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Neurobiological mechanisms involved in nicotine dependence and reward: participation of the endogenous opioid system

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Abstract

Nicotine is the primary component of tobacco that maintains the smoking habit and develops addiction. The adaptive changes of nicotinic acetylcholine receptors produced by repeated exposure to nicotine play a crucial role in the establishment of dependence. However, other neurochemical systems also participate in the addictive effects of nicotine including glutamate, cannabinoids, GABA and opioids. This review will cover the involvement of these neurotransmitters in nicotine addictive properties, with a special emphasis on the endogenous opioid system. Thus, endogenous enkephalins and beta-endorphins acting on mu-opioid receptors are involved in nicotine rewarding effects, whereas opioid peptides derived from prodynorphin participate in nicotine aversive responses. An upregulation of mu-opioid receptors has been reported after chronic nicotine treatment that could counteract the development of nicotine tolerance, whereas the downregulation induced on kappa-opioid receptors seems to facilitate nicotine tolerance. Endogenous enkephalins acting on mu-opioid receptors also play a role in the development of physical dependence to nicotine. In agreement with these actions of the endogenous opioid system, the opioid antagonist naltrexone has shown to be effective for smoking cessation in certain subpopulations of smokers.

Keywords

addiction; enkephalin; dynorphin; beta-endorphin; tolerance; withdrawal; naltrexone; opioid receptor

1. Introduction

Nicotine is the main addictive component of tobacco that maintains the smoking habit. Moreover, the reinforcing effects of nicotine are thought to be the primary reason why humans inhale tobacco smoke (Shoaib, 2006). Tobacco consumption is one of the main public health problems worldwide and represents a leading cause of preventable deaths in most developed countries. Tobacco smoke contains over 4,000 chemicals, many of which have marked irritant properties, are known carcinogens and can enhance the addictive effects of nicotine (Brennan et al., 2009). Tobacco use causes five million deaths per year, and if the present trend continues,

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10 million smokers per year are predicted to die by 2025 (Hatsukami et al., 2008). Although most smokers wish to stop, few succeed. Indeed, relapse rates are as high as 80% one year after the quit date, even with the help of the available medications and additional non-pharmacological therapies (Dwoskin et al., 2009).

2. Nicotinic acetylcholine receptors

Nicotine produces its pharmacological effects through the activation of nicotinic acetylcholine receptors (nAChRs), which are widely distributed through the central nervous system (CNS). These receptors are ligand-gated ion channels with a central cation pore composed of five subunits, which can either be homomeric or heteromeric (Millar and Gotti, 2009). So far, 12 different neuronal nAChR subunits have been identified: α_2-α_{10} and β_2-β_4. The most abundant nAChR subtypes in the nervous system are homomeric α_7 and heteromeric $\alpha_4\beta_2$ (Millar and Gotti, 2009). The nAChRs play a modulatory role on the activity of multiple neurotransmitters, as they have been detected on presynaptic terminals, cell bodies and dendrites of many neuronal subtypes (Dajas-Bailador and Wonnacott, 2004). The activation of nAChRs by nicotine increases the release of most neurotransmitters including dopamine (Pontieri et al., 1996), noradrenaline (Clarke and Reuben, 1996), acetylcholine (Wilkie et al., 1993), glutamate (McGehee et al., 1995) and GABA (Yang et al., 1996). As a consequence, nicotine modifies a large number of physiological processes such as locomotion, nociception, anxiety, learning and memory, as well as produces several behavioral responses directly related to its addictive properties, including rewarding effects and physical dependence (Decker et al., 1995). Due to the limited specificity of the available nAChR agonists and antagonists, the generation of mice with genetic nAChR subunit modifications has provided a useful experimental approach to assess the specific contribution of these subunits in the pharmacological actions induced by nicotine (Mineur and Picciotto, 2008). In addition, novel strategies have also been developed to re-express nAChR subunits in a region-specific manner using lentiviral vectors in a knockout background, which has further advanced the knowledge of these receptors (Maskos, 2007).

3. Behavioral models to evaluate nicotine addictive properties in animals

Nicotine addiction is a chronic brain disorder characterized by compulsive tobacco use, loss of control over tobacco consumption despite its harmful effects, the appearance of withdrawal symptoms upon cessation of tobacco smoking, and relapse after periods of abstinence (McLellan et al., 2000). Similar to other addictive processes, the initiation of nicotine addiction has been related to its capacity to induce reinforcing effects. On the other hand, the negative consequences of nicotine abstinence have a crucial motivational significance for the maintenance and relapse of this addictive behavior (Koob and Le Moal, 2008). Several behavioral models have evaluated the development of tolerance and physical dependence after repeated nicotine administration. However, the development of tolerance and physical dependence that is concurrent to the nicotine addictive process does not seem to be etiologically related to nicotine addiction (Volkow and Li, 2005). The negative consequences of nicotine withdrawal that are closely related to the maintenance of the addictive process can be evaluated in rodents by measuring several emotional symptoms such as increased anxiety, aversive effects and reward deficits (Jackson et al., 2008; Johnson et al., 2008). Thus, the aversive manifestations of withdrawal are mainly evaluated in rodents by using the place conditioning paradigm, whereas the associated reward deficits are currently evaluated using intracranial self-stimulation techniques (Jackson et al., 2009; Bruijnzeel et al., 2009). Both behavioral paradigms have been extensively used to evaluate nicotine-rewarding effects (Castañé et al., 2002; Hollander et al., 2008). In the place conditioned paradigms, the subjective effects of the drug (or its withdrawal) are repeatedly paired to a previously neutral spatial environmental stimulus. Through this repeated association process, the environment acts as a conditioned stimulus. The animal will then prefer (conditioned place preference) or avoid (conditioned

place aversion) this conditioned stimulus, depending on the rewarding or aversive effects produced by the presence of the drug or by its withdrawal. Although a conditioned approach/avoidance towards specific stimuli can also occur in humans as a result of drug consumption (Childs and Wit, 2009), the place conditioning paradigms are not primarily intended to model any particular feature of human behavior. These paradigms mainly represent an indirect assessment of the rewarding or aversive effects of a drug or its withdrawal by measuring the response of the animal towards the conditioned stimulus. Two different phases (acquisition and expression) of the place conditioning that have different psychological implications are evaluated in this paradigm. Indeed, acquisition seems to be related to reward and learning whereas expression would be more related to incentive motivation, memory recall or sign-tracking.

Intracranial electric self-stimulation procedures have been widely used to study the effects of drugs of abuse on the activity of the reward circuits (Sanchis-Segura and Spanagel, 2006). In this paradigm, animals are trained to maintain an operant behavior to obtain an electric pulse through an electrode placed in a reward-related brain site, most frequently the lateral hypothalamic area. The threshold of the minimal current needed to promote intracranial electric self-stimulation is usually estimated. A drug that stimulates the reward circuit will decrease this threshold, which would be related to its rewarding properties, whereas a drug or a state of withdrawal producing aversive effects will enhance the minimal current required to maintain the self-stimulation (Markou and Koob, 1993).

Another animal model that has been widely used to directly evaluate the reinforcing properties of nicotine is the operant self-administration procedure, which is a valid and reliable model of drug consumption in humans (Sanchis-Segura and Spanagel, 2006). High rates of operant responding for obtaining intravenous nicotine infusions have been described in various species (Goldberg et al., 1981; Risner and Goldberg, 1983; Corrigall and Coen, 1989; Shoaib et al., 1997; Stolerman et al., 1999; Martin-Garcia et al., 2009), confirming the abuse liability of this drug (Stolerman and Jarvis 1995). Operant models are based on the learning contingency defined as “positive reinforcement”. In these models, the drug serves as a positive reinforcer that is delivered in a contingent manner upon completion of the scheduled requirements (Sanchis-Segura and Spanagel, 2006). The operant chambers are equipped with manipulandi that transmit the operant response as well as devices that deliver the drug (reinforcer). The response in the active manipulandum is linked to the delivery of the drug, while the response in the inactive manipulandum results in the delivery of the drug vehicle or lacks any programmed consequence. The fixed ratio and progressive ratio schedule reinforcement programs are commonly used. Under a fixed ratio schedule, the drug is delivered each time a pre-selected number of responses are completed. For nicotine self-administration, the route of drug delivery is usually intravenous, and the number of responses required to obtain the drug is generally kept low, most frequently at a fixed ratio of one (continuous reinforcement, i.e., one nicotine infusion after each response in the active manipulandum). Under the progressive ratio schedule, the response requirement to deliver the drug escalates according to an arithmetic progression. The common index of performance evaluated in this schedule is the breaking point defined as the highest number of responses that the animal accomplishes to obtain a single infusion of drug, which provides information about its motivation for the drug.

4. Neurotransmitters involved in nicotine addictive properties

The neurobiology of nicotine addiction is a complex behavioral phenomenon in which various transmitter systems are involved. This section of the review summarizes the involvement of nicotinic acetylcholine receptors and several heterologous neurochemical systems in the addictive effects of nicotine. A particular emphasis is then devoted to the role played by the endogenous opioid system in the different processes that contribute to nicotine addiction.

4.1. Involvement of different nAChR subunits in nicotine reward, motivation and reinforcement

The mesocorticolimbic system mediates the rewarding properties of most drugs of abuse, including nicotine (Koob and Le Moal, 2008). An important component of this system is the dopaminergic projection from the ventral tegmental area (VTA) to the frontal cortex and limbic structures, such as the nucleus accumbens (NAc) and amygdala. However, other additional brain areas that interact with these mesolimbic structures also play an important role in acute drug reward and chronic changes in reward associated with addiction. These regions include the amygdala and related structures of the so-called 'extended amygdala', hippocampus, hypothalamus and several regions of the frontal cortex, among others (Nestler, 2005). Nicotine administration increases dopamine transmission in the NAc and other limbic structures (Di Chiara and Imperato, 1988) by direct stimulation of nAChRs within the VTA (Nisell et al., 1994). A great body of evidence suggests that nAChRs containing $\alpha_4\beta_2$ subunits located on dopamine cell bodies contribute to the final activation of VTA dopamine neurons (Mansvelder and McGehee, 2003). Indeed, local and systemic administration of the selective $\alpha_4\beta_2$ antagonist dihydro-beta-erythroidine (DHβE) blocks nicotine self-administration in rodents (Grottick et al., 2000). In agreement, mice with the β_2 subunit knocked out do not self-administer nicotine (Pons et al., 2008; Picciotto et al., 1998), and nicotine does not enhance dopamine levels in the NAc in these mutants (Picciotto et al., 1998). The specific location of nAChRs containing the β_2 subunit in the VTA plays a crucial role in the mediation of nicotine reinforcement as demonstrated by studies re-expressing this subunit by injecting a lentiviral vector into the VTA of mice carrying β_2 subunit deletions (Maskos et al., 2005). In contrast, re-expressing the β_2 subunit in the substantia nigra pars compacta instead of the VTA of β_2 knockout mice did not yield nicotine self-administration (Pons et al., 2008). In addition, α_4 knockout mice do not self-administer nicotine (Pons et al., 2008) and fail to show the nicotine-dependent enhancement of dopamine release in the ventral striatum (Marubio et al., 2003), whereas selective activation of α_4 containing nAChRs is sufficient to induce nicotine locomotor sensitization and conditioned place preference (Tapper et al., 2004). The α_6 subunit located in the VTA plays also a role in the reinforcing effects of nicotine (Pons et al., 2008). This result is consistent with a recent study showing a blockade of nicotine conditioned place preference in mice pre-treated with an α_6 subunit selective antagonist (Jackson et al., 2009). The precise role of the α_7 homomeric nAChRs in nicotine reinforcing effects remains unclear because conflicting results have been obtained in mutant mice lacking this subunit and in rodents injected with the relatively selective α_7 nAChR antagonist methyllycaconitine (Pons et al., 2008; Markou and Paterson, 2001; Walters et al., 2006). Along with research in animal models, recent genome-wide association studies in humans have revealed a clear linkage between genetic variations in the nAChRs and the risk for nicotine dependence (Bierut, 2009). Thus, the region on chromosome 15 that includes the family of α_5-α_3-β_4 nAChR genes has been associated with the development of nicotine dependence (Thorgeirsson et al., 2008; Berrettini et al., 2008) and lung cancer (Thorgeirsson et al., 2008; Hung et al., 2008; Amos et al., 2008). The connection between the genetic variant at chromosome 15 and lung cancer is thought to be either direct (Hung et al., 2008; Amos et al., 2008) or mediated through a modification of smoking behavior (Thorgeirsson et al., 2008).

4.2. Involvement of glutamatergic receptors in nicotine reward, motivation and reinforcement

Nicotine stimulates the release of glutamate through activation of nAChRs located on glutamatergic terminals in several brain regions including the VTA (Fu et al., 2000). Furthermore, considerable evidence indicates that glutamate, through activation of ionotropic and metabotropic glutamate receptors located on postsynaptic dopamine neurons, is critically involved in the reinforcing properties of nicotine (Liechti and Markou, 2008). Thus, nicotine-induced dopamine release in the NAc is blocked by systemic administration of NMDA and AMPA receptor antagonists (Kosowski et al., 2004). In addition, the NMDA receptor

antagonist, LY235959, administered systemically or directly into the VTA or the central amygdala, decreases intravenous nicotine self-administration in rats (Kenny et al., 2009). Several studies have also involved postsynaptic mGlu5 and presynaptic mGlu2/3 receptors in nicotine reinforcing effects. Thus, the mGlu5 receptor antagonist, MPEP, decreases nicotine self-administration in rats and mice (Paterson et al., 2003). The same antagonist also diminished the motivation to work for nicotine infusions as revealed by the reduction in the breakpoint on a progressive ratio schedule of reinforcement (Paterson and Markou, 2005). The administration of the mGlu2/3 agonist LY379268 either systemically or intra-VTA also decreases nicotine self-administration in rats (Liechti et al., 2007). This last result is in accordance with previous studies showing that presynaptic mGlu2/3 receptors negatively modulate glutamate release (Schoepp et al., 2003). Cholinergic and glutamatergic inputs from the pedunculopontine tegmental nucleus (PPTg) to the VTA seem to play a crucial role in nicotine reward and reinforcement because a complete lesion of the PPTg reduces nicotine self-administration behavior (Lança et al., 2000; Picciotto and Corrigall, 2002) and blocks conditioned place preference induced by the intra-VTA injection of nicotine (Laviolette et al., 2002). In contrast with these results, intravenous nicotine self-administration was significantly elevated after injuring the posterior, but not anterior, portion of the PPTg (Alderson et al., 2006).

4.3. Involvement of cannabinoid receptors in nicotine reward, motivation and reinforcement

A considerable number of studies demonstrate that the endocannabinoid system is also involved in the rewarding and reinforcing effects of nicotine (Maldonado et al., 2006; Scherma et al., 2008). Indeed, the selective CB_1 receptor antagonist rimonabant reduces nicotine self-administration in rats (Cohen et al., 2002) and nicotine-induced conditioned place preference in rats and mice (Le Foll and Goldberg, 2004; Merritt et al., 2008). In addition, *in vivo* microdialysis and voltammetry studies have revealed that rimonabant pre-treatment blocks nicotine-enhanced dopamine extracellular levels in the NAc (Cohen et al., 2002; Cheer et al., 2007) and in the bed nucleus of the stria terminalis (Cheer et al., 2007). Nicotine conditioned place preference was also absent in knockout mice lacking CB_1 receptors (Castañé et al., 2002; Merrit et al., 2008). Based on the behavioral and biochemical results obtained in rodents, several clinical trials were developed to evaluate the efficacy of rimonabant for smoking cessation (STRATUS, studies with rimonabant and tobacco use) (Cahill and Ussher, 2007). Rimonabant significantly reduced smoking in two clinical trials (STRATUS-NORTH AMERICA and STRATUS-WORLD WIDE), although this effect was not significant in the STRATUS-EUROPE trial. The different clinical trials performed with this cannabinoid antagonist on smoking cessation, obesity and type II diabetes have reported several gastrointestinal and psychiatric side effects including nausea, anxiety and depression. Due to these psychiatric side effects, the European Medicines Agency (EMEA) recommended the suspension of rimonabant marketing on October 23rd, 2008.

4.4. Other neurotransmitters involved in nicotine reward, motivation and reinforcement

Other neurotransmitters are also involved in the rewarding and reinforcing properties of nicotine. The serotonergic (5-HT) system, mainly through the 5-HT_{2c} receptor subtype, seems to play a role in nicotine reward by exerting an inhibitory influence on dopaminergic activity in the VTA (Di Matteo et al., 1999). Thus, the 5-HT_{2c} agonist, Ro 60-0175 reduces intravenous nicotine-self-administration (Grottick et al., 2001), although the same compound also attenuated the response to food. In contrast, no modification of nicotine-induced conditioned place preference was observed by the 5-HT_{2c} agonist, WAY 161503 in a recent report (Hayes et al., 2009). On the other hand, tobacco smoke contains monoamine oxidase (MAO) inhibitors, which are thought to enhance the reinforcing effects of nicotine. Behavioral studies confirmed that nicotine self-administration was facilitated in rats pre-treated with the irreversible and non-selective MAO inhibitor tranylcypromine (Villégier et al., 2006; 2007). Recently, the hypothalamic neuropeptides hypocretins acting in the insula have also been involved in

nicotine reward (Hollander et al., 2008). Dopamine neurons in the VTA are under inhibitory control of GABAergic inputs that also participate in nicotine rewarding effects. Hence, the administration of the GABA-B receptor agonists, baclofen and CGP44532, as well as several GABA-B receptor positive allosteric modulators, decrease nicotine self-administration in rats (Paterson et al., 2004; Paterson et al., 2008). Baclofen also inhibits the expression of nicotine-induced conditioned place preference in rats (Le Foll et al., 2008). Although GABA neurons are acutely activated by nicotine, following repeated exposure to this drug, $\alpha_4\beta_2$ nAChRs located on GABA cells tend to desensitize (Mansvelder et al., 2002), contributing to the final activation of mesolimbic dopamine neurons.

4.5. Neurotransmitters involved in nicotine tolerance and withdrawal

The different neuronal adaptations occurring following repeated exposure to nicotine, including desensitization and up-regulation of nAChRs (Quick and Lester, 2002), are involved in the development of nicotine tolerance and the appearance of a withdrawal syndrome following smoking cessation. Chronic nicotine administration produces tolerance to most of its pharmacological effects (Benowitz, 2008), such as hypolocomotion, convulsive effects, hypothermia and antinociception, whereas no tolerance has been observed to its effects on memory and attention (Marks et al., 1986; Miner and Collins, 1988; Collins et al., 1988; Damaj and Martin, 1996; Benowitz, 2008). In humans, cessation of tobacco intake precipitates both somatic and affective symptoms of withdrawal, which may include severe craving for nicotine, irritability, anxiety, loss of concentration, restlessness, decreased heart rate, depressed mood, impatience, insomnia, increased appetite and weight gain (Hughes and Hatsukami, 1986; Hughes, 2007). In rodents, nicotine withdrawal is also characterized by the manifestation of both somatic signs and affective changes similar to those observed in humans. The somatic signs include teeth chattering, palpebral ptosis, tremor, wet dog shakes, changes in locomotor activity and other behavioral signs (Malin et al., 1992). The mechanisms and brain regions underlying nicotine physical dependence have not yet been clarified, although an involvement of the medial habenula and the interpeduncular nucleus has been recently reported (Salas et al., 2009). The affective changes associated with nicotine withdrawal include increased anxiety-like behavior, aversive effects revealed in the place conditioning paradigm (Balerio et al., 2004; Jackson et al., 2008), and reward deficits demonstrated by intracranial self-stimulation techniques (Johnson et al., 2008). Similar to other drugs of abuse, hyperactivity of corticotropin-releasing-factor (CRF) neurons (Bruijnzeel et al., 2007) and c-fos induction in the central amygdala (Panagis et al., 2000), as well as decreased dopaminergic activity in the NAc (Hildebrand et al., 1999), have been related to the negative affective states associated with nicotine withdrawal. In addition, glutamate also contributes to the modulation of the negative affective symptoms of nicotine abstinence. Thus, mGlu2/3 receptor antagonists, which increase extracellular glutamate in the NAc, attenuate reward deficits associated with nicotine withdrawal in rodents and could also alleviate the depressive-like symptoms related to nicotine abstinence in humans (Kenny et al., 2003; Liechti and Markou, 2008).

4.6. Neurotransmitters involved in nicotine relapse

Animal models of relapse have shown that nicotine-seeking can be triggered by nicotine-associated (conditioned) cues (Martín-García et al., 2009), stressors (Bilkei-Gorzo et al., 2008) (e.g., mild footshocks), and re-exposure to nicotine (Dravolina et al., 2007), which are the same events that trigger nicotine craving and relapse in humans. The neurobiological mechanisms involved in the processes underlying relapse to nicotine-seeking are poorly understood. Recent studies have reported that GABA, glutamate and endocannabinoids could play a role in this phenomenon. Thus, the acute administration of the GABA-B receptor agonist, CGP44532 decreases cue-induced reinstatement of nicotine-seeking behavior (Paterson et al., 2005). In agreement, the GABA-B agonist baclofen prevents the reinstatement of nicotine-seeking and conditioned place-preference triggered by nicotine priming in rats (Fattore et al.,

2009). Glutamate is also involved in this process since the systemic administration of the mGlu5 receptor antagonist, MPEP (Bespalov et al., 2005) or the mGlu2/3 receptor agonist, LY-379268 (Liechti et al., 2007) decreases cue-induced reinstatement of nicotine-seeking in rats.

Recent evidence suggests the involvement of the endocannabinoid system in relapse to nicotine-seeking behavior (De Vries and Schoffelmeer, 2005). Pre-treatment with the CB1 antagonist, rimonabant attenuates the reinstatement of nicotine seeking-behavior induced by nicotine-associated cues in rats (Cohen et al., 2005). This cannabinoid antagonist also reduces reinstatement of operant nicotine-seeking behavior induced by associated cues (De Vries et al., 2005) and reinstatement of nicotine conditioned place-preference provoked by nicotine priming (Biala et al., 2009). The cannabinoid antagonist, AM251 also dose-dependently reduces reinstatement produced by the combination of nicotine-associated cues and a nicotine priming dose (Shoaib, 2008).

5. The endogenous opioid system

Multiple studies in animal models and humans indicate that the endogenous opioid system is an important neurobiological substrate for the addictive properties of nicotine. The endogenous opioid peptides and receptors are largely distributed within the CNS and are also present in several peripheral tissues. This wide distribution is related to the important functions played by this neuromodulatory system in the control of several physiological responses including nociception, emotional behavior, learning and memory, and reward processes (Bodnar et al., 2008). Three different subtypes of opioid receptors, mu (MOR), delta (DOR) and kappa (KOR), have been identified, cloned and characterized at the molecular, biochemical and pharmacological level (Kieffer and Evans, 2009). A fourth member of the opioid peptide receptor family, the N/OFQ receptor, was cloned in 1994 (Mollereau et al., 1994). Three families of endogenous opioid peptides derived from either proopiomelanocortin (POMC), proenkephalin (PENK) or prodynorphin (PDYN) have also been identified and cloned (Xue and Domino, 2008). These precursors generate several active peptides including β-endorphin, met- and leu-enkephalins, and dynorphins, respectively (Kieffer and Gavériaux-Ruff, 2002), that exhibit different affinities for each opioid receptor. β-endorphin binds with a higher affinity to MOR than DOR or KOR, and it is a main endogenous ligand for MOR. The affinity of met- and leu-enkephalin for DOR is 20-fold greater than that for MOR, and dynorphins are presumed to be the main endogenous ligands for KOR (Roth-Deri et al., 2008). More recently, another endogenous opioid peptide named nociceptin/orphanin FQ (N/OFQ) (Meunier et al., 1995; Reinscheid et al., 1995) has been discovered and proposed as the endogenous ligand of the N/OFQ receptor. Two putative endogenous opioid peptides, endomorphin-1 and -2, have also been proposed as MOR selective endogenous opioids (Zadina et al., 1997). However, no gene, precursor protein, or other mechanism for their endogenous synthesis have been identified.

Opioid receptors and their endogenous ligands play an important role in brain reward processes, and modulate the behavioral effects of nicotine and other drugs of abuse. Accordingly, opioid receptors and their endogenous ligands are highly expressed in areas of the brain involved in reward such as the VTA, NAc, prefrontal cortex and extended amygdala (Delfs et al., 1994; Mansour et al., 1995). Opioid receptor agonists also induce rewarding and/or aversive effects. Thus, morphine and other MOR agonists are self-administered by humans and experimental animals whereas systemic administration of the preferential MOR antagonists naloxone and naltrexone produces dysphoria in humans and conditioned aversive effects in animals (Shippenberg et al., 2008). DOR agonists also induce rewarding effects in animal models (Suzuki et al., 1997; Hutcheson et al., 2001). On the contrary, the dynorphin/KOR system participates in the addictive properties of drugs of abuse by opposing their rewarding effects

(see Shippenberg et al., 2007 for review). In agreement, KOR agonists induce dysphoria in humans and aversive effects in animal models (Hasebe et al., 2004).

6. Effects of nicotine administration on the endogenous opioid system

The acute administration of nicotine promotes the release of endogenous opioid peptides and induces changes in the expression of these peptides. Accordingly, an increase in met-enkephalin (Dhatt et al., 1995) and dynorphin (Isola et al., 2009) immunoreactivities was found in the striatum of mice after acute nicotine injection. An enhancement of β-endorphin secretion was also shown *in vitro* after nicotine exposure (Marty et al., 1985), although *in vivo* microdialysis did not reveal any changes in the rat NAc after acute nicotine administration (Olive et al., 2001). In humans, increased peripheral concentrations of β-endorphin have been observed in persons who smoked fewer than 10 cigarettes per day (del Arbol et al., 2000). However, changes in the peripheral levels of β-endorphin do not seem to be directly related to the central activity of the endogenous opioid system and have been more likely related to a peripheral response to stress (Rasmussen and Farr, 2009; Spaziante et al., 1990). On the other hand, acute nicotine administration increases PENK mRNA expression in brain regions related to drug-dependence and withdrawal such as striatum, amygdala, periaqueductal gray matter, locus coeruleus, raphe and hippocampus (Dhatt et al., 1995; Houdi et al., 1991; 1998). PDYN mRNA expression was also increased in mouse striatum and NAc after the administration of a single dose of nicotine (Isola et al., 2009).

The effects of repeated exposure to nicotine on the different components of the endogenous opioid system have also been investigated. Thus, chronic nicotine administration decreases PENK mRNA expression in striatum and hippocampus of rats (Houdi et al., 1998) and up-regulates MOR in the striatum (Wewers et al., 1999). Conversely, a recent study shows down-regulation of MOR in the hippocampus and striatum following subchronic nicotine in rats (Marco et al., 2007). In C57BL/6J mice, repeated administration of nicotine decreases MOR levels in the caudate-putamen, as well as in the core and shell of the NAc (Galeote et al., 2006). On the contrary, no changes in number, affinity or functional activity of MOR were found following chronic nicotine exposure in NMRI mice (Vihavainen et al., 2008). The contradictory results found in these studies might be attributed to the different routes of nicotine administration (subcutaneous vs. oral), doses (1.75 mg/kg vs. 50–500 μg/ml), and strain of mice (C57BL/6J vs. NMRI) used.

7. The role of the endogenous opioid system in nicotine reward, motivation and reinforcement

Neurochemical studies in rodents have shown that nicotine-induced dopamine release in the NAc is modulated by the activation of MOR in the VTA (Tanda and Di Chiara, 1998). Moreover, the increase of dopamine in the NAc induced by nicotine can be blocked by the administration of the MOR antagonist/KOR agonist, cyclazocine (Maisonneuve and Glick, 1999). Therefore, nicotine-induced dopamine release in the NAc depends on the integrity of the endogenous opioid system. Accordingly, the enhancement of extracellular levels of dopamine induced in the NAc by acute nicotine administration was decreased in mice lacking PENK (Berrendero et al., 2005). In addition, a recent study has highlighted the existence of a mechanistic overlap between the effects of nicotine and opiates within the dopamine reward pathway (Britt and McGehee, 2008).

Pharmacological studies have also provided evidence for the involvement of the endogenous opioid system, and more specifically for MOR in nicotine rewarding properties (Table 1). Thus, the administration of the MOR antagonist, glycyl-glutamine blocked nicotine conditioned place preference (Göktalay et al., 2006). Furthermore, the effectiveness of lobeline, a potential

pharmacotherapy for nicotine addiction, in reducing nicotine evoked dopamine overflow from striatum of rats (Miller et al., 2000) seems to be mediated by its ability to antagonize MOR (Miller et al., 2007). On the other hand, the role of DOR in nicotine rewarding effects has not yet been clarified, and this receptor does not seem to participate in nicotine sensitization since the administration of the DOR antagonist naltrindole did not modify locomotor sensitization induced by nicotine (Heidbreder et al., 1996). Nevertheless, the administration of KOR agonists blocks the expression of nicotine sensitization, and this effect was reversed by the KOR antagonist nor-binaltorphimine (Hahn et al., 2000). These pharmacological studies confirm the participation of the endogenous opioid system in nicotine reward. However, the useful data provided by these pharmacological tools are limited by the selectivity of the ligands and the lack of information about the neural pathways involved when using the systemic route.

Studies using genetically modified mice have clarified the differential involvement of the diverse opioid peptides and receptors in the rewarding properties of nicotine (Table 2). Thus, nicotine-induced conditioned place preference was blunted in mice lacking either the MOR or PENK gene(Berrendero et al., 2002,2005) and was attenuated in mice lacking β-endorphin (Trigo et al., 2009), indicating that the activation of MOR by endogenous enkephalins and β-endorphin is required to obtain this nicotine effect. Nevertheless, the use of these conventional knockout mice does not allow to distinguish effects on the acquisition and expression of the place conditioning which could have different psychological implications. On the other hand, the presence of MOR is also required for the development and expression of behavioral sensitization to nicotine in mice (Yoo et al., 2004). The kappa/dynorphin system seems to play an opposite role in nicotine reward. Thus, mice lacking PDYN showed an enhanced sensitivity to nicotine self-administration, which suggests that opioid peptides derived from PDYN would mediate nicotine aversive effects (Galeote et al., 2009). Accordingly, opioid peptides derived from PDYN also participate in the aversive effects of other drugs of abuse, such as cocaine (Shippenberg et al., 2007) and cannabinoids (Mendizabal et al., 2006). Recent findings suggest that the opioid peptide N/OFQ is involved in nicotine rewarding effects. Indeed, mice lacking N/OFQ show an increase in voluntary nicotine intake and a decrease in behavioral sensitization to low doses of nicotine (Sakoori and Murphy, 2009). The use of these conventional knockout mice has provided new information about the specific involvement of each component of the endogenous opioid system in nicotine reward. However, additional studies using conditional knockout mice with spatially and/or temporally restricted deletions will be required to exclude the possible influence of any compensatory change and to clarify the specific neural pathways involved in these responses.

The integrity of the endogenous opioid system is also critical for the expression of the molecular responses related to the rewarding properties of nicotine. Thus, CREB phosphorylation in response to either nicotine administration or its associated cues was inhibited in knockout mice lacking MOR (Walters et al., 2005). The same inhibition of CREB phosphorylation was observed in wild-type mice following the administration of naloxone, which blocked the behavioral expression of nicotine conditioned place preference (Walters et al., 2005). In agreement, β-arrestin-2, which regulates the activity of several receptors including MOR (Bohn et al., 1999; Oakley et al., 2000; Zheng et al., 2008), participates in the induction and expression of nicotine sensitization and the effects induced by nicotine on the BDNF content in the NAc (Correll et al., 2009). Further supporting these data, genome-wide association studies have revealed a significant association amongst β-arrestin-1 and –2 gene variants with nicotine dependence in a subpopulation of smokers of European origin in America (Sun et al., 2008).

Human imaging studies using positron emission tomography have shown that nicotine activates MORs in the rostral and dorsal anterior cingulate cortex (Scott et al., 2007). These brain structures are closely related to the anticipation of reward (Kilts et al., 2001) and the discrimination between potentially rewarding and non-rewarding outcomes (Knutson et al,

2003). In agreement, association analysis in humans has revealed that some polymorphisms in the MOR gene are involved in smoking initiation and dependence (Zhang et al., 2006), and smoking reward has also been associated with MOR genetic variance (Perkins et al., 2008). Therefore, the efficacy of naltrexone on smoking cessation in humans (see section 9 of this review) might be due to the ability of this opioid antagonist to reduce the reinforcing effects of nicotine (Rukstalis et al., 2005; Wewers et al., 1998).

8. The role of the endogenous opioid system in the development of nicotine tolerance and physical dependence

The participation of the endogenous opioid system in the development of tolerance to the pharmacological effects of nicotine has been shown using pharmacological and genetic tools. Indeed, cross-tolerance between the antinociceptive effects of nicotine and morphine has been reported (Biala and Weglinska, 2006). In addition, an increase in MOR activation of G-proteins has been found in the spinal cord during chronic nicotine treatment in tolerant mice, and MOR knockout mice developed faster tolerance to nicotine antinociceptive effects than wild-type animals (Galeote et al., 2006). These results suggest that the increased activation of MORs during chronic nicotine administration could be an adaptive mechanism to counteract the establishment of tolerance to nicotine antinociception. KORs have also been reported to participate in the development of nicotine tolerance. Thus, a decrease in the density of KORs has been shown in all layers of the spinal cord in nicotine tolerant mice, and bi-directional cross-tolerance between the antinociceptive effects of nicotine and the KOR agonist U50,488H has been reported during chronic treatment with these compounds (Galeote et al., 2008). This down-regulation of KOR in the spinal cord seems to contribute to the development of nicotine tolerance since these receptors are necessary for a complete manifestation of nicotine antinociception (Galeote et al., 2008). Therefore, the adaptive changes occurring during chronic nicotine administration in MORs and KORs seem to play an opposite role in the development of tolerance to nicotine antinociception.

Chronic nicotine exposure induces adaptive changes in the CNS that lead to physical dependence and withdrawal manifestations. Both human and animal studies have reported the involvement of the endogenous opioid system in the manifestations of nicotine withdrawal. In human studies, the opioid antagonist naloxone has been found to induce somatic signs of nicotine withdrawal in heavy chronic smokers (Sutherland et al., 1995; Krishnan-Sarin et al., 1999). The administration of opioid antagonists in humans smokers currently causes an initial compensatory increase in nicotine intake to overcome the blockade of some of its behavioral effects (Sutherland et al., 1995), similar to what occurs with the co-administration of the nicotine antagonist mecamylamine (Pomerleau, 1998). In animal studies, naloxone administration has been reported to precipitate a nicotine withdrawal syndrome in dependent mice (Balerio et al., 2004; Biala et al. 2005) and rats (Malin et al., 1993), whereas morphine attenuates the severity of the spontaneous (Malin et al., 1993) or mecamylamine-precipitated nicotine withdrawal syndrome (Ise et al., 2000). Nicotine abstinence resembles opiate withdrawal and the somatic manifestations of withdrawal to both drugs of abuse share several common signs, such as abdominal constriction (writhes), facial fasciculation, eyeblink, ptosis, escape attempts, foot licks, genital grooming, shakes, tremors, scratches, teeth chattering and difficult breathing (Malin et al., 1993; Malin et al., 1996; Hildebrand et al., 1997). These pharmacological results suggest the existence of common mechanisms in the regulation of opioid and nicotine physical dependence. Naloxone was even more effective than the nAChR antagonist mecamylamine in precipitating the negative emotional manifestations of nicotine withdrawal measured in the place conditioning paradigm in mice (Balerio et al., 2004). However, the opioid antagonists naloxone (Tome et al., 2001) and naltrexone (Almeida et al., 2000) also show some affinity to nAChRs, which could have some influence in the behavioral effects induced by these antagonists in nicotine-dependent animals and humans. On the other

hand, the administration of MOR, DOR or KOR agonists reduces the capability of mecamylamine to produce aversive manifestations of nicotine withdrawal in the place conditioning paradigm (Ise et al. 2000, 2002). A recent study has shown an increase in PDYN expression in the NAc in nicotine abstinent rodents (Isola et al., 2008) that could be related to the emergence of the negative affective states observed during withdrawal. In contrast to the attenuation of mecamylamine-precipitated nicotine withdrawal aversion by KOR agonists (Ise et al., 2002), this last study suggests that KOR antagonists might be considered for the amelioration of the negative affective states related to nicotine abstinence.

Studies using knockout mice have confirmed the role of the endogenous opioid system in the physical manifestations of nicotine withdrawal. Thus, the somatic expression of nicotine abstinence precipitated by mecamylamine in dependent mice was significantly attenuated in mice lacking the MOR (Berrendero et al., 2002) or the PENK gene (Berrendero et al., 2005). In contrast, the absence of the PDYN (Galeote et al., 2009) or β-endorphin (Trigo et al., 2009) gene did not modify the severity of nicotine withdrawal. These results indicate that endogenous enkephalins and the activation of MOR are necessary for the manifestation of the somatic signs of nicotine abstinence. In agreement, an increase in PENK mRNA levels has been reported in the striatum and hippocampus of rats during nicotine withdrawal (Houdi et al., 1998) as well as in the striatum of nicotine-abstinent mice (Isola et al., 2002).

9. Efficacy of opioid antagonists in the treatment for smoking cessation

Numerous clinical trials have been performed to evaluate the effectiveness of the non-selective MOR antagonists, naloxone and naltrexone, for smoking cessation in humans. However, the results of early studies were not conclusive since only moderate or even negative effects were observed (Karras and Kane, 1980; Gorelick et al., 1989; Nemeth-Coslett and Griffiths, 1986; Sutherland et al., 1995; Covey et al., 1999; Wewers et al., 1998). Recent studies have almost exclusively concentrated on naltrexone as a suitable opioid antagonist in smoking cessation treatment due to its longer-acting effects. Thus, several clinical trials have shown that the acute reinforcing value of nicotine is reduced by intermediate doses of naltrexone (50 mg) during short-term nicotine abstinence using cigarette-smoking choice paradigms (King and Meyer, 2000; Rukstalis et al., 2005). This effect was confirmed in a placebo-controlled laboratory study, where subjects received one dose of 50 mg and 4 h later were given the option of smoking a cigarette at half-hour intervals. In this study, naltrexone significantly decreased the number of first and second cigarettes chosen (Epstein and King, 2004). Studies evaluating the potential efficacy of naltrexone (50 mg for 8 weeks) as a co-adjunct of nicotine replacement therapy in smoking cessation show higher continuous abstinence rates for naltrexone (56%) as compared to placebo (31%) treatment (Krishnan-Sarin et al., 2003). However, these findings were not supported in a randomized partially-blind 2 × 2 factorial design trial since naltrexone at the dose of 50 mg for 12 weeks did not show a significant effect on smoking cessation or craving as compared to placebo (Wong et al., 1999). These discrepancies could be due to a differential effectiveness of naltrexone depending on the specific individual differences of smokers. In this sense, the dose of 50 mg of naltrexone appears to be more effective for smoking cessation in female smokers when given alone (King et al., 2006) or in combination with nicotine replacement therapy (Byars et al., 2005). In addition, treatment with this dose of naltrexone was related to better rates of smoking cessation than placebo in smokers reporting higher rates of depressive symptoms (Walsh et al., 2008). These studies suggest that individual differences regarding gender or the incidence of mood disorders, such as depression/anxiety, should be taken into account in future clinical studies evaluating the response to naltrexone treatment.

One of the mayor issues in nicotine addiction is the high incidence of relapse, mostly induced by environmental cues that have been associated with cigarette smoking. Studies evaluating the effects of naltrexone (50 mg single dose) in preventing nicotine relapse have also shown

mixed results. One trial shows blunting of the urge to smoke and no negative affect following the smoking cues in subjects treated with naltrexone (Hutchison et al., 1999), while another study found reduced cue-elicited withdrawal symptoms, but no significant effects on the urges to smoke or deprivation-induced withdrawal prior to cue exposure (Rohsenow et al., 2007). In addition, because naltrexone has some efficacy for alcohol addiction, its effects on concomitant smoking and drinking behaviors have been examined. Thus, naltrexone (50 mg for 3 days) decreases the progression of craving for cigarettes during alcohol intoxication in a laboratory double-blind placebo-controlled design study (Ray et al., 2007). Conversely, another study found that low doses of naltrexone (25 mg) plus nicotine replacement therapy reduces the risk of hazardous drinking in a placebo-controlled trial for smoking cessation (O'Malley et al., 2008). In summary, mixed results have been obtained with respect to the effects of naltrexone with or without nicotine replacement therapy on smoking cessation, probably due to differential effectiveness of naltrexone in different sub-populations of smokers. Future efforts for identifying more suitable opioid targets may focus on evaluating the role of specific genetic variations in these sub-populations, including the MOR gene variant A118G, which has been linked to the relative reinforcing value of nicotine (Lerman et al. 2004; Ray et al., 2006). In addition, the study of DOR and KOR ligands as possible therapies for smoking cessation could also be of interest given the recognized role of these receptors in the behavioral responses induced by nicotine (Balerio et al., 2005; Hasebe et al., 2004).

10. Concluding remarks

Nicotine addiction is a complex disorder involving adaptive changes on nAChRs and alterations in other neurochemical systems that modulate the behavioral responses to nicotine. The glutamate, GABA and cannabinoid system are involved in the initiation of nicotine addiction as they participate in the rewarding properties of this drug. Some of these neurochemical systems also participate in the development of nicotine tolerance and dependence, as well as relapse to nicotine seeking. The endogenous opioid system also plays a crucial role in several aspects of the addictive process induced by nicotine. Hence, acute nicotine administration enhances the levels of endogenous opioid peptides in different brain structures, which has been related to several nicotine pharmacological effects, including reward. Chronic nicotine exposure and withdrawal also modify endogenous opioid peptide content in different brain structures in addition to the activity of MORs and KORs in the spinal cord. These changes possibly mediate the development of nicotine tolerance and physical dependence. Studies using pharmacological tools and genetically modified mice have revealed that MOR is a crucial component for nicotine rewarding effects and for the development of nicotine tolerance and dependence. Endogenous enkephalins and beta-endorphins are responsible for these rewarding effects of nicotine, and enkephalins also participate in the development of nicotine physical dependence. The PDYN/KOR system plays an opposite role to the other components of the endogenous opioid system in modulating nicotine effects. Indeed, endogenous opioid peptides derived from PDYN are involved in nicotine aversive effects, which would counteract the rewarding responses of nicotine mediated by enkephalins and beta-endorphins. KOR also plays an opposite role to MOR in the development of nicotine tolerance. Recent genetic studies revealing the association between genetic variations of MOR and the risk for smoking initiation and dependence sustain the results of animal studies and provide an additional finding to support the involvement of MORs in the different aspects of nicotine addiction.

Most of these animal studies have focused on the involvement of the different components of the endogenous opioid system in nicotine tolerance, dependence and reward. However, addiction is not just the self-administration of drugs but rather constitutes a relapsing disorder characterized by compulsive drug use despite adverse consequences for the user (DSM-IV, 2000). New animal models are now available to evaluate other behavioral responses more

directly related to the nicotine addictive process, such as reinstatement to nicotine seeking. The pharmacological and genetic tools described in the present review, combined with the use of these new animal models, will soon provide a better understanding of the neurobiological mechanisms involved in nicotine addiction. Furthermore, behavioral models of compulsive drug seeking that resemble the main diagnosis criteria for addiction in humans have been recently described in rodents (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). However, these models were substantiated for cocaine consumption and are not still available for nicotine. The future validation of these new models for nicotine addiction will represent a definitive advance in the knowledge of the substrates involved in this complex pathological behavior.

In humans, the clinical trials performed with the opioid antagonist naltrexone have reported controversial results about its effectiveness in smoking cessation. These discrepancies could be due to a differential effect of naltrexone depending on specific individual factors of smokers. In this sense, the rates of smoking cessation after naltrexone treatment were better in smokers reporting higher rates of depressive symptoms and females than in other sub-populations. New clinical trials focused on the specific populations that present a better response to naltrexone will be necessary to clearly define the therapeutic value of this opioid antagonist for smoking cessation, and further genetic studies can also be useful to better identify these specific populations. The elucidation of the roles played by each specific component of the endogenous opioid system in nicotine addiction represents an important advance in the identification of new therapeutic targets for this disorder, which constitutes one of the main causes of preventable deaths in developed countries.

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Table 1

Changes on nicotine addictive properties in opioid receptor or peptide precursor knockout mice

Knockout mice	Behavioral/Molecular Response	Effect	Reference
μ-opoid receptor	Conditioned place preference	Attenuation	[Berrendero et al., 2002]
	Physical dependence	Attenuation	[Berrendero et al., 2002]
	CREB phosphorylation	Suppression	[Walters et al., 2005]
	Sensitization	Suppression	[Yoo et al., 2004]
	Neuronal nitric oxide synthase expression	Attenuation	[Yoo et al., 2005]
	Tolerance	Faster development	[Galeote et al., 2006]
Pre-proenkephalin gene	Conditioned place preference	Attenuation	[Berrendero et al., 2005]
	Physical dependence	Attenuation	[Berrendero et al., 2005]
	DA release in Nacc	Attenuation	[Berrendero et al., 2005]
β-endorphin	Conditioned place preference	Attenuation	[Trigo et al., 2009]
	Physical dependence	No change	[Trigo et al., 2009]
Prodynorphin	Conditioned place preference	No change	[Galeote et al., 2008]
	Physical dependence	No change	[Galeote et al., 2008]
	Self-administration	Enhanced sensitivity and acquisition	[Galeote et al., 2009]
Nociceptin	Two-bottle choice	Increased intake	[Sakoori et al., 2009]
	Conditioned place aversion	Manifestation	[Sakoori et al., 2009]

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Table 2

Effects of pharmacological interventions on the opioid system on nicotine addictive properties

Drug	Behavioral/Molecular Response	Dose	Effect	Animal	Reference
Morphine	Physical dependence expression	4.5 mg/kg, s.c.	Suppression	Rat	[Malin et al., 1993]
	Physical dependence development	3 mg/kg, s.c.	Suppression	Rat	[Ise et al., 2000]
	Cross-tolerance	12.5 or 25 mg/kg, s.c	Manifestation	Rat	[Zarrindast et al., 2003]
	Tolerance	50 mg/k, s.c.	Enhanced	Mice	[Biala and Weglinska, 2006]
Naloxone	Withdrawal syndrome	4.5 mg/kg, s.c.	Manifestation	Rat	[Malin et al., 1993]
	Conditioned place preference	0.5, 1 and 2 mg/kg, i.p.	Suppression	Mice	[Zarrindast et al., 2003]
	Conditioned place aversion	0.5 and 1 mg/kg, i.p.	Attenuation	Mice	[Zarrindast et al., 2003]
	Physical dependence expression	3 mg/kg, s.c.	Manifestation	Mice	[Balerio et al., 2004]
	Withdrawal syndrome	1 mg/kg, i.p.	Manifestation	Mice	[Biala et al., 2005]
	Conditioned place preference	1 mg/kg, s.c.	Suppression	Mice	[Walters et al., 2005]
	CREB phosphorylation	1 mg/kg, s.c.	Suppression	Mice	[Walters et al., 2005]
TAN-67	Physical dependence	56 mg/kg, s.c.	Suppression	Rat	[Ise et al., 2000]
Cyclazocine	DA release in Nac	0.5 mg/kg, i.p.	Suppression	Rat	[Maisonneuve and Glick, 1999]
Glycyl-glutamine	Conditioned place preference	100 nmol i.c.v.	Suppression	Rat	[Göktalay et al., 2006]
	Physical dependence expression	100 nmol i.c.v.	Attenuation	Rat	[Göktalay et al., 2006]
Naltrindole	Sensitization	0.3, 1.0 mg/kg s.c.	No change	Rat	[Heidbreder et al., 1996]
U50,488H	Hyperlocomotion	3 mg/kg s.c.	Suppression	Rat	[Hahn et al., 2000]
	Conditioned place aversion	1.0 mg/kg, s.c.	Attenuation	Rat	[Ise et al., 2002]
	Cross-tolerance	10 mg/kg, s.c.	Manifestation	Mice	[Galeote et al., 2008]
U69,593	Hyperlocomotion	0.32 mg/kg i.p.	Suppression	Rat	[Hahn et al., 2000]
CI-977	Hyperlocomotion	0.02 mg/kg s.c.	Suppression	Rat	[Hahn et al., 2000]
TRK-820	Conditioned place aversion	0.03 mg/kg, s.c.	Attenuation	Rat	[Ise et al., 2002]