments have demonstrated that previous drug experience may increase subsequent self-administration of both amphetamine (Piazza et al. 1990; Pierre and Vezina 1997) and cocaine (Horger et al. 1990, 1992). Moreover, sensitization enhances the reinforcing effects of different psychostimulants and opiates in the conditioned place preference paradigm (Lett 1989; Shippenberg and Heidbreder 1995) and prior cocaine sensitization increases the ability of amphetamine to enhance responding for conditioned reinforcers (Taylor and Horger 1999). Taken together, these and other findings imply that drug-induced sensitization of the mesocorticolimbic DA neurons may be involved in the increased control of behavior exerted by stimuli associated with the effects of the reinforcing drugs.

Besides the incentive motivational processes possibly related to drug-induced DA sensitization, also the role of inhibitory control of behavior, or impulse control, in the development of drug abuse has lately received increased attention (Jentsch and Taylor 1999; Olausson et al. 1999, 2000; Robbins and Everitt 1999). Repeated drug exposure has been proposed to produce a state of impaired inhibitory control that may contribute to the compulsive drug-seeking and/or drug-intake encountered in drug addicts (Jentsch and Taylor 1999; Olausson et al. 1999). Supporting this notion, it is well established that drug addicts using nicotine or psychostimulants have an impulsive personality and display decreased inhibitory control when assessed in neuropsychological tests (Allen et al. 1998; Bickel et al. 1999; Kirby et al. 1999; von Knorring and Oreland 1985; Rogers et al. 1999). Furthermore, psychostimulant abusers also display decision-making deficits (Bechara et al. 1999; Rogers et al. 1999). Together these impairments may contribute to the inability of the drug addict to control the drug use (O’Brien and McLennan 1996).

Besides DA, serotonin (5-HT) also appears to have a significant role in these behaviors. The neuroanatomical as well as the functional substrates for an interaction between the brain 5-HT systems and the mesocorticolimbic DA system are well established (Kelland and Chiodo 1996; Steinbusch 1984). 5-HT appears to be involved in neuronal processes related to conflict behavior, inhibitory control, impulsivity, and decision-making (Engel et al. 1984; Rogers et al. 1999; Roy and Linnoila 1988; Söderpalm 1990; Soubrie 1986; Stein et al. 1996), as well as in reward-related mechanisms (Blomqvist et al. 1994; Callaway et al. 1990; Cunningham et al. 1992; LeMarquand et al. 1994; Olausson et al. 1999; Svensson et al. 1989). Interestingly, some studies (King et al. 1997, 1998; Olausson et al. 1999; Parsons and Justice 1993) suggest that the development of behavioral sensitization to drugs of abuse also involve serotonergic mechanisms.

5-HT has also been implicated in the pharmacological effects of nicotine. Studies have shown that systemic injections of nicotine elevate the extracellular levels of 5-HT in the frontal cortex (Ribeiro et al. 1993) and increases 5-HT release from striatal synaptosomes (Reuben and Clarke 2000). On the other hand, both acute and chronic nicotine exposure decreases 5-HT biosynthesis in hippocampal synaptosomes (Benwell and Balfour 1982) as well as the 5-hydroxyindoleacetic acid (5-HIAA) levels in this brain region (Balfour et al. 1986). Recently, we demonstrated that in the rat nicotine-induced locomotor sensitization is associated with nicotine-induced behavioral disinhibition in the elevated plus-maze (Olausson et al. 1999), and that chronic treatment with the selective 5-HT reuptake inhibitor (SSRI) citalopram counteracted the expression of both behaviors (Olausson et al. 1999). Therefore, to further study the influence of 5-HT on behavioral sensitization to nicotine, the effect of a selective 5,7-dihydroxytryptamine (5,7-DHT)-induced depletions of brain 5-HT on the development of locomotor sensitization and on the associated evivo brain neurochemistry was examined. Moreover, by means of in vivo microdialysis in awake, freely moving animals the effects of 5-HT depletions on nicotine-induced enhancements of extracellular DA levels in the N Acc were investigated in nicotine-sensitized male Sprague-Dawley rats.