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Review

The role of the cannabinoid system in nicotine addiction

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Abstract

Nicotine, the main psychoactive component in tobacco smoke, appears to play a major role in tobacco addiction, producing a high morbidity and mortality in the world. A great amount of research has been developed to elucidate the neural pathways and neurotransmitter systems involved in such a complex addictive behaviour. One possible candidate is the cannabinoid system, which has been reported to participate in the addictive properties of other drugs of abuse. This review is focused on the recent pharmacological and molecular studies assessing cannabinoid–nicotine interactions, with special attention to those studies evaluating the behavioural responses related to the development of nicotine addiction.

Keywords: Addiction; Cannabinoid; Dependence; Nicotine; Reward; Withdrawal

Contents

1. Introduction

Nicotine is one of the main active components in tobacco smoke that initiates and sustains tobacco addiction. Nicotine induces its central pharmacological effects by acting on nicotinic acetylcholine receptors (nAChRs), which are pentameric complexes consisting of the combination of different α (α2–α10) and β (β2–β4) protein subunits (Le Novère et al., 2002). The nAChRs are ubiquitously distributed in the central nervous system (CNS), mainly at a pre-synaptic level, and they serve as ligand-gated ion channels that promote neurotransmitter release (Wonnacott, 1997). Thus, nAChR activation plays a neuromodulatory role in the CNS and is involved in a large number of physiological and pathological processes such as pain neurotransmission, control of movement, cognitive processes, emotional responses, and drug abuse (Buisson and Bertrand, 2002; File et al., 2002; Jain, 2004; Katner et al., 2004; Schochet et al., 2004).

An intense research has been developed to elucidate the neural pathways and neurotransmitter systems involved in nicotine addictive properties. Numerous candidates including GABA, glutamate, noradrenaline, serotonin, corticotropin-releasing factor (CRF), dopamine

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(DA) and endogenous opioids have been shown to play a role in nicotine addiction (Cryan et al., 2003). More recently, pharmacological and molecular studies have suggested that the endocannabinoid system could also play an important role in nicotine addictive properties. So far, two cannabinoid receptors have been identified and cloned, the CB1 cannabinoid receptor, mainly located in the CNS (Matsuda et al., 1990), and the CB2 receptor, which has a predominant distribution in immune cells (Munro et al., 1993). However, recent data suggest the presence of a third and still uncloned cannabinoid receptor in the brain, namely the "CB3" or "CBx" receptor (Breivogel et al., 2001; Di Marzo et al., 2000; Hájos and Freund, 2002; Járai et al., 1999). The activation of CB1 cannabinoid receptors mediates the main effects of cannabinoids in the CNS (Ledent et al., 1999; Zimmer et al., 1999), and is responsible for the addicting properties of cannabinoids (Ledent et al., 1999). These cannabinoid receptors participate in similar physiological functions than nAChRs, such as nociceptive transmission, motor activity, learning and memory processes and emotional responses. Interestingly, CB1 cannabinoid receptors have been shown to be involved in the addictive properties of other drugs of abuse, such as opioids, ethanol, cocaine and MDMA (Braida and Sala, 2002; De Vries et al., 2001; Fattore et al., 2003; Mechoulam and Parker, 2003; Navarro et al., 2001), suggesting that the cannabinoid system may be a common neurobiological substrate for the addictive properties of drugs of abuse.

This review is focused on the involvement of the cannabinoid system in the different responses induced by acute and chronic administration of nicotine that are related to its addictive properties. We will examine the pharmacological and molecular studies concerning cannabinoid–nicotine interactions, with special attention to those studies evaluating the adaptive and motivational responses induced by chronic nicotine administration.

2. Acute cannabinoid–nicotine interactions

Two pharmacological studies have investigated the acute interaction between the effects induced by nicotine and cannabinoid agonists. Significant interactions between Δ^9-tetrahydrocannabinol (THC) and nicotine were reported on locomotion, heart rate, body temperature, anxiety and nociception (Pryor et al., 1978; Valjent et al., 2002). Thus, nicotine potentiated hypothermia, bradycardia, hypolocomotion and impaired rotarod performance induced by THC (Pryor et al., 1978). In agreement, a more recent study showed that nicotine strongly facilitated hypolocomotion, antinociception, hypothermia and anxiolytic-like effects induced by acute administration of THC (Valjent et al., 2002). The facilitating effect of nicotine in THC acute responses was also observed at the biochemical level. Accordingly, co-administration of both nicotine and THC potentiated the enhancement of c-Fos inmunoreactivity in several brain regions such as the shell of the nucleus accumbens (NAcc), central and basolateral amygdala, bed-nucleus of stria terminalis, cingular and piriform cortex and paraventricular nucleus of the hypothalamus (Valjent et al., 2002). Most of these areas are highly innervated by DA inputs, suggesting that the interaction between nicotine and cannabinoids could occur via the stimulation of mesolimbic and mesocortical dopaminergic system.

So far, only one study has evaluated the possible role of the CB1 cannabinoid receptors in nicotine acute pharmacological responses by using CB1 knockout mice (Castañé et al., 2002). Thus, nicotine-induced antinociceptive responses in the tail-immersion test, which are mainly mediated through a spinal mechanism, were enhanced in mice lacking CB1 cannabinoid receptors. However, the effects of acute nicotine administration on the hot-plate test and locomotor activity were not modified in these CB1 knockout mice (Castañé et al., 2002).

3. The role of the cannabinoid system in nicotine-induced reinforcing effects

From a neurobiological and behavioural point of view processes involved in the initiation and maintenance of drug addictive behaviour are complex. One important aspect for the initiation of the addictive process is the capacity of the drug to induce reinforcing effects. On the other hand, the negative consequences of drug abstinence have a crucial motivational significance for relapse and maintenance of the addictive behaviour (Koob and Le Moal, 2001).

Similar to other drugs of abuse, nicotine induces reinforcing effects, as revealed by conditioned place preference (CPP), intracranial self-stimulation (ICSS) and intravenous self-administration (SA) paradigms (Laviolette and van der Kooy, 2004; Malin, 2001). The possible involvement of the cannabinoid system in the rewarding effects of nicotine has been evaluated by using CPP and SA paradigms. The CPP paradigm measures a learning process where the animal shows a preference for a context due to the contingent association between the context and a drug-associated stimulus. Therefore, after the conditioning period, drug-free animals spend more time in a previously drug-paired compartment in comparison with a neutral vehicle-paired compartment (Fig. 1a). On the other hand, the SA procedure directly evaluates the reinforcing properties of a drug and provides a unique model to reveal drug consumption in animals (Fig. 1b). In this paradigm, the reinforcing aspects of the drug are reflected by the number of injections that the animal self-administers. On the CPP paradigm, a first pharmacological study showed that the co-administration of sub-threshold doses of THC and nicotine

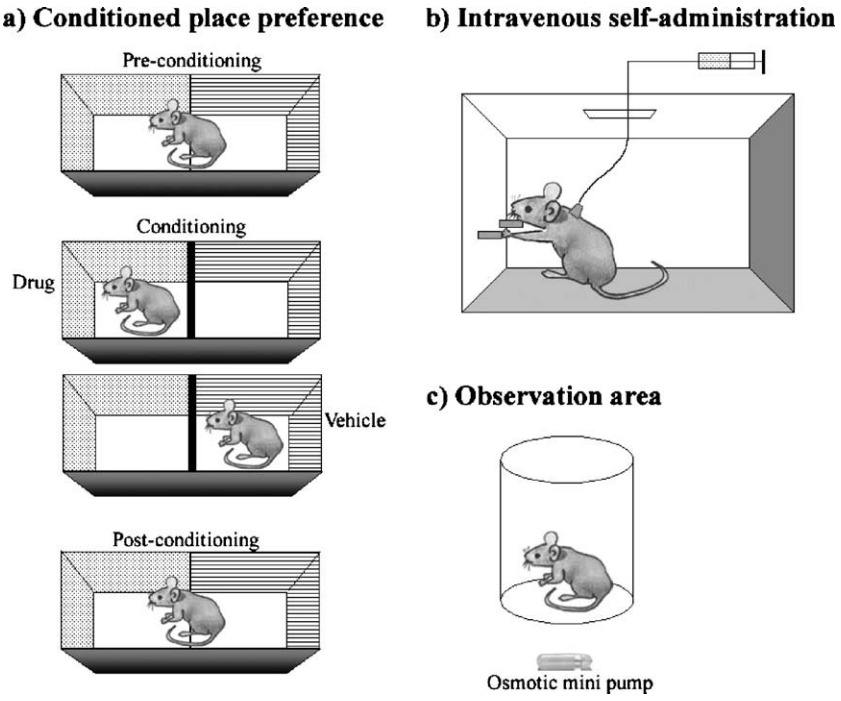

Fig. 1. Experimental procedures for evaluating behavioural responses related to nicotine addiction in rodents. (a) The conditioned place preference procedure is commonly used to reveal the rewarding properties of nicotine. This paradigm consists of three different phases. In the first phase, namely pre-conditioning, animals are allowed to freely explore a box with two compartments that have distinct visual and tactile characteristics and the time spent in each compartment is recorded. In the conditioning phase, mice receive alternative injections of nicotine in one compartment and vehicle in the opposite compartment during several days. The last phase, namely post-conditioning, is conducted exactly as the pre-conditioning phase, animals have free access to both compartments of the conditioning apparatus and the time spend in each compartment is recorded. Results are usually expressed as a score calculated by the time spent in the drug associated compartment during the post-conditioning minus the time spent in the same compartment during the pre-conditioning. A positive score means that the compound tested induces rewarding effects. CPP paradigm also allows to evaluate the aversive properties induced by a stimulus and has been used to reveal the dysphoric aspects of nicotine withdrawal. (b) Intravenous self-administration is another common model used to study the reinforcing properties of nicotine. This model resembles the drug-taking behaviour in humans. Animals are first implanted with indwelling vein catheters. After several days of recovery, animals are trained to make an operant response (nose-poke or lever-press) in order to receive an infusion of nicotine under a fixed ratio or progressive ratio schedule of reinforcement. (c) Nicotine physical dependence can be induced by using two different strategies: the subcutaneous implantation of osmotic mini pumps that deliver a constant flow of nicotine solution or a discontinuing treatment based on intermittent administration of this drug during several days. The spontaneous or antagonist-precipitated interruption of nicotine chronic treatment precipitates several somatic signs of withdrawal which are usually evaluated placing mice inside a circular clear plastic area.

induced rewarding effects (Valjent et al., 2002) (Fig. 2a). In addition, the previous priming of THC usually needed to induce this response (Valjent and Maldonado, 2000) was not required when low doses of THC were co-administered with nicotine. This result indicates that low doses of cannabinoids associated with nicotine could have a higher capability to induce behavioural responses related to addictive processes than THC administration alone (Valjent et al., 2002).

Recent studies using knockout mice have attempted to clarify the involvement of CB1 cannabinoid receptors in nicotine rewarding properties, although the results obtained

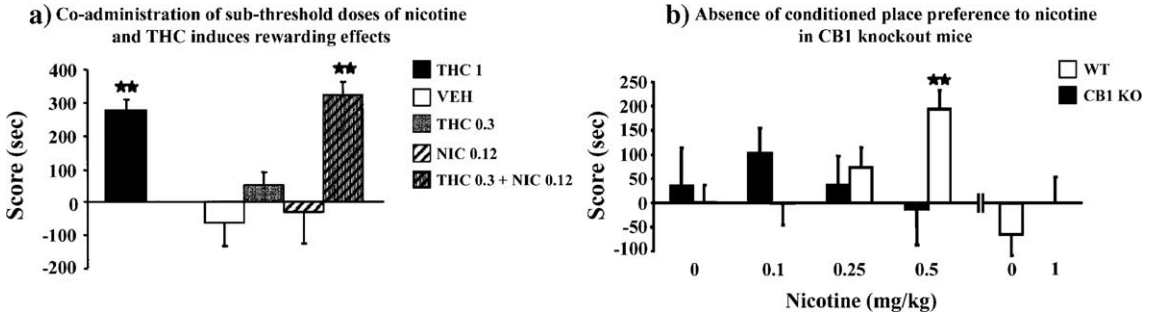

Fig. 2. Cannabinoid–nicotine interactions on the conditioned place preference paradigm. (a) ★★ $p<0.01$ versus vehicle (VEH) group (Newman–Keuls test). Adapted with permission from Valjent et al. (2002). (b) ★★ $p<0.01$ versus control group of the same genotype (Dunnett test). Adapted with the permission from Castañé et al. (2002).

with these animals have provided conflicting data. Indeed, the rewarding effects of nicotine, assessed in the CPP paradigm, were abolished in CB1 receptor knockout mice (Castañé et al., 2002) (Fig. 2b), while the absence of CB1 cannabinoid receptors did not modify the acquisition of nicotine self-administration in an acute reinforcement paradigm (Cossu et al., 2001). However, the acquisition and maintenance of a stable operant self-administration responding for nicotine has not been yet evaluated in mice lacking CB1 cannabinoid receptors. Although data from these mutant mice show apparent discrepancies, the CB1 receptor antagonist SR 141716 has been shown to decrease nicotine stable operant self-administration in rats (Cohen et al., 2002), suggesting an involvement of CB1 cannabinoid receptors in nicotine rewarding effects. Therefore, CB1 cannabinoid receptor antagonists could be of interest to reduce the reinforcing value of nicotine in order to facilitate tobacco smoking cessation. In this sense, SR 141716A (Rimonabant) has been tested in Phase II clinical trials as a new possible therapeutic treatment for reduction of tobacco intake with promising results, and this cannabinoid antagonist is now being tested in Phase III clinical trials (Fernandez and Allison, 2004).

Nicotine produces its rewarding action by stimulating mesolimbic dopaminergic transmission (Dani and De Biasi, 2001; Di Chiara, 2000; Pontieri et al., 1996), a common feature of all the prototypical addictive drugs (Koob and Le Moal, 2001). The activation of DA activity by nicotine depends on a functional balance between excitatory and inhibitory inputs to the ventral tegmental area (VTA) DA neurons, in addition to the direct nicotine effects on DA neurons themselves (Mansvelder and McGehee, 2002). The cannabinoid system may also contribute to the regulation of this balance. Indeed, in vivo brain microdialysis studies have revealed that SR 141716 blocked nicotine-induced DA release in the shell of the NAcc (Cohen et al., 2002). Different nAChR subtypes modulate GABAergic and glutamatergic inputs to VTA DA neurons. Indeed, while heteromeric α4β2-nAChRs modulate GABA release, homomeric α7-nAChRs influence glutamate transmission (Mansvelder and McGehee, 2002). Recently, endocannabinoids have been shown to inhibit the function of α7-nAChRs expressed in *Xenopus* oocytes (Oz et al., 2004). Therefore, the activity of α7-nAChRs could be also modulated by endocannabinoids in vivo, thus contributing to the regulation of the rewarding properties of nicotine.

4. The role of the cannabinoid system in nicotine-induced physical dependence

Clinical and animal studies have shown that chronic nicotine administration develops physical dependence revealed by the presence of a withdrawal syndrome when the treatment is disrupted. Thus, both spontaneous (Damaj et al., 2003) and mecamylamine-precipitated nicotine withdrawal (Malin, 2001) have been reported in several animal species by using different experimental protocols (Fig. 1c). The most characteristic somatic manifestations of nicotine withdrawal in rodents are tremors, wet dog shakes, teeth chatters, ptosis, abdominal constrictions and scratching (Isola et al., 1999). The first evidence demonstrating an interaction between nicotine and cannabinoids in the development of physical dependence processes was reported by Valjent et al. (2002). Indeed, mice co-treated with nicotine and THC displayed an enhancement in the somatic expression of cannabinoid antagonist-precipitated THC withdrawal syndrome.

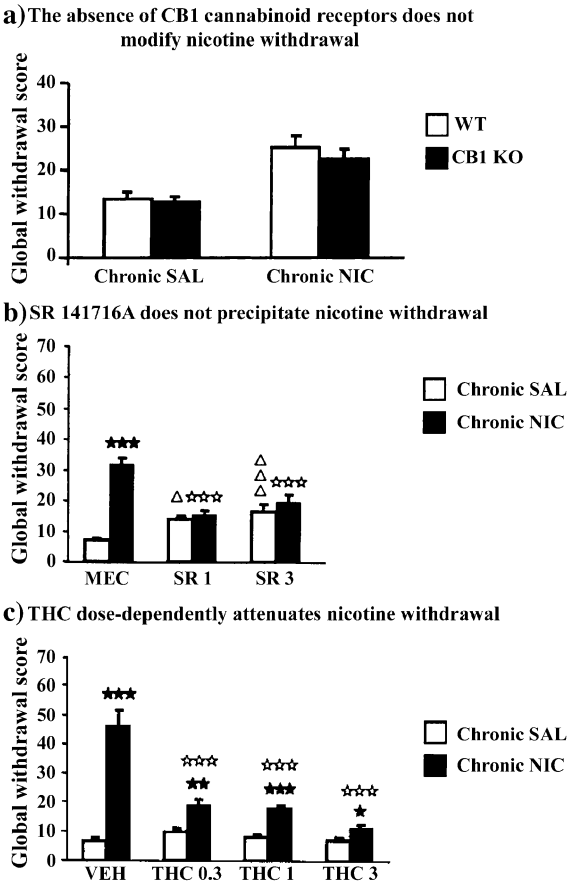

Fig. 3. The role of the cannabinoid system in nicotine-induced physical dependence. (a) Abstinence was precipitated by acute administration of mecamylamine (1 mg/kg, s.c.) after a 6-day period of nicotine (10 mg/kg/day) or saline infusion. Adapted with the permission from Castañé et al. (2002). (b) Abstinence was precipitated by acute administration of mecamylamine (MEC) (1 mg/kg, s.c.) or SR 141716A (SR) (1 and 3 mg/kg, i.p.) after a 6-day period of nicotine (25 mg/kg/day) or saline infusion. ★★★ $p<0.001$ versus chronic saline (SAL) (one-way ANOVA). ☆☆☆ $p<0.001$ versus nicotine-mecamylamine group (Dunnett test). △ $p<0.05$, △△△ $p<0.001$ versus saline-mecamylamine group (Dunnett test). Adapted with the permission from Balerio et al. (2004). (c) Abstinence was precipitated by acute administration of mecamylamine (MEC) (1 mg/kg, s.c.) after a 6-day period of nicotine (25 mg/kg/day) or saline infusion. THC (0, 0.3, 1 and 3 mg/kg, i.p.) was administered 15 min before withdrawal. ★ $p<0.05$, ★★ $p<0.01$, ★★★ $p<0.001$ versus chronic saline (SAL) (one-way ANOVA). ☆☆☆ $p<0.001$ versus vehicle (VEH) group (Dunnett test).

The involvement of CB1 cannabinoid receptors in nicotine dependence has been studied by using CB1 knockout mice. Thus, the nicotinic antagonist mecamylamine precipitated a withdrawal syndrome in nicotine-treated animals that was similar in wild-type and CB1 knockout mice (Castañé et al., 2002) (Fig. 3a). In agreement, the CB1 antagonist SR 141716A was not able to precipitate a withdrawal syndrome in nicotine-dependent animals (Balerio et al., 2004) (Fig. 3b), suggesting that the endogenous cannabinoid system, through CB1 cannabinoid receptors, does not participate in the development and expression of nicotine physical dependence. Biochemical studies also support these findings since no modification in CB1 cannabinoid receptor levels was reported following chronic nicotine exposure (Balerio et al., 2004; González et al., 2002). However, Izenwasser et al. (2004) have recently observed that this treatment induces changes in cannabinoid receptor density in adolescent male, but not in female or adult rats. Therefore, we cannot exclude the participation of cannabinoid receptors in the effects of nicotine when administered at younger animals. On the other hand, cannabinoid agonists seem to attenuate the severity of the somatic manifestations of nicotine withdrawal (Balerio et al., 2004) (Fig. 3c). Similar to other drugs of abuse, nicotine abstinence is associated with a selective up-regulation of the cyclic AMP pathway (Tzavara et al., 2002) pointing to this cascade as a possible target for cannabinoids in ameliorating nicotine withdrawal symptoms. Further studies must be performed to clarify the neurobiological substrate of nicotine dependence, and the possible role of the cannabinoid system in this nicotine behavioural response.

5. Final remarks

Nicotine addiction is a complex behavioural and neurochemical process in which many neuroanatomical pathways and neurotransmitters are involved. The pharmacological and molecular studies described in the present review support the specific role of the endogenous cannabinoid system in the modulation of nicotine responses related to its addictive properties. These findings improve our understanding of nicotine addiction and could open new possibilities in the treatment of this major public health disorder.

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