



Review

CB₁ receptor antagonists for the treatment of nicotine addiction

Caroline Cohen*, Ercem Kudas, Guy Griebel

*Sanofi-Aventis, CNS Research Department, 31 Avenue Paul Vaillant-Couturier, 92220-Bagneux, France***Abstract**

Tobacco smoking is the largest cause of avoidable death and disease in developed countries. It is now viewed as a complex bio-psycho-social problem for which effective pharmacological treatments are needed. Nicotine is considered to be the primary compound of tobacco smoke that establishes and maintains tobacco dependence. The addictive effect of nicotine is mediated by activation of the mesolimbic system and the release of dopamine in the nucleus accumbens. Recently, the existence of a specific functional interaction between nicotine and the endocannabinoid system has been reported. Co-administration of sub-threshold doses of a cannabinoid agonist and nicotine produces rewarding effects and chronic nicotine treatment increases endocannabinoid levels in limbic regions. The CB₁ receptor plays a key role in this interaction. CB₁ knockout mice are less sensitive to the motivational effects of nicotine although this depends on the experimental model. The selective CB₁ antagonist, rimonabant (SR141716), reduces nicotine self-administration and nicotine-seeking behavior induced by conditioned cues in rats. Rimonabant appears to reduce nicotine addiction by attenuating the hyperactivation of the endocannabinoid system and the mesolimbic dopaminergic neuronal pathway. Rimonabant may be considered as a potential alternative to the current substitutive treatments of nicotine addiction and may offer a new hope for the treatment of smokers who wish to quit.

© 2005 Elsevier Inc. All rights reserved.

Keywords: Nicotine; Addiction; Cannabinoid antagonist**Contents**

1. Tobacco and nicotine impact on health	387
2. Addiction to nicotine	388
3. Animal models of nicotine addiction	388
4. Site and mechanism of action of nicotine in the brain	389
4.1. Nicotinic acetylcholine receptors (nAChR)	389
4.2. The rewarding properties of nicotine	389
4.3. Neuronal plasticity	389
5. Reinforcing effects of cannabinoid agonists	390
6. Interaction between the endocannabinoid system and nicotine	390
7. Blockade of CB ₁ receptors and nicotine addiction: CB ₁ knockout mice.	391
8. Blockade of CB ₁ receptors and nicotine addiction: CB ₁ antagonists.	391
References	393

1. Tobacco and nicotine impact on health

Tobacco smoking is a major worldwide health problem (Peto et al., 1996). According to a recent study (Ezzati and Lopez, 2003), about 5 million premature deaths in the world are attributable to smoking. The leading causes of

* Corresponding author. Tel.: +33 1 45 36 20 21; fax: +33 1 45 36 20 70.

E-mail address: caroline.cohen@sanofi-aventis.com (C. Cohen).

death from smoking are cardiovascular diseases, chronic obstructive pulmonary disease and lung cancer. Worldwide, it is estimated that the prevalence of smoking averages 33% of the population aged 15 years and older. Tobacco use exists along a continuum from minimal use to abuse and then to addictive use. Substantial evidence that cigarettes and other forms of tobacco are addictive and that actions of nicotine provide the pharmacologic basis of tobacco addiction was originally compiled in the 1988 report of the US Surgeon General (US Department of Health and Human services, 1988; Royal College of Physicians, 2000). Since then the possibility that other tobacco compounds might participate in the addictive effects of tobacco has been raised. However, the large number of substances presented in tobacco smoke and the lack of data on their psychoactive effects and plasma concentrations attained during smoking have hindered progress in this area. The first constituents identified that might contribute to the addictive effects of tobacco are inhibitors of monoamine oxidase B (Fowler et al., 1996; Rommelspacher et al., 2002). By increasing dopaminergic transmission, they could theoretically potentiate the addictive effects of nicotine (see below). The term (nicotine) *addiction* when used in this chapter will refer to the operational definition given in the DSM-IV and ICD-10 for drug dependence, i.e., failure to abstain from taking the drug (American Psychiatric Association, 1995; World Health Organization, 1992).

2. Addiction to nicotine

Tobacco addiction is now viewed as a complex biopsychosocial problem for which several pharmacological treatments are available but many smokers find these treatments either unacceptable or ineffective, thus supporting a need for additional types of treatment (Goodman, 1990; O'Brien, 1996; Royal College of Physicians, 2000; Fiore et al., 2000; George and O'Malley, 2004). Absorption of cigarette smoke from the lung produces with each inhalation a high concentration arterial bolus of nicotine that reaches the brain within a few seconds (Henningfield et al., 1990). Nicotine produces discernable central nervous system effects. They have been compared to those of stimulants such as cocaine or amphetamine, although of lower magnitude (Stolerman and Jarvis, 1995). Smokers show a strong tendency to regulate their nicotine intake from cigarettes within quite narrow limits. Experiments aimed at investigating whether nicotine provides the reinforcement for the smoking of cigarettes have used a variety of strategies such as switching between cigarettes, which differ only in their nicotine yield, providing nicotine by other routes of administration, manipulating renal nicotine excretion or antagonizing the action of nicotine (Scherer, 1999; Harvey et al., 2004). Manipulations of nicotine availability produced compen-

satory puffing or inhalation ensuring that nicotine blood levels are not too low (provoking withdrawal), not too high (leading to unpleasant effects). Thus, smoking behavior is probably maintained by the positive reinforcing effects of nicotine as well as the avoidance of a withdrawal phase characterized by somatic and affective (craving) symptoms.

3. Animal models of nicotine addiction

Inasmuch as nicotine is thought to be the primary compound in tobacco smoke that establishes and maintains tobacco dependence, animal models of nicotine addiction have been developed. A systematic evaluation of these procedures by Stolerman (1999) revealed that animal studies of the behavioral pharmacology of nicotine dependence show good inter-species consistency. Nicotine is a positive reinforcer in animals (Goldberg and Henningfield, 1988). Similar to other drugs of abuse, animals learn to emit a specific response (lever press, nose poke) in order to receive intravenous injections of nicotine (Donny et al., 1998). Responding is function of the unit dose of nicotine and the schedule of reinforcement, i.e., increasing response requirement increases the number of responses. Environmental cues are particularly important for nicotine self-administration behavior (Goldberg et al., 1981; Caggiula et al., 2002; Cohen et al., 2005). Such stimuli, through pavlovian conditioning, acquire conditioned reinforcing and motivational properties and are therefore able to generate and maintain drug-seeking behavior. Motivational effects of nicotine-associated stimuli can be measured using second-order schedules of drug reinforcement, extinction/reinstatement models and place-conditioning paradigms. In the former, operant responding has been maintained in squirrel monkeys not only by nicotine but also by presentation of stimuli previously paired with the delivery of nicotine (Goldberg et al., 1981). In models of relapse, extinguished drug-seeking behavior is reinstated by presentation of drug-associated stimuli. Conditioned stimuli can maintain responding after extensive testing in the absence of nicotine. In a recent study in rats, lever pressing reinforced by contingent presentation of nicotine-associated cues persisted for 3 months after nicotine was withdrawn (Cohen et al., 2005). Conditioned place preference is another paradigm developed to assess the rewarding/aversive effects of drugs. Nicotine has been shown to induce in animals a preference for the box compartment repeatedly associated with the drug administration (Shoaib et al., 1994; Risinger and Oakes, 1995). Chronic administration of nicotine in rodents results in a state of "physical dependence" characterized by the occurrence of a withdrawal syndrome (Malin, 2001). The difficulty in developing such models using nicotine has certainly been one limiting factor in understanding nicotine addiction.

4. Site and mechanism of action of nicotine in the brain

4.1. Nicotinic acetylcholine receptors (nAChR)

The primary site of action of nicotine is the nicotinic acetylcholine receptor, a ligand-gated ion channel composed of five subunits (Sargent, 2000). To date, molecular cloning techniques have identified 16 genes encoding nAChR subunits. Most neuronal nAChRs are formed by a heteropentameric assembly of α - and β -subunits, the functional properties depending on the subunit composition. The regional distribution of α_4 and β_2 subunits coincides with high-affinity binding sites for [3 H]nicotine and chronic exposure to nicotine in humans and rodents increases the density of nicotine binding, mainly of the $\alpha_4\beta_2$ nAChR type (Marks et al., 1992; Perry et al., 1999).

4.2. The rewarding properties of nicotine

Several findings suggest that the $\alpha_4\beta_2$ nAChR subtype plays a major role in the reinforcing effects of nicotine. Nicotine self-administration is reduced in rats pretreated with dihydro- β -erythroidine or with SSR591813, a selective $\alpha_4\beta_2$ nAChR antagonist and partial agonist, respectively (Watkins et al., 1999; Cohen et al., 2003) or in genetically modified mice with functional deletion of the β_2 subunit (Picciotto et al., 1998). Positive reinforcing effects of nicotine are associated with *c-fos* expression in sensory as well as limbic structures in the rat brain (Pagliusi et al., 1996). Furthermore, nicotine and cocaine produced overlapping patterns of *c-fos* expression (Pich et al., 1997), supporting the idea that common neural substrates for the addictive properties of these drugs exist (Wise, 1996). Several neuronal pathways (dopaminergic, glutamatergic, GABAergic) are certainly involved in tobacco dependence and substances in addition to nicotine probably contribute to the powerful dependence producing effects of smoked tobacco (Royal College of Physicians, 2000). The dopamine hypothesis of drug addiction postulates that increased mesolimbic dopaminergic transmission is a common mechanism of action for drugs of abuse, including nicotine, morphine, ethanol, amphetamine and cocaine (Wise and Bozarth, 1987; Di Chiara and Imperato, 1988). Nicotine self-administration is reduced by pretreatment with dopamine antagonists and is reduced by lesions of dopaminergic neurons (Corrigall and Coen, 1991; Corrigall et al., 1992). Nicotine produces discriminative stimuli in animals, and some cross-generalization between nicotine and other addictive drugs has been found (Desai et al., 2003; Cohen et al., 2003). In rats, nicotine increases extracellular levels of dopamine in limbic areas, in particular in the shell of the nucleus accumbens, and in the bed nucleus of the stria terminalis (an area which is part of the so-called extended amygdala and which is interconnected with the nucleus accumbens and the ventral tegmental area) (Pontieri et al., 1996; Carboni et al.,

2000). Both the α_4 and the β_2 subunits are crucial in mediating the dopamine-releasing effects of nicotine as indicated by the absence of striatal dopamine release in α_4 or β_2 subunit knockout mice treated with nicotine (Picciotto et al., 1998; Marubio et al., 2003) and by the reduction of nicotine-induced dopamine release in the nucleus accumbens shell after pre-treatment with the selective $\alpha_4\beta_2$ nAChR partial agonist, SSR591813 (Cohen et al., 2003). The effects of nicotine on dopamine function could be mediated by $\alpha_4\beta_2$ nAChRs located on dopamine-containing neurons of the ventral tegmental area and on terminal fields of these neurons in the nucleus accumbens (Wonnacott et al., 1990; Mansvelder and McGehee, 2002). Several studies have implicated other nAChR subunits, including the α_3 , α_6 , α_7 and β_3 subunits in the control of dopamine release induced by nicotine. Different nAChR subtypes have been found on glutamatergic (α_7) and GABAergic ($\alpha_4\beta_2$) terminals in the ventral tegmental area suggesting an indirect modulatory action of nicotine on dopamine neurons (Fig. 1). A particularity in the mode of action of nicotine is that the drug desensitizes nAChRs after their stimulation. nAChR subtypes show different levels of desensitization: the $\alpha_4\beta_2$ subunit desensitizes more rapidly than the α_7 subunit (Mansvelder and McGehee, 2002). Nicotine first activates then desensitizes the $\alpha_4\beta_2$ nAChRs on dopamine and GABA neurons. In contrast, the drug induces much less desensitization of α_7 nAChRs on glutamate neurons, resulting in a prolonged excitatory input to dopamine neurons and long-term potentiation. Thus, the dopamine-releasing effects of nicotine may result from a modification of the balance between excitatory and inhibitory inputs to dopamine neurons (Mansvelder and McGehee, 2002).

4.3. Neuronal plasticity

Repeated administration of nicotine produces changes in gene expression that may contribute to the long-term neural and behavioral plasticity that underlies addiction (Chao and Nestler, 2004). Repeated administration of nicotine is associated with behavioral and neurochemical sensitizations. Such mechanisms may participate in the development of nicotine addiction. Sensitization of the hyperlocomotor activity of nicotine appears mediated by the $\alpha_4\beta_2$ subunit (Grottick et al., 2000; Cohen et al., 2003). Sensitization of the motivational effects of nicotine has been demonstrated using self-administration and place preference paradigms (Shoaib et al., 1994, 1997). A sensitization of nicotine-induced stimulation of dopamine release in the nucleus accumbens core has been demonstrated, while an opposite action was found in the corresponding shell (Di Chiara, 2000). It has thus been suggested that the transition from voluntary drug seeking to a compulsive habit might be brought about by mechanisms of long-lasting synaptic plasticity in striatal function. The recruitment of dorsal striatal pathways and the disruption of executive control

physical dependence (Valjent et al., 2002). Acute nicotine administration (0.5 mg/kg s.c.) potentiated the hypolocomotion, antinociception and hypothermia induced by the acute administration of Δ^9 -THC. Co-administration of subactive doses of Δ^9 -THC (0.3 mg/kg i.p.) and nicotine (0.12 mg/kg s.c.) produced conditioned place preference. Δ^9 -THC (5 mg/kg i.p.) and nicotine (0.5 mg/kg s.c.) enhanced *c-fos* expression in limbic areas. Furthermore, animals co-treated with nicotine (0.5 mg/kg s.c.) and Δ^9 -THC (5–10 mg/kg i.p.) twice a day for 5 days displayed an enhancement in the somatic expression of Δ^9 -THC withdrawal precipitated by a cannabinoid antagonist.

Taken together, these data demonstrate the existence of a specific functional interaction between nicotine and the endocannabinoid system, in particular in brain areas involved in motivational processes.

Two types of cannabinoid receptors have been cloned and characterized in many vertebrates: the cannabinoid receptor type 1 (CB₁) (Matsuda et al., 1990), and the cannabinoid receptor type 2 (CB₂) (Munro et al., 1993). CB₁ receptors are expressed predominantly in the central nervous system with particularly high levels in the basal ganglia (caudate putamen, globus pallidus, substantia nigra and entopeduncular nucleus), the cerebellum and the hippocampus, i.e., in the areas controlling motor, cognitive, emotional and sensory function (Herkenham et al., 1991; Tsou et al., 1998). CB₁ receptors are also present in the nucleus accumbens, which is associated with motivational processes. Recently, expression of CB₁ receptors has also been found in peripheral tissues (Cota et al., 2003). Cannabinoid receptor type 2 (CB₂) is present almost exclusively in the periphery, in particular in immune tissues. Recent pharmacological and biochemical indications suggest the existence of non-CB₁ and non-CB₂ G-protein-coupled receptor for endocannabinoids (Di Marzo et al., 2000). They have not been characterized as yet. Several CB₁ receptor antagonists are available. Among these, rimonabant has been extensively characterized. The drug shows high affinity for the central cannabinoid CB₁ receptor ($K_i=2$ nM) and displays low affinity for the peripheral cannabinoid receptor ($K_i>1000$ nM) (Rinaldi-Carmona et al., 2004). Other CB₁ receptor antagonists have been developed, including SR147778 (Rinaldi-Carmona et al., 1994), LY320135 (Felder et al., 1998), AM251 and AM281 (Palmer et al., 2002).

7. Blockade of CB₁ receptors and nicotine addiction: CB₁ knockout mice

Studies using CB₁ knockout mice have investigated the functional interaction between the endogenous cannabinoid system, via CB₁ receptors, and nicotine. Castane et al. (2002) have shown that nicotine (0.5 mg/kg s.c.) produced a significant rewarding effect in wild-type mice, as measured by a conditioned place preference paradigm. This response

was absent in CB₁ knockout mice. The behavioral expression of mecamylamine-precipitated withdrawal was evaluated in chronic nicotine-treated mice (10 mg/kg/day, for 6 days using a minipump). Mecamylamine (1 mg/kg s.c.) precipitated several somatic signs of nicotine withdrawal in wild-type dependent mice and in CB₁ knockout mice. These results demonstrate that the endogenous cannabinoid system mediates the motivational effects of nicotine, via the CB₁ receptor, whereas it is not essential for the development of nicotine physical dependence.

In contrast with this study, Cossu et al. (2001) have reported that the absence of CB₁ cannabinoid receptors did not modify self-administration induced by nicotine (0.075 mg/kg/injection i.v.). Their results suggest that the activation of CB₁ receptors is not necessary for nicotine self-administration. Molecular compensation and adaptation might also explain the negative results with knockout animals.

8. Blockade of CB₁ receptors and nicotine addiction: CB₁ antagonists

The efficacy of the CB₁ antagonist, rimonabant, on nicotine intake has been tested using a self-administration paradigm (Cohen et al., 2002). In rats trained to press a lever for 30 min/day to obtain i.v. infusions of nicotine (0.03 mg/kg/infusion), pretreatment with rimonabant (0.3 mg/kg and 1 mg/kg i.p.) significantly reduces the number of responses on the nicotine-associated lever and the number of nicotine infusions (Fig. 2). At this dose, the drug does not produce any major behavioral effects suggesting that the reduction of responding does not result from non-specific (motor) deleterious effects.

In the transition from normal to addictive behavior, environmental cues associated with nicotine delivery take on powerful incentive properties that are critically important for sustaining smoking in humans and nicotine self-administration in animals (Goldberg et al., 1981; Caggiula et al., 2002). Adding cues to nicotine has been shown to increase the average number of infusions and the proportion of rats that acquired self-administration (Caggiula et al., 2002). The importance of nicotine-associated cues in extinction of nicotine-seeking behavior has been clearly demonstrated in a recent study showing that nicotine-associated cues can sustain responding, even after several months of nicotine abstinence (Cohen et al., 2005). Conditioned responding is still observed following 60 testing sessions (i.e., 3 months) without nicotine reinforcement, whereas removal of the cues following 3 months of nicotine withdrawal produces a progressive decrease of responding. In addition, responding can be reinstated by contingent presentation of the cues, after 1 month extinction (i.e., testing with no nicotine and no cues reinforcement). In contrast, cues paired with saline delivery did not acquire motivational effects. As shown

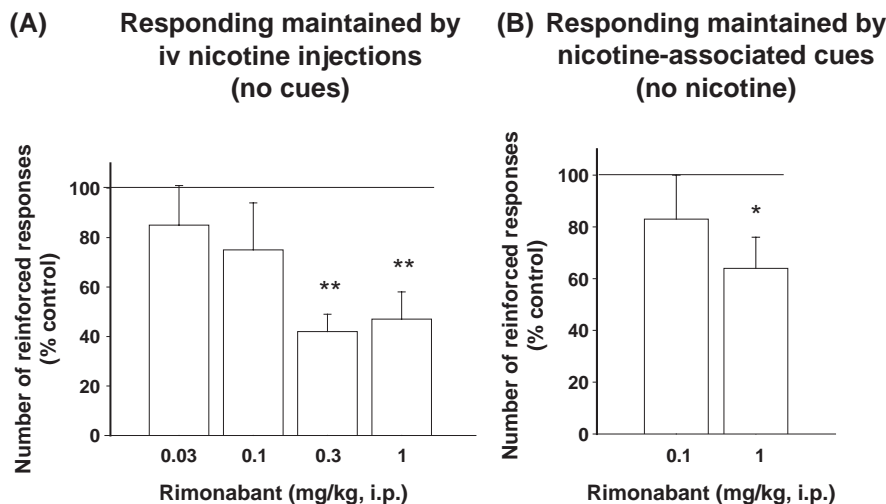


Fig. 2. Effects of rimonabant on responding maintained by nicotine injections (A, Experiment 1, $n=8-9$ rats) or by nicotine-associated cues (B, Experiment 2, $n=7$ rats). Rats screened for their locomotor response to an acute injection of a stimulant dose of nicotine were trained to self-administer nicotine (0.03 mg/kg/injection i.v.). In Experiment 1 (A), no cues were used, responses were reinforced according to a FR-4 schedule during a 30-min session. The effects of rimonabant were evaluated on nicotine self-administration following acquisition. In Experiment 2 (B), each nicotine injection was paired with a brief tone and light cue. Responses were reinforced according to a FR-1 schedule during a 60-min session. After self-administration acquisition, nicotine was withdrawn and lever pressing was only reinforced by contingent presentation of the audiovisual stimuli. The effects of rimonabant were evaluated on conditioned responding, 1 month following nicotine withdrawal. Materials and methods are described in Cohen et al. (2002, 2005). * $p<0.05$, ** $p<0.01$ versus respective control values.

in Fig. 2, pretreatment with rimonabant (1 mg/kg i.p.) reduced responding maintained by nicotine-associated cues, in the absence of nicotine (following 1 month of nicotine withdrawal). The effects of rimonabant have been evaluated on the expression of nicotine-induced place preference in rats (Le Foll and Goldberg, 2004). Nicotine produces a conditioned place preference, i.e., rats spend more time on the compartment previously associated with nicotine than on the one paired with vehicle. Rimonabant (1 and 3 mg/kg i.p.) administered before the test session significantly reduces the expression of a conditioned place preference associated to nicotine. These results are in agreement with those obtained in the self-administration paradigm. They suggest that rimonabant does not only reduce the motivational and reinforcing effects of nicotine but also environmental cue-induced nicotine craving and relapse.

The mechanism of action of rimonabant on nicotine addiction has been investigated using brain microdialysis in rats. Because mesolimbic dopaminergic transmission is currently considered as a critical neuronal substrate in drug addiction (Pontieri et al., 1996), the interaction between nicotine and rimonabant on the dopamine transmission has been studied. Nicotine (0.4 mg/kg s.c.) increases extracellular levels of dopamine in the shell of the nucleus accumbens and in the bed nucleus of the stria terminalis. Pretreatment with rimonabant (3 mg/kg i.p.) blocks nicotine-induced dopamine release in these limbic regions (Cohen et al., 2002). The interaction between the dopaminergic effects of nicotine and rimonabant has been further investigated in drug discrimination studies. The effects of rimonabant on nicotine discriminative stimulus

properties have been evaluated in two different drug discrimination experiments. In rats trained to discriminate nicotine from saline, rimonabant (0.3–3 mg/kg i.p.) does not substitute for nicotine or block nicotine discriminative effects. These *in vivo* findings confirm *in vitro* studies indicating that rimonabant does not interact directly with nicotinic acetylcholine receptors. In rats trained to discriminate amphetamine from saline, rimonabant (0.3 mg/kg i.p.) antagonizes the substitution of nicotine for amphetamine. These findings, in addition to showing that nicotine and amphetamine share a common neuronal substrate, suggest that rimonabant selectively prevents the dopaminergic effects of nicotine.

The effects of rimonabant on the dopamine-releasing properties of nicotine might theoretically be explained by several mechanisms. A direct effect on the dopamine-containing neurons is unlikely since CB₁ receptors are not localized on dopamine cell bodies or on their nerve terminals (Herkenham et al., 1991; Mailleux and Vanderhaeghen, 1992). Rimonabant might thus modulate dopaminergic systems through a multisynaptic neuronal circuit. Given the inhibitory effects of cannabinoid agonists on the release of a number of neurotransmitters, including GABA and glutamate, it is possible that rimonabant acts in the ventral tegmental area downstream from the dopaminergic synapse (Schlicker and Kathmann, 2001). Rimonabant might block the disinhibitory action of an endocannabinoid tone on GABA-containing neurons (Fig. 1). This tone, insufficient to evoke dopamine release, per se, may play a permissive role on the ability of nicotine to evoke dopamine release in limbic terminal areas. Rimonabant might also block the modulatory action of endocannabinoids on the

excitatory glutamatergic input to the GABA-containing neuron that projects from the nucleus accumbens to ventral tegmental area and subserves a long-loop feedback (Schlicker and Kathmann, 2001) (Fig. 1). This action may explain the reducing effects of rimonabant on nicotine and ethanol self-administration (e.g., drugs which indirectly activate the mesolimbic dopaminergic transmission) and its lack of effect on cocaine self-administration (e.g., a drug which inhibits dopamine uptake in terminal regions) (Arnone et al., 1997; Colombo et al., 1998; Fattore et al., 1999). A similar blockade of ethanol-induced dopamine release has been shown in the nucleus accumbens shell of rats pretreated with rimonabant (Cohen et al., 2002) or in CB₁ knockout mice (Hungund et al., 2003). In contrast, rimonabant does not block dopamine release induced by heroin in the rat nucleus accumbens shell (Tanda et al., 1997). Persistent changes during the progression of addiction might be brought about by mechanisms of long-lasting synaptic plasticity. In particular, such mechanisms might explain how nicotine-associated cues become conditioned reinforcers and sustain nicotine-seeking behavior. In the striatum, it has been shown that long-lasting synaptic plasticity is regulated by dopamine signaling and by the endocannabinoid system (Gerdeman et al., 2003). Chronic nicotine or ethanol treatment is associated with an increase in endocannabinoid levels in the limbic forebrain (Gonzalez et al., 2002). CB₁ receptors are highly expressed in the amygdala, cortex and hippocampus (Mailleux and Vanderhaeghen, 1992), and cannabinoid agonists have been shown to inhibit excitatory inputs from these brain regions to neurons in the nucleus accumbens (Pistis et al., 2002), suggesting several sites of action for rimonabant in drug addiction phenomena.

In conclusion, in the past 10 years, the endocannabinoid system has emerged as a potential regulator of motivational processes. According to animal models, CB₁ cannabinoid antagonists might be useful in nicotine, alcohol and cannabis related addictions. In particular, rimonabant may be useful in smoking cessation by attenuating the hyperactivation of the endocannabinoid system and the mesolimbic dopaminergic neuronal pathway, and can thereby be differentiated from substitutive treatments of nicotine addiction.

References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Washington, DC: American Psychiatric Press; 1995.
- Arnone M, Maruani J, Chaperon F, Thiebot MH, Poncelet M, Soubrie P, et al. Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB₁) receptors. *Psychopharmacology (Berl)* 1997;132:104–6.
- Caggiula AR, Donny EC, White AR, Chaudhri N, Booth S, Gharib MA, et al. Environmental stimuli promote the acquisition of nicotine self-administration in rats. *Psychopharmacology (Berl)* 2002;163:230–7.
- Carboni E, Silvagni A, Rolando MTP, DiChiara G. Stimulation of in vivo dopamine transmission in the bed nucleus of stria terminalis by reinforcing drugs. *J Neurosci* 2000;20:U6–10.
- Castane A, Valjent E, Ledent C, Parmentier M, Maldonado R, Valverde O. Lack of CB₁ cannabinoid receptors modifies nicotine behavioural responses, but not nicotine abstinence. *Neuropharmacology* 2002;43:857–67.
- Chao J, Nestler EJ. Molecular neurobiology of drug addiction. *Annu Rev Med* 2004;55:113–32.
- Cohen C, Perrault G, Voltz C, Steinberg R, Soubrie P. SR141716, a central cannabinoid (CB₁) receptor antagonist, blocks the motivational and dopamine-releasing effects of nicotine in rats. *Behav Pharmacol* 2002;13:451–63.
- Cohen C, Bergis OE, Galli F, Lochead AW, Jegham S, Biton B, et al. SSR591813, a novel selective and partial alpha4beta2 nicotinic receptor agonist with potential as an aid to smoking cessation. *J Pharmacol Exp Ther* 2003;306:407–20.
- Cohen, C., Perrault, G., Griebel, G., Soubrie, P. Nicotine-associated cues maintain nicotine-seeking behavior in rats several weeks after nicotine withdrawal: reversal by the cannabinoid (CB₁) receptor antagonist, rimonabant (SR141716). *Neuropsychopharmacology* 2005;30:145–55.
- Colombo G, Agabio R, Fa M, Guano L, Lobina C, Loche A, et al. Reduction of voluntary ethanol intake in ethanol-preferring sP rats by the cannabinoid antagonist SR-141716. *Alcohol Alcohol* 1998;33:126–30.
- Corrigall WA, Coen KM. Selective dopamine antagonists reduce nicotine self-administration. *Psychopharmacology* 1991;104:171–6.
- 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.
- Cossu G, Ledent C, Fattore L, Imperato A, Bohme GA, Parmentier M, et al. Cannabinoid CB₁ receptor knockout mice fail to self-administer morphine but not other drugs of abuse. *Behav Brain Res* 2001;118:61–5.
- Cota D, Marsicano G, Tschöp M, Grübler Flachskamm C, Schubert M, Auer D, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* 2003;112:423–31.
- Desai RI, Barber DJ, Terry P. Dopaminergic and cholinergic involvement in the discriminative stimulus effects of nicotine and cocaine in rats. *Psychopharmacology (Berl)* 2003;167:335–43.
- Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. *Eur J Pharmacol* 2000;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. *Proc Natl Acad Sci U S A* 1988;85:5274–8.
- Di Marzo V, Breivogel CS, Tao Q, Bridgen DT, Razdan RK, Zimmer AM, et al. Levels metabolism, and pharmacological activity of anandamide in CB₁ cannabinoid receptor knockout mice: evidence for non-CB₁, non-CB₂ receptor-mediated actions of anandamide in mouse brain. *J Neurochem* 2000;75:2434–44.
- Donny EC, Caggiula AR, Mielke MM, Jacobs KS, Rose C, Sved AF. Acquisition of nicotine self-administration in rats: the effects of dose, feeding schedule, and drug contingency. *Psychopharmacology (Berl)* 1998;136:83–90.
- Ezzati M, Lopez AD. Estimates of global mortality attributable to smoking in 2000. *Lancet* 2003;362:847–52.
- Fattore L, Martellotta MC, Cossu G, Mascia MS, Fratta W. CB₁ cannabinoid receptor agonist WIN 55,212-2 decreases intravenous cocaine self-administration in rats. *Behav Brain Res* 1999;104:141–6.
- Felder CC, Joyce KE, Briley EM, Glass M, Mackie KP, Fahey KJ, et al. LY320135, a novel cannabinoid CB₁ receptor antagonist, unmasks coupling of the CB₁ receptor to stimulation of cAMP accumulation. *J Pharmacol Exp Ther* 1998;284:291–7.
- Fiore MC, Bailey WC, Cohen JS, Dorfman SF, Goldstein MG, Gritz ER, et al. Treating tobacco use and dependence US Department of Health

- and Human Services Clinical Practice Guideline. Washington: US Department of Health and Human Services; 2000.
- Fowler JS, Volkow ND, Wang GJ, Pappas N, Logan J, Shea C, et al. Brain monoamine oxidase A inhibition in cigarette smokers. *Proc Natl Acad Sci U S A* 1996;93:14065–9.
- French ED. delta9-Tetrahydrocannabinol excites rat VTA dopamine neurons through activation of cannabinoid CB1 but not opioid receptors. *Neurosci Lett* 1997;226:159–62.
- Gaoni Y, Mechoulam R, 1964. *J Am Chem Soc* 1964;86:1646–7.
- George TP, O'Malley SS. Current pharmacological treatments for nicotine dependence. *Trends Pharmacol Sci* 2004;25:42–8.
- Gerdeman GL, Partridge JG, Lupica CR, Lovinger DM. It could be habit forming: drugs of abuse and striatal synaptic plasticity. *Trends Neurosci* 2003;26:184–92.
- Goldberg SR, Henningfield JE. Reinforcing effects of nicotine in humans and experimental animals responding under intermittent schedules of iv drug injection. *Pharmacol Biochem Behav* 1988;30:227–34.
- Goldberg SR, Speelman RD, Goldberg DM. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science* 1981;214:573–5.
- Gonzalez S, Cascio MG, Fernandez-Ruiz J, Fezza F, Di Marzo V, Ramos JA. Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. *Brain Res* 2002; 954:73–81.
- Goodman A. Addiction: definition and implications. *Br J Addict* 1990; 85:1403–8.
- Grottick AJ, Trube G, Corrigan WA, Huwyler J, Malherbe P, Wylar R, et al. Evidence that nicotinic alpha(7) receptors are not involved in the hyperlocomotor and rewarding effects of nicotine. *J Pharmacol Exp Ther* 2000;294:1112–9.
- Harvey DM, Yasar S, Heishman SJ, Panlilio LV, Henningfield JE, Goldberg SR. Nicotine serves as an effective reinforcer of intravenous drug-taking behavior in human cigarette smokers. *Psychopharmacology (Berl)* 2004;175:518–9.
- Henningfield JE, London ED, Benowitz NL. Arterial-venous differences in plasma concentrations of nicotine after cigarette smoking. *J Am Med Assoc* 1990;263:2049–50.
- Herkenham M, Lynn AB, de Costa BR, Richfieldm EK. Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. *Brain Res* 1991;547:267–74.
- Hungund BL, Szakall I, Adam A, Basavarajappa BS, Vadasz C. Cannabinoid CB1 receptor knockout mice exhibit markedly reduced voluntary alcohol consumption and lack alcohol-induced dopamine release in the nucleus accumbens. *J Neurochem* 2003;84:698–704.
- Ledent C, Valverde O, Cossu C, Petitot F, Aubert LF, Beslot F, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. *Science* 1999;283:401–4.
- Le Foll B, Goldberg SR. Rimobant, a CB1 antagonist, blocks nicotine-conditioned place preferences. *Neuroreport* 2004;15:2139–43.
- Mailleux P, Vanderhaeghen JJ. Distribution of neuronal cannabinoid receptor in the adult rat brain: a comparative receptor binding radioautography and in situ hybridization histochemistry. *Neuroscience* 1992;48:655–68.
- Malin DH. Nicotine dependence: studies with a laboratory model. *Pharmacol Biochem Behav* 2001;70:551–9.
- Mansvelder HD, McGehee DS. Cellular and synaptic mechanisms of nicotine addiction. *J Neurobiol* 2002;53:606–17.
- Marks MJ, Pauly JR, Gross SD, Deneris ES, Hermans-Borgmeyer I, Heinemann SF, et al. Nicotine binding and nicotinic receptor subunit RNA after chronic nicotine treatment. *J Neurosci* 1992;12:2765–84.
- Marubio LM, Gardier AM, Durier S, David D, Klink R, Arroyo-Jimenez MM, et al. Effects of nicotine in the dopaminergic system of mice lacking the alpha4 subunit of neuronal nicotinic acetylcholine receptors. *Eur J Neurosci* 2003;17:1329–37.
- Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 1990;346:561–4.
- Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993;365:61–5.
- O'Brien CP. Drug addiction and drug abuse. In: Goodman LS, Gilman A, editors. *The pharmacological basis of therapeutics*. New York: Mc Graw Hill; 1996.
- Pagliusi SR, Tessari M, DeVevey S, Chiamulera C, Pich EM. The reinforcing properties of nicotine are associated with a specific patterning of c-fos expression in the rat brain. *Eur J Neurosci* 1996;8:2247–56.
- Palmer SL, Thakur GA, Makriyannis A. Cannabinergic ligands. *Chem Phys Lipids* 2002;121:3–19.
- Perry DC, Davila-Garcia MI, Stockmeier CA, Kellar KJ. Increased nicotinic receptors in brains from smokers: membrane binding and autoradiography studies. *J Pharmacol Exp Ther* 1999;289:1545–52.
- Peto R, Lopez AD, Boreham J, Thun M, Heath Jr C, Doll R. Mortality from smoking worldwide. *Br Med Bull* 1996;52:12–21.
- Piccio MR. Nicotine as a modulator of behavior: beyond the inverted U. *Trends Pharmacol Sci* 2003;24:493–9.
- Piccio MR, Zoli M, Rimondini R, Lena C, Marubio LM, Pich EM, et al. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. *Nature* 1998;391:173–7.
- Pich EM, Pagliusi SR, Tessari M, Talbot Ayer D, Hooft van HR, Chiamulera C. Common neural substrates for the addictive properties of nicotine and cocaine. *Science* 1997;275:83–6.
- Pistis M, Muntoni AL, Pillolla G, Gessa GL. Cannabinoids inhibit excitatory inputs to neurons in the shell of the nucleus accumbens: an in vivo electrophysiological study. *Eur J Neurosci* 2002;15:1795–802.
- Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature* 1996;382:255–7.
- Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, et al. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett* 1994;350:240–4.
- Rinaldi-Carmona M, Barth F, Congy C, Martinez S, Oustric D, Perio A, et al. SR147778, a new potent and selective antagonist of the CB1 cannabinoid receptor. *Biochemical and pharmacological characterization*. *J Pharmacol Exp Ther* 2004;310:905–14.
- Risinger FO, Oakes RA. Nicotine-induced conditioned place preference and conditioned place aversion in mice. *Pharmacol Biochem Behav* 1995; 51:457–61.
- Rommelspacher H, Meier-Henco M, Smolka M, Kloft C. The levels of norharman are high enough after smoking to affect monoamineoxidase B in platelets. *Eur J Pharmacol* 2002;441:115–25.
- Royal College of Physicians. Nicotine Addiction in Britain. A report of the Tobacco Advisory Group of the Royal College of Physicians. London: Royal College of Physicians of London; 2000.
- Sargent PB. The distribution of neuronal nicotinic acetylcholine receptors. In: Clementi F, Fornasari D, Gotti C, editors. *Neuronal nicotinic receptors*. Handbook of Experimental Pharmacology, vol. 144; 2000. p. 163–92.
- Scherer G. Smoking behaviour and compensation: a review of the literature. *Psychopharmacology* 1999;145:1–20.
- Schlicker E, Kathmann M. Modulation of transmitter release via presynaptic cannabinoid receptors. *Trends Pharmacol Sci* 2001;22: 565–72.
- Shoaib M, Stolerman IP, Kumar RC. Nicotine-induced place preferences following prior nicotine exposure in rats. *Psychopharmacology* 1994; 113:445–52.
- Shoaib M, Schindler CW, Goldberg SR. Nicotine self-administration in rats: strain and nicotine pre-exposure effects on acquisition. *Psychopharmacology* 1997;129:35–43.
- Stolerman IP. Inter-species consistency in the behavioural pharmacology of nicotine dependence. *Behav Pharmacol* 1999;10:559–80.
- Stolerman IP, Jarvis MJ. The scientific case that nicotine is addictive. *Psychopharmacology* 1995;117:2–10.
- Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. *Science* 1997;276:2048–50.

- Tanda G, Munzar P, Goldberg SR. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. *Nat Neurosci* 2000;3:1073–4.
- Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. *Neuroscience* 1998;83:393–411.
- US Department of Health and Human Services. The health consequences of smoking: nicotine addiction. Office on smoking and health. Maryland, Washington DC: US Government Printing Office; 1988.
- Valjent E, Mitchell JM, Besson MJ, Caboche J, Maldonado R. Behavioural and biochemical evidence for interactions between Delta 9-tetrahydrocannabinol and nicotine. *Br J Pharmacol* 2002;135:564–78.
- Watkins SS, EppingJordan MP, Koob GF, Markou A. Blockade of nicotine self-administration with nicotinic antagonists in rats. *Pharmacol Biochem Behav* 1999;62:743–51.
- Wise RA. Addictive drugs and brain stimulation reward. *Annu Rev Neurosci* 1996;19:319–40.
- Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. *Psychol Rev* 1987;94:469–92.
- Wonnacott S, Drasdo A, Sanderson E, Rowell P. Presynaptic nicotinic receptors and the modulation of transmitter release. *Ciba Found Symp* 1990;152:87–101.
- World Health Organization. International classification of diseases, 10th edn. Geneva: WHO; 1992.