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REVIEW

Endogenous opioid system: a promising target for future smoking cessation medications

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Abstract
Background Nicotine addiction continues to be a health challenge across the world. Despite several approved medications, smokers continue to relapse. Several human and animal studies have evaluated the role of the endogenous opioid system as a potential target for smoking cessation medications.
Methods In this review, studies that have elucidated the role of the mu (MORs), delta (DORs), and kappa (KORs) opioid receptors in nicotine reward, nicotine withdrawal, and reinstatement of nicotine seeking will be discussed. Additionally, the review will discuss discrepancies in the literature and therapeutic potential of the endogenous opioid system, and suggest studies to address gaps in knowledge with respect to the role of the opioid receptors in nicotine dependence.
Results Data available till date suggest that blockade of the MORs and DORs decreased the rewarding effects of nicotine, while activation of the MORs and DORs decreased nicotine withdrawal-induced aversive effects. In contrast, activation of the KORs decreased the rewarding effects of nicotine, while blockade of the KORs decreased nicotine withdrawal-induced aversive effects. Interestingly, blockade of the MORs and KORs attenuated reinstatement of nicotine seeking. In humans, MOR antagonists have shown benefits in select subpopulations of smokers and further investigation is required to realize their full therapeutic potential.
Conclusion Future work must assess the influence of polymorphisms in opioid receptor-linked genes in nicotine dependence, which will help in both identifying individuals vulnerable to nicotine addiction and the development of opioid-based smoking cessation medications. Overall, the endogenous opioid system continues to be a promising target for future smoking cessation medications.

Keywords Morphine · Nicotine · Mu · Kappa · Delta · Nucleus accumbens

Abbreviations

AMPA	Amino-3-hydroxy-5-methyl-4-isoxazolepropionate/kainate
CPP	Conditioned place preference
CPA	Conditioned place version
DAMGO	[D-Ala2,N-Me-Phe4,Gly-ol5]-enkephalin
DORs	Delta opioid receptors
GNTI	Guanidinonaltrindole
ICSS	Intracranial self-stimulation
KORs	Kappa opioid receptors
MK-801	(5*R*,10*S*)-(−)-5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cylcohepten-5,10-imine
MORs	Mu opioid receptors
NAcc	Nucleus accumbens
NMDA	*N*-methyl-D-aspartate
VTA	Ventral tegmental area

Introduction

Tobacco smoking continues to attract healthcare resources due to the considerable morbidity and mortality associated with it (USDHHS 2014). Aggressive efforts on the part of healthcare professionals and organizations have certainly helped in slowing down the tobacco epidemic. Despite these efforts,

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several millions of smokers continue to smoke and suffer the consequences of smoking. Nicotine is a major component of tobacco smoke that is primarily responsible for continued tobacco smoking (Stolerman and Jarvis 1995). The availability of nicotine to teenagers in the form of E-cigarettes has compounded the problem of tobacco smoking, and it appears that the battle against nicotine addiction will continue for some time in the future (Callahan-Lyon 2014). Even though the Food and Drug Administration (FDA) has approved several smoking cessation medications, long-term abstinence is still a challenge for many smokers (D'Souza and Markou 2011). Hence, there is a continuous need to identify novel targets for smoking cessation medications.

High rates of smoking are observed in disease states involving the endogenous opioid system. For example, high rates of smoking have been reported in individuals suffering from chronic pain compared to the general population (Andersson et al. 1998; Hutchinson et al. 2001; Jamison et al. 1991; Zvolensky et al. 2010). The reasons for the high rates of smoking in patients suffering from chronic pain are not fully understood. One hypothesis put forth to explain this phenomenon is that people suffering from chronic pain compared to the general population may have higher vulnerability to get addicted to drugs of abuse including nicotine (Ditre et al. 2011; Hooten 2016). The endogenous opioid system plays an important role in modulating pain (Kirkpatrick et al. 2015). So does the endogenous opioid system have a role in this increased vulnerability to nicotine addiction in patients suffering from chronic pain? Incidentally, high rates of tobacco smoking are observed in heroin-dependent and methadone-maintained patients (Guydish et al. 2011; Miller and Sigmon 2015; Talka et al. 2015b). Both methadone and heroin act by stimulating the mu opioid receptors. Again, it is not clear if high rates of smoking in opioid-dependent patients is due to stimulation of the endogenous opioid system or due to an independent vulnerability to nicotine addiction. However, it has been reported that opioid-dependent smokers respond poorly to smoking cessation medications and may be at higher risk of relapse (Miller and Sigmon 2015). Therefore, opioid-dependent smokers may represent a unique subset of smokers. Overall, the above findings suggest prevalence of nicotine addiction in disease states that involve the endogenous opioid system. Further, patients suffering from chronic pain and opioid-dependent patients provide significant opportunities to promote smoking cessation.

Support for a role of the endogenous opioid system in nicotine dependence comes from a large body of preclinical and clinical studies. In fact, several studies have reported changes in levels of opioid peptides and/or expression of opioid receptors after exposure to acute and chronic nicotine (for review, see Berrendero et al. 2010; Drews and Zimmer 2010; Hadjiconstantinou et al. 2011; Kishioka et al. 2014). There is also evidence to suggest that genetic polymorphisms in opioid receptors may increase vulnerability to development of nicotine addiction and influence response to smoking cessation medications (Crist and Berrettini 2014). Taken together, the above studies suggest a possible role for the endogenous opioid system in development and treatment of nicotine dependence.

This review discusses our current state of knowledge with respect to the role of the endogenous opioid system in nicotine dependence using animal models. Additionally, the review discusses relevant human studies that further our understanding of the role of the opioid system in nicotine dependence. Importantly, the review identifies several gaps in the literature and challenges that exist and must be addressed for promoting smoking cessation via manipulation of the endogenous opioid system. The review thus adds to the above described erudite reviews on the subject.

Development of nicotine dependence

Research in nicotine dependence largely focuses on three important phases. First is the acquisition and maintenance phase, which is mediated by the reinforcing effects of nicotine. Tobacco smoking produces a pleasurable rush, mild euphoria, increased arousal, decreased fatigue, and relaxation in humans (Henningfield et al. 1985). Similarly, nicotine administration in animals maintains nicotine-seeking behavior (Markou 2008; Watkins et al. 2000a). The second phase of nicotine dependence is characterized by withdrawal symptoms upon abstinence from smoking, which occur due to alteration of brain reward systems following chronic nicotine exposure. Withdrawal symptoms in nicotine-dependent smokers include depressed mood, anxiety, irritability, craving, insomnia, and weight gain (Hughes et al. 1991; Shiffman and Jarvik 1976). Similarly, withdrawal of nicotine in nicotine-dependent animals results in increased rearing, jumping, shakes, abdominal constrictions, chewing, scratching, facial tremors, aversion demonstrated by conditioned place aversion (CPA), and depression-like state characterized by elevation of brain reward thresholds (Epping-Jordan et al. 1998; Jackson et al. 2015; Jonkman et al. 2008; Malin et al. 2006; Watkins et al. 2000a). Nicotine withdrawal in animals can be either spontaneous when administration of nicotine is stopped or precipitated when nicotine withdrawal is induced by administrating a nicotinic acetylcholine receptor (nAChR) antagonist. Finally, the last phase in nicotine dependence is relapse amongst abstinent smokers. Relapse can occur on exposure to stressful situations, nicotine, or cues associated with tobacco smoking (Brigham et al. 1990). Learned associations between nicotine and environmental stimuli largely contribute to relapse amongst abstinent smokers (Crombag et al. 2008). In animals, presentation of environmental cues and contexts associated with nicotine facilitates either preference for nicotine-associated chambers or reinitiation of nicotine-seeking behavior after a period of abstinence and/or extinction training (Caggiula

et al. 2002; Paterson et al. 2005; Stoker and Markou 2015). Further, stress or priming with nicotine can also produce reinstatement of nicotine-seeking behavior in animals (Buczek et al. 1999; Chiamulera et al. 1996; Shaham et al. 2003). Below, we will discuss the role of endogenous opioids in the above described phases of nicotine dependence.

Endogenous opioid system and nAChR systems

Neuronal nAChRs

The actions of nicotine in the brain are mediated by neuronal nAChRs, which also serve as receptors for the endogenous ligand acetylcholine. The activation of the neuronal nAChRs opens an ion channel that allows for entry of sodium and calcium ions and results in excitation of the neuron. Neuronal nAChRs are composed of five subunits of either only alpha type (i.e., homomeric) or mixture of alpha and beta type subunits (i.e., heteromeric) (Dani and Bertrand 2007). Based on the type of alpha (α2-α9) and beta (β1-β4) subunits that come together to form the heteromeric nAChRs, these receptors generally have a lot of diversity and vary in pharmacological response to nicotine and acetylcholine. In contrast, homomeric nAChRs are most commonly formed of five α7 subunits and are frequently located on glutamatergic neurons (Mansvelder and McGehee 2000, 2002; McGehee et al. 1995). Neuronal nAChRs are widely distributed throughout the CNS and can be found in several brain regions such as the nucleus accumbens (NAcc), amygdala, hippocampus, cortex, globus pallidus, thalamus, hypothalamus, and ventral tegmental area (VTA).

Opioid receptors and peptides

Opioid receptors were first discovered in the 1970s and are broadly classified into three types: mu opioid receptors (MORs), kappa opioid receptors (KORs), and delta opioid receptors (DORs) (Kieffer and Evans 2009; Pert and Snyder 1973). Several endogenous peptides activate these opioid receptors including β-endorphin, met- and leu-enkephalin, and dynorphins (Berrendero et al. 2010). These endogenous peptides have differing affinity for the opioid receptors. The β-endorphin has the highest affinity for the MORs, the met- and leu-enkephalin preferentially bind to the DORs, and dynorphins are endogenous ligands for the KORs (Lutz and Pfister 1992). The opioid receptors are coupled to inhibitory-type G-proteins (G_i/G_0), and therefore, activation of these receptors by endogenous ligands or exogenous agonists have an inhibitory effect on neuronal activation or neurochemical release (Kieffer and Evans 2009). These inhibitory actions are mediated by a number of intracellular events and can include the following: inhibition of adenyl cyclase, reduction in the opening of voltage-gated calcium channels, and stimulation of potassium current through several channels including G-protein inwardly rectifying potassium channels (GIRKs). Opioid receptors are located at both pre- and post-synaptic sites and are associated with modulation of neurotransmitter release. Further, repeated agonist stimulation results in changes in functional activity and/or expression of opioid receptors (Dang and Christie 2012). Finally, heterodimerization has been reported between the MORs and KORs and also between the MORs and DORs (Chakrabarti et al. 2010; Pradhan et al. 2011).

Opioid receptors and their endogenous ligands are distributed throughout the CNS and peripheral tissues (Le Merrer et al. 2009; Mansour et al. 1995). Specifically, opioid receptors are found in several limbic and cortical nuclei such as the NAcc, amygdala, hippocampus, prefrontal cortex, globus pallidus, thalamus, hypothalamus, and VTA. These brain regions form parts of circuitries mediating reward, pain, mood, anxiety, and emotional responses. In summary, there is significant overlap in distribution of neuronal nACh and opioid receptors in the brain. Additionally, while nAChRs are excitatory in nature, the opioid receptors are inhibitory in nature.

Interaction between opioid and nACh receptor systems

Nicotine does not bind directly to opioid receptors. Instead, nicotine binds to nAChRs located on presynaptic terminals of neurons containing opioid peptides. Thus, the effect of nicotine on opioid peptide release is largely indirect. Additionally, nAChRs are also located on somatodendritic regions and can influence excitability of opioid-containing neurons (Barik and Wonnacott 2009). The nicotine-induced release of different opioid peptides is regulated differently depending on the peptide. Nicotine-induced increase in met-enkephalin is glutamate-dependent and occurs via activation of α7-containing nAChRs (Isola et al. 2000). Thus, blockade of the ionotropic glutamate receptors (i.e., *N*-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazolepropionate/kainate (AMPA)) located on opioid-containing neurons can attenuate nicotine-induced met-enkephalin release. In contrast to met-enkephalin, nicotine-induced increase in β-endorphin is dependent on nicotine-induced dopamine release and D_2 dopamine receptors (Hadjiconstantinou and Neff 2011). Finally, nicotine-induced increase in dynorphin release was blocked by nAChR antagonists, D_2 receptor antagonists, and NMDA receptor antagonists (Isola et al. 2009). Therefore, nicotine-induced dynorphin release is regulated by multiple neurotransmitter systems. Repeated exposure to nicotine can alter expression and/or functioning of the different opioid receptors, which are discussed in detail below.

It must be mentioned here that endogenous acetylcholine release can be altered by presynaptic opioid receptors located on cholinergic neurons. For example, pharmacological activation of opioid receptors located on striatal, cortical, and hippocampal brain slices resulted in inhibition of acetylcholine

release (Lapchak et al. 1989). It is not known if these in vitro findings also occur under in vivo conditions. Theoretically, inhibition of ACh release in vivo by endogenous opioids can result in upregulation of the corresponding nAChRs. This will make the nAChRs more sensitive to nicotine and can in turn influence release of endogenous opioids. Together, these data suggest reciprocal regulation of nACh and opioid receptors by nicotine and endogenous opioid peptides. In summary, the data suggest complex interactions between the neuronal nACh and opioid receptors, which requires further exploration.

MORs and nicotine-induced effects

MORs are involved in drug reward and several drugs of abuse such as morphine and heroin act primarily by stimulating the MORs (Charbogne et al. 2014; Le Merrer et al. 2009). In this section, we focus on the role of MORs in the reinforcing effects of nicotine, nicotine withdrawal, and reinstatement of nicotine seeking (see Fig. 1). Effects of pharmacological and genetic manipulations of MORs on nicotine-induced behaviors are summarized in Tables 1 and 2, respectively.

MORs and reinforcing effects of nicotine

Based on the role of MORs in reward, it is hypothesized that indirect nicotine-induced stimulation of the MORs will facilitate the rewarding effects of nicotine, while blockade of the MORs will attenuate the rewarding effects of nicotine. Consistent with this hypothesis, MOR antagonists naloxanazine and naloxone attenuated intravenous nicotine self-administration in rats (Ismayilova and Shoaib 2010; Liu and Jernigan 2011, but see also DeNoble and Mele 2006) (see Table 1)]. Interestingly, naltrexone, another MOR antagonist did not attenuate nicotine self-administration in Sprague-Dawley rats (Corrigall and Coen 1991; Liu et al. 2009). It is not clear if differences in pharmacology of naltrexone vs. naloxanazine contributed to differences in the above findings. Naloxanazine specifically targets type 1 MORs, while naltrexone targets both type 1 and type 2 MORs. Further, nicotine self-administration protocols and rat strains were different between the studies and could have contributed to the reported findings. Additionally, MOR antagonists naloxone and glycyl-glutamine attenuated nicotine-induced conditioned place preference (CPP) (Goktalay et al. 2006; Walters et al. 2005). Further, naloxone-mediated decrease in nicotine-

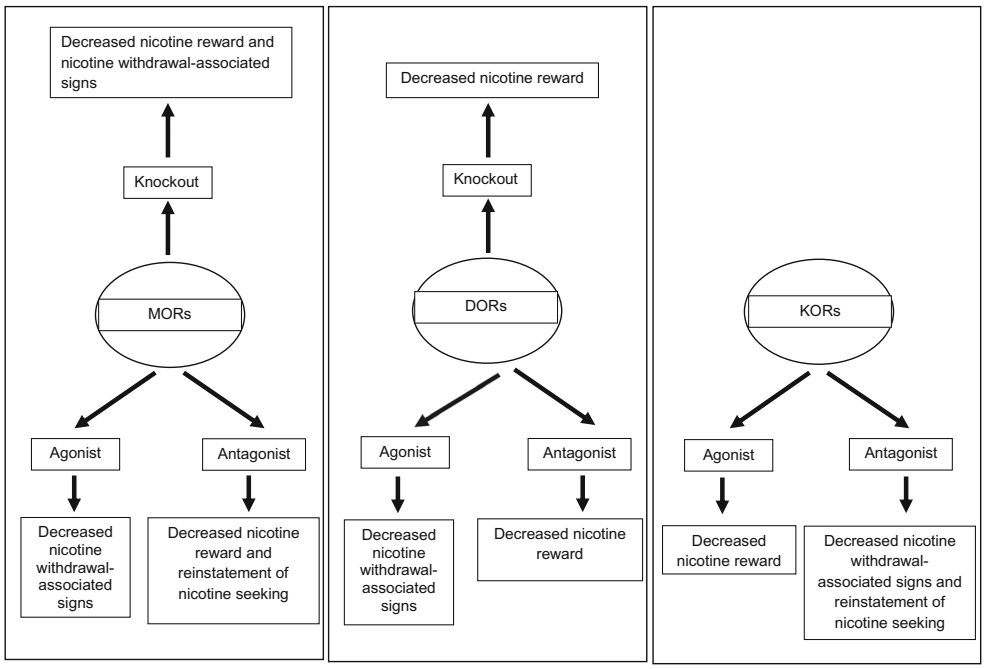

Fig. 1 The figure represents effects of pharmacological and genetic manipulations of the endogenous opioid system on nicotine-dependent behaviors such as nicotine reward, nicotine withdrawal-induced effects, and reinstatement of nicotine seeking. As shown in the figure, it appears that mu opioid receptors (MORs) and delta opioid receptors (DORs) play a similar role in nicotine-dependent behaviors. Knockout of the MORs and DORs decreased the rewarding effects of nicotine. These findings are consistent with pharmacological studies, which suggest that blockade of the MORs and DORs decreased the rewarding effects of nicotine. Further, activation of the MORs and DORs decreased the aversive effects associated with nicotine withdrawal. In comparison to the MORs and DORs, the kappa opioid receptors (KORs) appear to play an opposite role in nicotine reward and nicotine withdrawal. Pharmacological activation of the KORs decreased the rewarding effects of nicotine, while blockade of the KORs blocked the aversive effects associated with nicotine withdrawal. Interestingly, blockade of the MORs and KORs attenuated reinstatement of nicotine seeking in animals suggesting that such compounds may help to prevent relapse in humans. The effects of knockout of the KORs in nicotine-dependent behaviors has not been investigated

Table 1 Effects of pharmacological manipulation of opioid receptors on nicotine-induced behaviors

Opioid receptor	Pharmacological class	Ligand	Species/strain	Nicotine-induced behavior	Effect observed	Reference
MORs	Agonist	Morphine	Sprague-Dawley rats	Mecamylamine-precipitated nicotine withdrawal-induced CPA	Decreased	Ise et al. (2000)
		Morphine		Somatic signs associated with spontaneous nicotine withdrawal	Decreased	Malin et al. (1993)
	Antagonist	Naloxone	Lister rats	Nicotine self-administration	Decreased	Ismayilova and Shoaib (2010)
		Naloxone	Long Evans rats	Nicotine self-administration	No effect	DeNoble and Mele (2006)
		Naloxone	Long Evans rats	Nicotine self-administration	No effect	Corrigall and Coen (1991)
		Naloxanazine	Sprague-Dawley rats	Nicotine self-administration	Decreased	Liu and Jernigan (2011)
		Naltrexone	Sprague-Dawley rats	Nicotine self-administration	No effect	Liu et al. (2009)
		Glycyl-glutamine	Sprague-Dawley rats	Nicotine-induced CPP	Decreased	Goktalay et al. (2006)
		Naloxone	Swiss mice	Somatic signs in nicotine-dependent mice	Increased	Biala et al. (2005)
		Naloxone	Sprague-Dawley rats	Somatic signs in nicotine-dependent rats	Increased	Malin et al. (1993)
		Naloxone	Wistar rats	CPA in nicotine-dependent rats	Increased	Watkins et al. (2000b)
		Naltrexone	Sprague-Dawley rats	Cue-induced reinstatement of nicotine seeking	Decreased	Liu et al. (2009)
DORs	Agonist	TAN-67	Sprague-Dawley rats	Mecamylamine-precipitated nicotine withdrawal-induced CPA	Decreased (less aversion)	Ise et al. (2000)
	Antagonist	Naltrindole	Sprague-Dawley rats	Nicotine-induced locomotor activity	No effect	Heidbreder et al. (1996)
		Naltrindole	Sprague-Dawley rats	Nicotine self-administration	No effect	Liu and Jernigan (2011)
		Naltrindole	Lister rats	Nicotine self-administration	No effect	Ismayilova and Shoaib (2010)
		Naltrindole	C57Bl/6 mice	Nicotine self-administration	Decreased	Berrendero et al. (2012)
KORs	Agonist	CI-977	Lister rats	Nicotine-induced locomotor activity	Decreased	Hahn et al. (2000)
		U69,593	Lister rats	Nicotine-induced locomotor activity	Decreased	Hahn et al. (2000)
		U50,488	Lister rats	Nicotine self-administration	Decreased	Ismayilova and Shoaib (2010)
		ICI 204,448	Wistar rats	Nicotine withdrawal signs	Decreased	Sudakov et al. (2014)
		U50,488H	Sprague-Dawley rats	Nicotine withdrawal-induced CPA	Decreased	Ise et al. (2002)
	Antagonist	GNTI	Sprague-Dawley rats	Nicotine self-administration	No effect	Liu and Jernigan (2011)
		JDTic	ICR mice	Nicotine-induced CPP	No effect	Jackson et al. (2010)
		Nor-BNI	C57Bl/6 mice	Nicotine-induced CPP	Decreased	Smith et al. (2012)

Table 1 (continued)

Opioid receptor	Pharmacological class	Ligand	Species/strain	Nicotine-induced behavior	Effect observed	Reference
		JDTic	ICR mice	Nicotine withdrawal-induced CPA	Decreased	Jackson et al. (2010)
		JDTic	ICR mice	Nicotine withdrawal-induced somatic signs	Decreased	Jackson et al. (2010)
		Nor-BNI	ICR mice	Nicotine withdrawal-induced CPA	Decreased	Jackson et al. (2010)
		Nor-BNI	ICR mice	Nicotine withdrawal-induced somatic signs	Decreased	Jackson et al. (2010)
		LY2456302	ICR mice	Nicotine withdrawal-induced CPA	Decreased	Jackson et al. (2015)
		LY2456302	ICR mice	Nicotine withdrawal-induced somatic signs	Decreased	Jackson et al. (2015)
		Nor-BNI	ICR mice	Reinstatement of nicotine-CPP	Decreased	Jackson et al. (2013)
		Nor-BNI	Long Evans rats	Cue-induced reinstatement of nicotine seeking	Decreased	Grella et al. (2014)

DORs delta opioid receptors, *CPA* conditioned place aversion, *CPP* conditioned place preference, *KORs* kappa opioid receptors, *MORs* mu opioid receptors

induced CPP was shown to be mediated via a decrease in cAMP response element binding protein (CREB) phosphorylation (Walters et al. 2005). Even though these pharmacological studies reveal the role of MORs in the reinforcing effects of nicotine, the role of MORs in animal models with extended access to nicotine have not been demonstrated. Additionally, it remains to be determined if effects of repeated administration of the MOR antagonists such as naloxone and naltrexone on nicotine self-administration are similar to effects of acute administration of these compounds as described above. The latter studies will help in determining development of tolerance to the effects of MOR receptor antagonists on the reinforcing effects of nicotine.

Consistent with the role of MORs in nicotine reward, both nicotine-induced behavioral sensitization and nicotine-induced CPP was attenuated in mice lacking the MORs compared to the wild-type mice (Berrendero et al. 2002; Walters et al. 2005; Yoo et al. 2004). Additionally, mice lacking β-endorphin, the endogenous ligand for the MORs, showed attenuated nicotine-induced CPP (Trigo et al. 2009). There is indirect evidence to suggest that nicotine increases release of β-endorphin and activates the MORs (Davenport et al. 1990). However, direct evidence is lacking, and in fact, an in vivo microdialysis study showed no increase in β-endorphin levels in the NAcc after acute nicotine administration (Olive and Becker 2008). Taken together, these data suggest that MORs and its endogenous ligand β-endorphin mediate the reinforcing effects of nicotine.

The rewarding effects of nicotine like other drugs of abuse are mediated by mesolimbic dopaminergic neurons, which originate in the VTA and project to different brain regions including the NAcc and amygdala (Koob and Volkow 2010). MORs are extensively distributed in both the NAcc and VTA (Mansour et al. 1988). Activation of MORs in the VTA increased dopamine levels in the NAcc and inhibited VTA dopaminergic neurons projecting to the amygdala (Devine et al. 1993; Ford et al. 2006). Similarly, nicotine administration also increased dopamine levels in the NAcc and VTA (D'Souza et al. 2011; Di Chiara and Imperato 1988a; Rahman et al. 2004). Future studies need to explore the effects of pharmacological and/or genetic manipulation of MORs in specific brain regions such as the NAcc and VTA on nicotine self-administration and/or nicotine-induced CPP.

High rates of smoking have been reported in both heroin-dependent and methadone-maintained patients (Guydish et al. 2011; Mello et al. 1980). Additionally, an increase in cigarette consumption has been reported in patients using buprenorphine, a partial agonist of the MORs (Mello et al. 1985; Mutschler et al. 2002). Interestingly, activation of MORs in the frontal cortices was associated with reports of cigarette liking and wanting in human smokers (Kuwabara et al. 2014). It is not clear if the high rates of smoking in methadone-maintained patients are because of stimulation of

Table 2 Effects of nicotine in mice lacking specific opioid receptors

Opioid receptor knockout (e.g., MOR, DOR)	Dose of nicotine	Background mice strain	Behavioral assay	Effect observed in knockout animals vs. wild-type animals	Reference
MORs	Nicotine (0, 1, and 3 mg/kg, base; s.c.)	C57/BL6 mice	Locomotor activity	No effect	Berrendero et al. (2002)
	Nicotine (0.05 mg/kg, base; s.c. for 7 days; challenge dose 0.05 mg/kg, base; s.c.)	C57/BL6 and 129/OLA mice	Locomotor sensitization	Decreased	Yoo et al. (2004)
	Nicotine (0.5 and 0.7 mg/kg, base; s.c.)	C57/BL6 mice	CPP	Decreased	Berrendero et al. (2002)
	Nicotine (1 and 2 mg/kg, base; s.c.)	C57/BL6 mice	CPP	Decreased	Walters et al. (2005)
	Nicotine (10 mg/kg/day; 6 days; infusion via nicotine pump)	C57/BL6 mice	Mecamylamine-precipitated withdrawal	Decreased withdrawal signs	Berrendero et al. (2002)
DORs	Nicotine (0, 0.35, 1.05, and 2.10 mg/kg, base; s.c.)	C57BL/6J mice	Locomotor activity	No effect	Berrendero et al. (2012)
	Nicotine (0.17 mg/kg, base; s.c.)	C57BL/6J mice	CPP	Decreased	Berrendero et al. (2012)
	Nicotine (15 and 30 μg/kg/infusion, base; s.c.)	C57BL/6J mice	Self-administration	Decreased	Berrendero et al. (2012)
	Nicotine (8.77 mg/kg/day; 6 days; infusion via nicotine pump)	C57BL/6J mice	Mecamylamine-precipitated withdrawal	No effect	Berrendero et al. (2012)

CPP conditioned place preference;

MORs or blockade of nAChRs. Studies suggest that methadone blocks α3β4-containing nAChRs and activates α7-containing nAChRs (Talka et al. 2015a; Xiao et al. 2001). It is possible that the high rates of smoking in opioid-dependent abusers may be independent of opioid abuse and could be due to concurrent increased vulnerability to addiction in these individuals, a hypothesis that needs further exploration. To understand this phenomenon better, there is a need to develop animal models assessing effects of both nicotine and heroin in the same model. This could be done by exposing animals to heroin prior to nicotine self-administration. Alternately, the effects of nicotine exposure on heroin self-administration also need to be assessed. Here, it must be mentioned that repeated administration of nicotine sensitized animals to the rewarding effects of morphine (Vihavainen et al. 2008). Such models will facilitate our understanding of neurobiological changes occurring with coabuse of heroin and nicotine. Further, these models will potentially help in the development of better treatments for heroin abusers with high rates of smoking. As a caveat, it must be mentioned here that high rates of smoking are not exclusive to opioid-dependent subjects and is also reported amongst abusers of other drugs of abuse such as stimulants and alcohol (Dawson 2000; Weinberger and Sofuoglu 2009).

In human smokers, MOR antagonists attenuated the rewarding effects of smoking. A decrease in the number of cigarettes smoked has been reported in patients taking MOR antagonists naltrexone and naloxone compared to placebo (Epstein and King 2004; Gorelick et al. 1988; Karras and Kane 1980; King et al. 2013a; King and Meyer 2000; Lee et al. 2005, but see also Wong et al. 1999). This decrease in cigarettes smoked amongst smokers after administration of MOR antagonists reflects a decrease in the rewarding effects of nicotine. Additionally, smokers reported decreased satisfaction from smoking after naltrexone administration (Wewers et al. 1998). Overall, both experimental studies in animals and humans suggest a role for MORs in nicotine reward and blockade of these receptors decreased the rewarding effects of nicotine.

MORs and chronic nicotine exposure

Chronic nicotine exposure resulted in alteration in MOR expression/functioning depending on the protocol of nicotine treatment, time of collection of tissue, biomarker measured, and species/strain of animals used (see Table 3). For example, MORs were upregulated in the striatum after chronic nicotine treatment (14 days) in Sprague-Dawley rats, when measured

Table 3 Effects of chronic nicotine treatment and withdrawal on opioid signaling biomarkers

Opioid biomarker	Nicotine treatment	Species	Brain region	Time point of tissue collection	Effect	Reference
MOR function	0.3 mg/kg, base; s.c.; three times/day separated by 4 1/2 h for 14 days	Sprague-Dawley rats	Striatum	1 h after last nicotine dose	Upregulation	Wewers et al. (1999)
MOR function/binding	50–500 μg, base for 7 weeks; oral administration in drinking water	NMRI mice	Striatum, thalamus, VTA, amygdala, cingulate cortex	24 h after last nicotine dose	No change	Vihavainen et al. (2008)
MOR expression	5 mg/kg, base, s.c.; three times/day separated by 4 h for 12 days	C57BL/6J mice	Striatum	1 h after last nicotine dose	Decreased	Galeote et al. (2006)
MOR expression	0.4 mg/kg, base; s.c.; once daily for 10 days	Wistar rats	Striatum, hippocampus	2 h after last nicotine dose	Decreased	Marco et al. (2007)
MOR mRNA	1 mg/kg, base; s.c.; alternate day over a period of 8 days	C57BL/6J mice	VTA	Approximately 24 h after last dose	Increased	Walters et al. (2005)
MOR mRNA	1 mg/kg, base; s.c.; alternate day over a period of 8 days	C57BL/6J mice	NAcc	Approximately 24 h after last dose	No effect	Walters et al. (2005)
POMC mRNA	0.4–0.5 mg/kg, base; s.c.; three times/day separated by 4 h for 28 days	Sprague-Dawley rats	Hypothalamus	24 h after last nicotine dose	Decreased	Rasmussen (1998)
β-Endorphin	1.2 mg/kg, base; s.c.; once daily for 30 days	C57BL/6J mice	Hypothalamus	24 h after last nicotine dose	Decreased	Rosecrans et al. (1985)
Preproenkephalin mRNA	0.6 mg/kg, base; s.c.; twice daily for 14 days	Sprague-Dawley rats	Striatum and hippocampus	24 h after last nicotine dose	Increased	Houdi et al. (1998)
Met-enkephalin levels	0.3 mg/kg, base; s.c.; three times/day separated by 4 1/2 h for 14 days	Sprague-Dawley rats	Striatum	1 h after last nicotine dose	Decreased	Wewers et al. (1999)
Met-enkephalin levels	2 mg/kg, base; s.c.; four times/day separated by 4 h for 14 days	Swiss-Webster mice	Ventral striatum	24 h after last nicotine dose	Increased	Isola et al. (2002)
Preproenkephalin mRNA	2 mg/kg, base; s.c.; four times/day separated by 4 h for 14 days	Swiss-Webster mice	Ventral striatum	24 h after last nicotine dose	Increased	Isola et al. (2002)
DOR mRNA	2 mg/kg, base; s.c.; four times/day separated by 4 h for 14 days	Swiss-Webster mice	Hippocampus	24–72 h after last nicotine dose	Increased	McCarthy et al. (2011)
DOR mRNA	2 mg/kg, base; s.c.; four times/day separated by 4 h for 14 days	Swiss-Webster mice	Ventral striatum	72 h after last nicotine dose	Increased	McCarthy et al. (2011)
DOR mRNA	2 mg/kg, base; s.c.; four times/day separated by 4 h for 14 days	Swiss-Webster mice	Prefrontal cortex	48–72 h after last nicotine dose	Increased	McCarthy et al. (2011)
Dynorphin	2 mg/kg, base; s.c.; four times/day separated by 4 h for 14 days	Swiss-Webster mice	Striatum	4–72 h after last nicotine dose	Decreased	Isola et al. (2008)
Prodynorphin mRNA	2 mg/kg, base; s.c.; four times/day separated by 4 h for 14 days	Swiss-Webster mice	Striatum	8–96 h after last nicotine dose	Increased	Isola et al. (2008)
Prodynorphin mRNA	0.4 mg/kg, base; s.c.; once daily for 4 days	Sprague-Dawley rats	NAcc	4 h after last nicotine dose	Decreased	Carboni et al. (2016)
Prodynorphin mRNA	0.4 mg/kg, base; s.c.; once daily for 4 days	Sprague-Dawley rats	Caudate putamen and prefrontal cortex	4 h after last nicotine dose	Increased	Carboni et al. (2016)
KOR function	2 mg/kg, base; s.c.; four times/day separated by 4 h for 14 days	Swiss-Webster mice	Nucleus accumbens	24–72 h after last nicotine dose	Decreased	McCarthy et al. (2010)

using [3H]-[D-Ala2,N-Me-Phe4,Gly-ol5]-enkephalin (DAMGO) binding (Wewers et al. 1999). Interestingly, this upregulation of MORs was sex-dependent with more prominent effects in females than males. Additionally, MOR mRNA expression was increased in the VTA, but not in the NAcc, after chronic nicotine administration (8 days) in C57BL/6 mice (Walters et al. 2005). The dose of nicotine that produced this increase in MOR mRNA expression also produced nicotine-induced CPP, thus suggesting that increased MOR expression in the VTA expression possibly mediates the reinforcing effects of nicotine. Together, these findings suggest increased MOR-mediated transmission after chronic nicotine exposure. In contrast to the above findings, chronic nicotine exposure via the oral route (7 weeks) in NMRI mice resulted in no changes in MOR functioning or DAMGO binding in the striatum and VTA (Vihavainen et al. 2008). Finally, a decrease in MOR density was reported in the striatum (dorsal and ventral) in C57BL/6 mice after chronic nicotine treatment (Galeote et al. 2006). Overall, the above studies suggest that MOR expression/function is altered by chronic nicotine treatment, but these alterations depended on the nicotine administration protocol, biomarker measured, time of collection of brain tissue, and species/strain used in the study.

In addition to changes in MORs expression/functioning, decreases in hypothalamic β-endorphin levels and proopiomelanocortin (POMC) mRNA levels have been reported following chronic nicotine administration (Rasmussen 1998; Rosecrans et al. 1985). The hypothalamic-pituitary axis plays an important role in the aversive effects associated with nicotine withdrawal (Koob and Volkow 2010). The hypothalamus also plays an important role in regulating appetite, and changes in appetite and weight gain are frequently associated with nicotine withdrawal. Therefore, dysregulation in the β-endorphin-MOR system in the hypothalamus-pituitary axis possibly suggests a role for MOR signaling in nicotine withdrawal. In current smokers, increases in plasma levels of β-endorphin have been reported (Gilbert et al. 1992; Pomerleau et al. 1983). The increase in plasma β-endorphin was seen after smoking high doses of nicotine and was accompanied by aversive symptoms such as nausea, malaise, and general discomfort (Gilbert et al. 1992). This suggests that the increase in peripheral β-endorphin levels is more a reflection of aversive effects associated with smoking. However, it is not fully understood if this increase in plasma β-endorphin reflects a brain region-specific increase or generalized increase in brain β-endorphin levels.

The role of MORs in nicotine withdrawal has also been investigated. Administration of MOR antagonist naloxone in nicotine-dependent animals resulted in expression of somatic signs of nicotine withdrawal (Biala et al. 2005; Malin et al. 1993). It is hypothesized that this naloxone-precipitated nicotine withdrawal syndrome could be mediated by binding of naloxone to nAChRs. In fact, in vitro studies have demonstrated that naloxone can block nicotine-induced effects in cell systems that lack opioid receptors (Tome et al. 2001). As a caveat, it must be mentioned here that interaction of naloxone with the nAChRs occurs at very high doses (Watkins et al. 2000b). Additionally, MOR agonist morphine attenuated aversive somatic signs associated with spontaneous nicotine withdrawal (Malin et al. 1993). In addition to precipitation of somatic signs of nicotine withdrawal, low doses of the MOR antagonist naloxone induced CPA in nicotine-dependent rats (Ise et al. 2000; Watkins et al. 2000b). Administration of MOR agonist morphine reversed mecamylamine-induced CPA in nicotine-dependent animals (Ise et al. 2000). Watkins et al. (2000b) reported elevation of brain reward thresholds in nicotine-dependent rats only after administration of high doses of naloxone. Interestingly, this high dose naloxone-induced elevation of brain reward thresholds was also observed in saline controls, suggesting that the effect of naloxone at high doses on brain reward thresholds was not due to chronic nicotine exposure. Together, these pharmacological studies suggest increased MOR-mediated transmission following chronic nicotine exposure. Importantly, the data suggest that decrease in MOR-mediated neurotransmission via blockade of MORs in nicotine-dependent animals precipitated aversive affective and somatic withdrawal signs. Further, activation of MORs in nicotine-dependent animals attenuated aversive somatic and affective signs associated with nicotine withdrawal. Thus, MORs are involved in nicotine withdrawal and can serve as targets to alleviate nicotine withdrawal-associated symptoms.

Intriguingly, somatic signs associated with mecamylamine-precipitated nicotine withdrawal in nicotine-dependent mice were attenuated in MOR knockout mice compared to their respective wild-type controls (Berrendero et al. 2002). Somatic manifestation of nicotine withdrawal are largely mediated by peripherally located receptors, and thus these findings suggest that peripherally located MORs play an important role in mediating the effects of nicotine withdrawal. The apparent discrepancy between findings of this study using a genetic approach and pharmacological studies discussed above could be explained by compensatory neuroadaptations that can occur following congenital knockout of a specific gene in knockout animals. Further, as discussed above knockout of the MORs makes the animal less sensitive to the rewarding effects of nicotine (Berrendero et al. 2002). Together, these findings suggest that knockout of the MORs makes animals less sensitive to the effects of nicotine. Future studies should focus on compensatory changes occurring following genetic knockout of MORs as such studies will help identify factors that decrease sensitivity to nicotine. Such factors can possibly be used in the future as targets for promoting smoking cessation.

The role of MORs has also been investigated in human smokers after a period of overnight abstinence (early withdrawal). Using [^{11}C]-carfentanil, clinical studies have reported lower availability of MORs in several brain regions such as the

thalamus, amygdala, and basal ganglia in abstinent smokers compared to non-smoking controls (Scott et al. 2007; Weerts et al. 2014, but see also Falcone et al. 2012). Lower availability of MORs is suggestive of decreased MOR-mediated neurotransmission. Importantly, the availability of MORs during early abstinence was inversely proportional to the severity of nicotine dependence. Additionally, lower availability of MORs in several mesolimbic brain regions (globus pallidus, thalamus, ventral striatum, and amygdala) was associated with higher craving for nicotine in nicotine-dependent smokers (Weerts et al. 2014). In summary, these neuroimaging studies suggest that decreased MOR-mediated neurotransmission is associated with aversive effects of smoking cessation. However, it is not known if these changes in availability of MORs are sustained or restricted to the time point used in the above studies. Further, the above described findings were observed after smoking of denicotinized cigarettes and could reflect a response to cues associated with smoking. Nevertheless, findings from animals studies discussed above are consistent with neuroimaging findings in abstinent smokers.

Clinical pharmacological studies evaluating the effects of MOR antagonists on nicotine withdrawal symptoms suggest either no effect or attenuation of nicotine withdrawal symptoms. For example, administration of naloxone had no effect on nicotine withdrawal symptoms in nicotine-dependent human subjects (Gorelick et al. 1988, but see also Krishnan-Sarin et al. 1999). Similarly, naltrexone administration had no effect on withdrawal symptom scores (Covey et al. 1999; Knott and Fisher 2007; Rohsenow et al. 2007; Sutherland et al. 1995; Wong et al. 1999). Importantly, naltrexone reduced craving in nicotine-dependent smokers (King et al. 2013a; King et al. 2006; King et al. 2012). Studies also support use of naltrexone prior to quit date in smokers wanting to quit. In fact, initiation of the MOR antagonist naltrexone prior to the quit date in nicotine-dependent smokers may help predict response to naltrexone during abstinence from smoking (King et al. 2013a). In other words, patients who are sensitive to naltrexone prior to quitting may continue to respond to naltrexone after smoking cessation. In summary, blockade of MOR-mediated neurotransmission in nicotine-dependent patients does not exacerbate nicotine withdrawal symptoms and infact may help in decreasing craving for nicotine. These findings from clinical pharmacological studies in humans thus appear to be contradictory to findings from neuroimaging studies in human abstinent smokers and animal studies described above. The reasons for this discrepancy are not entirely clear. One possible reason could be due to assessment at a specific time-point closer to withdrawal from nicotine in human neuroimaging and animal studies.

MORs and nicotine-seeking behaviors

MORs also play a role in reinstatement of nicotine seeking. Blockade of MORs using naltrexone attenuated cue-induced reinstatement of nicotine seeking (Liu et al. 2009). The role of MORs in nicotine seeking is consistent with its role in reinstatement of other drugs such as alcohol and cocaine (Giuliano et al. 2015; Gutierrez-Cuesta et al. 2014; Simmons and Self 2009). Additionally, MORs play a role in learning and memory recall, which plays a role in reinstatement of drug-seeking behavior (Bianchi et al. 2013; Farahmandfar et al. 2012). Interestingly, direct injections of the MOR agonist DAMGO in the VTA did not reinstate extinguished responding for nicotine, which implies that MORs in the VTA may not have a role in reinstatement of nicotine seeking (Corrigall et al. 2000). However, MORs are extensively found in brain regions such as the NAcc, anterior cingulate, hippocampus, and amygdala, which play a role in reinstatement of drug seeking including nicotine seeking (Koob and Volkow 2010; Le Merrer et al. 2009). The role of MORs in reinstatement of nicotine seeking in the above mentioned brain regions has not been investigated. Future studies will need to address this gap in knowledge.

Differential regulation of the MORs in the brain has been reported after cocaine-induced and cue-induced reinstatement of cocaine seeking (Georgiou et al. 2015). Using quantitative radiography, cocaine-induced but not cue-induced reinstatement of cocaine seeking upregulated MOR binding in the basolateral amygdala. In contrast, cue-induced but not cocaine-induced reinstatement of cocaine seeking upregulated MOR binding in the caudate putamen and NAcc core. It is not clear if these findings are restricted to cocaine or will extend to nicotine. Future work will need to determine if MOR functioning is differentially regulated by nicotine-induced vs. cue-induced reinstatement of nicotine seeking.

The effect of nicotine-associated cues on MORs has also been investigated in humans. PET imaging and [^{11}C]-carfentanil displacement studies have reported a decrease in availability of MORs in the anterior cingulate, thalamus, NAcc, and amygdala following smoking of denicotinized cigarette in overnight abstinent smokers (Nuechterlein et al. 2016). These brain regions play an important role in relapse. Therefore, the decrease in MOR availability in these brain regions following smoking of denicotinized cigarettes could be due to activation of MORs by nicotine-associated environmental and sensory cues, which can act as powerful substitutes during nicotine withdrawal-induced craving (Rose et al. 2010). In summary, MORs play a role in relapse to smoking and could serve as potential targets to prevent relapse in abstinent smokers.

MORs: therapeutic potential and future directions

Based on the preclinical data described above, one can conclude that blockade of MORs may help in attenuating the rewarding effects of nicotine and in preventing reinstatement of nicotine-seeking behavior. Further, the studies described above suggest that stimulation of MORs may help in

attenuating nicotine withdrawal effects. To date, the MOR antagonists naltrexone and naloxone have had limited success in promoting long-term cessation in human smokers. Several studies report no significant effect on long-term abstinence with naltrexone compared to placebo either alone or in combination with nicotine replacement therapy (Baltieri et al. 2009; Covey et al. 1999; King et al. 2006; King et al. 2012; Toll et al. 2010; Wong et al. 1999, see also reviews David et al. 2014; David et al. 2013).

Although naltrexone has not been very effective in improving long-term smoking cessation, administration of naltrexone was more efficacious compared to placebo in limiting smoking cessation-induced weight gain in women, but not in men (King et al. 2012; King et al. 2013b). These findings suggest that MOR antagonists may have gender-based effects, the mechanisms of which are not fully understood. These data are consistent with other studies discussed below that suggest gender-based differences in functioning of the endogenous opioid system. Addition of naltrexone to nicotine replacement therapy improved short-term abstinence rates amongst smokers and reduced smoking cessation-induced weight gain (Krishnan-Sarin et al. 2003; O'Malley et al. 2006). Overall, the data support the use of naltrexone for limiting negative consequences associated with smoking cessation such as weight gain, especially amongst women smokers.

Naltrexone may also be of use in certain subpopulations of smokers desiring to quit, such as those suffering from comorbid mental disorders including depression and alcohol dependence. Addition of naltrexone to nicotine replacement treatment improved quit rates in smokers suffering from depression (Walsh et al. 2008). Naltrexone, which has been approved by the FDA for treatment of alcohol, was also effective in smokers with heavy alcohol consumption habits. Smokers with high alcohol consumption constitute approximately 20–25% of smokers and have a distinct clinical profile compared to smokers who do not drink heavily (Dani and Harris 2005; Toll et al. 2012). In fact, administration of naltrexone was shown to improve quit rates in heavy drinking smokers (King et al. 2009). Further, combining varenicline with low-dose naltrexone (25 mg/day) attenuated consumption of both alcohol and cigarettes compared to placebo in smokers who were classified as heavy drinkers (Ray et al. 2014). Additionally, the study reported decreased craving for cigarettes and attenuation of "high" associated with smoking and alcohol consumption. Moreover, naltrexone in combination with varenicline compared to placebo attenuated activation of anterior cingulate cortex, a brain region involved in cigarette craving, in response to cigarette-related cues (Ray et al. 2015). Together, these data suggest that naltrexone may have potential for improving efficacy of currently approved smoking cessation medications in smokers with high alcohol consumption. As a caveat, the treatment period in both studies was relatively short (only 9–12 days), and therefore, these findings must at best be considered preliminary in nature. However, smokers with significant alcohol consumption history are generally less responsive to currently approved smoking cessation medications and are more likely to relapse (Kahler et al. 2010). Thus, combining smoking cessation treatments with naltrexone may be beneficial in this subgroup of smokers and further work is warranted. In summary, although MOR antagonists such as naltrexone have not shown efficacy in maintaining long-term abstinence in smokers to date, identifying subpopulation of smokers based on gender, comorbid alcohol abuse, and psychiatric comorbidity (e.g., depression) may improve response to naltrexone in smokers. Also, MOR antagonists may have greater success in promoting smoking cessation when combined with currently approved smoking cessation medications such as nicotine replacement and varenicline.

Polymorphism of the OPRM1 gene is associated with differences in subjective experiences of nicotine reward and susceptibility to nicotine dependence. In humans, a single nucleotide polymorphism in the OPRM1 gene, OPRM1 A118G, has been extensively investigated (Crist and Berrettini 2014). This polymorphism is associated with substitution of adenine by guanine in exon1 of the OPRM1 gene. Lower brain MOR mRNA and protein has been reported in individuals possessing the OPRM1 A118G polymorphism (Zhang et al. 2005). Although not exactly similar, G allele carriers are like MOR receptor knockout mice which have been shown to be less sensitive to nicotine. Importantly, women carrying the low-activity G allele (A/G and G/G) have reported reduced reinforcing value of nicotine and were less likely to differentiate between nicotine vs. denicotinized cigarettes (Ray et al. 2006). In contrast, there was no association of nicotine reinforcement with this genotype amongst male smokers. Additionally, smokers homozygous for the A allele (i.e., OPRM1 A118A) were more susceptible to nicotine dependence compared to smokers with G allele (i.e., OPRM1 A118G) (Verhagen et al. 2012). Consistent with these findings, neuroimaging studies have reported increased availability of free MORs in smokers homozygous for the A allele compared to smokers carrying the G allele in the brain regions such as the amygdala and NAcc (Domino et al. 2015; Ray et al. 2011). Further, these neuroimaging studies reported blunted release of endogenous opioids after nicotine smoking in smokers carrying the G allele compared to smokers homozygous for the A allele. In nicotine-dependent smokers, overnight abstinence from smoking resulted in increased blood flow to regions associated with craving in individuals who were homozygous for A allele (OPRM1 A118A) (Wang et al. 2008). However, OPRM1 A118G polymorphism has not been strongly associated with smoking initiation or response to smoking cessation treatment (Munafo et al. 2013; Verhagen et al. 2012). In summary, the above studies suggest that polymorphism in the OPRM1 gene determines susceptibility to nicotine dependence and A allele carriers may be more susceptible to craving upon abstinence from smoking and are more likely to relapse. The discovery of the OPRM1 A118G polymorphism spurs the need to look for

other polymorphisms in the MORs that may be involved in development of nicotine dependence and/or response to smoking cessation treatment.

Other MOR gene polymorphisms have been reported that determine opioid withdrawal severity in humans (Jones et al. 2016). It remains to be seen if these polymorphisms influence other nicotine-dependent behaviors such as nicotine reward and nicotine withdrawal-induced craving. Future studies must also focus on understanding the interaction effects of OPRM1 polymorphism with polymorphisms of other genes, such as those regulating other neurotransmitters (dopamine and glutamate) involved in nicotine reward, on nicotine dependence.

It must be mentioned here that OPRM1 A118G polymorphism was initially reported to predispose individuals to the risk of developing alcoholism and also determine response to naltrexone in alcoholic patients (Kim et al. 2009; Ray and Hutchison 2004, 2007). More recent studies have not supported a role for OPRM1 A118G polymorphism in predicting susceptibility to development of alcohol dependence or response to naltrexone (Anton et al. 2012; Arias et al. 2006; Schacht et al. 2013).

Future work must explore the influence of gender and age on the role of MORs in nicotine-dependent behaviors. Gender-dependent differences in response to opioid analgesics that act via MORs have been reported (Bodnar and Kest 2010; Cicero et al. 1997; Kepler et al. 1989). As discussed above, Wewers et al. (1999) reported gender-dependent effects on MOR functioning after chronic nicotine exposure. Also, King et al. (2012) reported greater effect of naltrexone compared to placebo on smoking cessation-induced weight gain in women and not in men. Finally, as described above, gene-gender interaction effects have been associated with polymorphism of OPRM1 A118G gene. However, the interaction of gender and MORs on nicotine-induced behaviors such as nicotine self-administration, cue-induced nicotine seeking, and nicotine withdrawal has not been explored in detail and further work is warranted. Another factor that needs further investigation is the influence of age on MOR function and nicotine-dependent behaviors. Chronic exposure to nicotine in adolescent animals compared to adult animals resulted in downregulation of MORs in the hippocampus and striatum (Marco et al. 2007). Importantly, the effects of chronic nicotine exposure during adolescence on MOR function in the striatum were more marked in males than in females. In summary, the interaction of age (adolescents vs. adults) and gender on the role of MORs in nicotine-dependent behaviors needs to be further explored.

The role of MORs in specific brain regions on nicotine reward and other nicotine-dependent behaviors also needs further investigation. Based on their location in the NAcc, MORs play a differential role in hedonia (pleasure) experienced after food reward compared to motivation to consume food reward. It was reported that stimulation of MORs in a small (1 mm^3) rostrodorsal region of the NAcc shell enhanced hedonic reactions as assessed by measuring the orofacial reaction to sucrose taste (Castro and Berridge 2014). In contrast to this hedonic hotspot in the rostrodorsal region of the NAcc shell, stimulation of MORs in the caudal region of the NAcc shell inhibited hedonic reactions for sucrose. However, irrespective of their location in the NAcc shell, stimulation of MORs increased motivation to consume food rewards. Together, these data suggest a differential role for MORs based on their distribution in different parts of the NAcc shell in hedonia experienced after consumption of food vs. motivation to consume food rewards. It is not clear if this heterogeneity in the role of MORs based on their localization is restricted to food reward or if it influences other types of reward such as nicotine reward. Future studies must explore the role of MORs in the different parts of the NAcc shell (rostrodorsal vs. caudal) in hedonic reaction to nicotine vs. motivation to consume nicotine. In summary, more work is required to understand the role of MORs in nicotine dependence and to fully exploit the MORs as a target for smoking cessation treatment.

DORs and nicotine-induced effects

DORs are widely distributed in the mesolimbic brain regions that play a role in reward, emotional processing, and drug addiction (Cahill et al. 2001; Mansour et al. 1996). Direct intracerebroventricular injection of DOR agonists induced CPP on its own (Shippenberg et al. 1987; Suzuki et al. 1997). Additionally, direct injection of a DOR agonist in the NAcc reduced brain reward thresholds, suggesting that activation of DORs was rewarding (Duvauchelle et al. 1997). Pharmacological blockade or genetic elimination of the DORs induced anxiety- and depression-like behaviors (Filliol et al. 2000; Perrine et al. 2006; Saitoh et al. 2005). Further, knockout of pro-enkephalin (PENK) gene, which is responsible for met- and leu-enkephalin synthesis, resulted in increased anxiety in mice compared to wild-type mice (Konig et al. 1996). Moreover, activation of DORs has also been shown to have anxiolytic and antidepressant-like actions (Broom et al. 2002; Saitoh et al. 2004; Vergura et al. 2008). Finally, activation of DORs via inhibition of enkephalin breakdown resulted in anxiolytic and antidepressant-like effects (Nieto et al. 2005). In summary, the above studies suggest a role for DORs in reward and emotional processing. Effects of pharmacological and genetic manipulation of the DORs on nicotine-induced behaviors are summarized in Tables 1 and 2, respectively (see also Fig. 1).

DORs and reinforcing effects of nicotine

Several studies have explored the role of DORs in the reinforcing effects of nicotine. Nicotine increased the levels of endogenous DOR agonist met-enkephalin in the ventral and dorsal striatum in mice (Dhatt et al. 1995). Importantly, DOR antagonist natrindole

attenuated nicotine-self-administration in mice (Berrendero et al. 2012). Additionally, nicotine-induced CPP was attenuated in DOR knockout mice compared to wild-type counterparts. Moreover, fewer DOR knockout mice acquired nicotine self-administration compared to wild-type mice and the DOR knockout mice showed lower levels of nicotine-induced increase in NAcc dopamine compared to wild-type mice (Berrendero et al. 2012). In contrast to studies in mice, DOR antagonists did not influence nicotine self-administration in rats (Ismayilova and Shoaib 2010; Liu and Jernigan 2011). It is not clear if these differences in findings were due to use of different species in the above studies. Interestingly, blockade of DORs, using DOR antagonist natrindole, did not have any effect on nicotine-induced locomotor sensitization (Heidbreder et al. 1996). To date, the role of DORs in specific brain regions such as the NAcc and VTA in the reinforcing effects of nicotine have not been evaluated. Overall, the above studies suggest that the DORs play a role in mediating the rewarding effects of nicotine. There are similarities between the role played by MORs and DORs in nicotine reward. Further like MOR knockout mice, DOR knockout mice appear to be less sensitive to the rewarding effects of nicotine. However, more work is required to understand the role of DORs in nicotine reward in specific brain regions such as the NAcc and VTA. There is also a need to explore the role of DORs in animals with extended access to nicotine.

DORs and chronic nicotine exposure

Chronic nicotine administration altered met-enkephalin levels and DOR signaling (see Table 3). The nicotine-induced changes in preproenkephalin mRNA and met-enkephalin levels were time sensitive. For example, striatal met-enkephalin levels were decreased in rats after chronic nicotine when brain tissue was collected 1 h after the last nicotine dose (Wewers et al. 1999). Interestingly, striatal and hippocampal preproenkephalin mRNA levels were increased 24 h after withdrawal from nicotine in rats with chronic nicotine exposure (Houdi et al. 1998). Together, these findings suggest a compensatory increase in preproenkephalin mRNA in response to decrease in met-enkephalin levels. Consistent with these findings, both preproenkephalin mRNA and met-enkephalin levels were increased in the ventral striatum, 24 h after last dose of nicotine, in mice with chronic nicotine treatment (Isola et al. 2002).

Withdrawal from nicotine did not alter DOR binding in the NAcc and caudate/putamen (McCarthy et al. 2011). However, DOR mRNA was significantly elevated in the NAcc, prefrontal cortex, and hippocampus during nicotine withdrawal and this increase in DOR mRNA was sensitive to time since withdrawal from nicotine (see Table 3). Additionally DOR signaling, which was measured via uncoupling of the DOR-associated G-protein, was decreased in the NAcc during nicotine withdrawal. In summary, even though there may be compensatory increase in PENK mRNA and met-enkephalin levels, the decrease in DOR signaling suggest that there is an overall decrease in DOR-mediated functioning during nicotine withdrawal.

Temporal changes in DOR signaling during nicotine withdrawal overlaps with some of the affective aversive effects associated with nicotine withdrawal. Nicotine withdrawal-induced anhedonia and anxiety usually peaks between 4 and 24 h, and this coincides with DOR dysregulation (Costall et al. 1989; Epping-Jordan et al. 1998; Jackson et al. 2009; Jonkman et al. 2005; Stoker et al. 2008). As described above, decreased DOR-mediated transmission has anxiogenic and depression-like effects. Together, these data suggest that DOR dysregulation possibly mediates some of the aversive effects associated with nicotine withdrawal. In fact, activation of DORs attenuated mecamylamine precipitated nicotine withdrawal-induced CPA (Ise et al. 2000). In contrast, DORs are not involved in nicotine withdrawal-induced somatic aversive effects. There was no difference in mecamylamine-precipitated nicotine withdrawal-associated somatic signs between DOR wild-type and knockout mice (Berrendero et al. 2012). These findings are unlike findings in MOR knockout mice, which showed decreased aversive somatic signs during mecamylamine-precipitated nicotine withdrawal. Together, the above studies suggest that DORs are involved in aversive affective symptoms associated with nicotine withdrawal, which are mediated by receptors located in the brain. However, DORs are not involved in somatic effects associated with nicotine withdrawal, which are predominantly mediated by peripherally located receptors. In summary, central but not peripheral DORs play a role in nicotine withdrawal.

DORs and nicotine-seeking behavior

The role of DORs in reinstatement of nicotine seeking has not been explored. However, cue-induced reinstatement of cocaine seeking was attenuated in DOR knockout mice compared to their wild-type littermates (Gutierrez-Cuesta et al. 2014). Consistent with this finding, activation of DORs using DOR-specific peptides facilitated cocaine-induced reinstatement of CPP (Kotlinska et al. 2010). Similarly, DORs have been shown to play a role in reinstatement of morphine-induced CPP and expression of ethanol-induced CPP (Bie et al. 2012; Bie et al. 2009). Further behavioral, genetic, and electrophysiological evidence suggests that DORs play an important role in learning and memory, which support their possible role in reinstatement of drug-seeking behavior (Chavkin et al. 1985; Klenowski et al. 2015; Le Merrer et al. 2013). Based on the data described above, we hypothesize that blockade of DORs will attenuate cue-induced nicotine seeking. Further work is required to fully understand the role of DORs in nicotine seeking.

DORs: therapeutic potential and future directions

Currently, there are no FDA-approved medications available that exclusively target the DORs. However, clinical studies using compounds selectively targeting the DORs have been conducted (Richards et al. 2016). The DORs have been considered as a therapeutic target for the treatment of pain for a couple of decades (Gendron et al. 2015; Pradhan et al. 2011). There has been a growing interest in targeting the DORs for the treatment of addiction (Charbogne et al. 2014; Klenowski et al. 2015; Lutz and Kieffer 2013). Studies discussed above have shown that blockade of DORs attenuated the rewarding effects of nicotine and can potentially attenuate reinstatement of nicotine seeking. Further, activation of DORs has been shown to alleviate the aversive effects associated with nicotine withdrawal. DORs can be activated by both peptide- and non-peptide-based agonists and/or by inhibiting the enzyme that is responsible for breakdown of enkephalin (Gendron et al. 2015). It is hypothesized that DOR agonists are less likely to produce dependence compared to MOR agonists, which can be advantageous for using DOR agonists therapeutically. Taken together, both DOR antagonists and agonist have the potential to promote smoking cessation.

Several challenges exist in targeting the DORs. Over the last few years, significant advances have been made in understanding the structure and downstream effects of DOR activation. Using pharmacological agonist and antagonists, the DORs have been classified into at least two subtypes (e.g., DOR1 and DOR2) (Gendron et al. 2015). Additionally, several different types of secondary messenger systems have been found to be associated with the DORs. However, the DOR gene codes for only one type of protein and no alternative splicing of the gene has been reported. In humans, polymorphisms in the DOR gene have been reported (Simonin et al. 1994; Wei and Loh 2011). Future studies will need to assess if differences in DOR subtypes, DOR secondary messenger signaling, and/or polymorphisms in the genes coding for the DORs affect development of nicotine dependence.

Gender-based differences in DOR-mediated analgesia have been reported. For example, DOR agonists produced greater analgesic effects in male rats compared to female rats (Bartok and Craft 1997). Further, the effects of age (adolescent vs. adults) on DOR-mediated effects have not been investigated as has been for KORs (see below). More recently, a study reported increased ethanol consumption during adolescence in animals with a history of prenatal ethanol exposure (Fabio et al. 2015). As a caveat, this study reported only an increase in MOR mRNA in the VTA, but no change in DOR mRNA, suggesting no role for DORs in the VTA in the observed findings. Nevertheless, future studies must assess the impact of gender and age on DOR-mediated effects in nicotine dependence.

KORs and nicotine-induced effects

KORs and their endogenous ligand dynorphin are widely distributed throughout the brain, including the mesolimbic dopaminergic system in both humans and rodents (Mansour et al. 1996; Schmidt et al. 1994). Activation of KORs increased brain reward thresholds during the intracranial self-stimulation procedure, suggesting development of a depression-like state (Todtenkopf et al. 2004). Further, activation of KORs decreased the rewarding effects of drugs of abuse (Bruijnzeel 2009; Shippenberg et al. 2007; Wee and Koob 2010). In contrast, blockade of KORs decreased immobility time in animals in the forced swim test, suggesting antidepressant-like effects (Mague et al. 2003). Together, the data suggest that KORs mediate negative motivational and affective states. Below we discuss the role of KORs in nicotine-induced behaviors. The effects of pharmacological manipulation of KORs on nicotine-induced behaviors are summarized in Table 1 and Fig. 1.

KORs and reinforcing effects of nicotine

Acute nicotine administration changes dynorphin-KOR signaling. Increase in striatal dynorphin levels and prodynorphin mRNA have been reported following acute subcutaneous administration of high doses of nicotine (>0.5 mg/kg, base) (Isola et al. 2009). The nicotine-induced increase in dynorphin was temporally phasic in nature with an initial increase at 1 h followed by a decrease at 2 h and then again an increase between 6 and 24 h. Further, Isola et al. (2009) showed that the nicotine-induced increase in synthesis and release of dynorphin was mediated via other neurotransmitters such as glutamate and dopamine. In contrast, low doses of nicotine (<0.5 mg/kg) decreased or had no effect on preprodynorphin mRNA levels (Isola et al. 2009; Le Foll et al. 2003). Overall, the data suggest temporal dose-dependent changes in dynorphin and prodynorphin mRNA levels after acute nicotine administration.

Studies have also evaluated the role of KORs in the reinforcing effects of nicotine. Consistent with the role of KORs in negative emotional states described above, administration of low doses of the KOR agonist (±)U-50,488H (1–3 mg/kg) decreased nicotine self-administration in Lister hooded rats, suggesting that KOR activation attenuated the reinforcing effects of nicotine (Ismayilova and Shoaib 2010). Further, KOR agonists attenuated nicotine-induced locomotor activity (Hahn et al. 2000). Additionally, mice lacking the prodynorphin gene compared to wild-type mice self-administered nicotine at lower doses, suggesting that the dynorphin-KOR system plays an inhibitory role in the reinforcing effects of nicotine (Galeote et al. 2009). Interestingly, activation of the KORs, using the KOR agonist GNTI, did not affect the reinforcing effects of nicotine as assessed using intravenous nicotine self-administration in male Sprague-Dawley rats (Liu and Jernigan 2011). As compared to

Ismayilova and Shoaib (2010) described above, Liu and Jernigan used a different strain of rats (Lister hooded vs. Sprague-Dawley rats) and a different KOR agonist [(±)U-50,488H vs. GNTI]. It is possible that the difference in findings between the above described studies could be due to the above described differences. In summary, the data suggest that activation of KORs has an inhibitory effect on reinforcing effects of nicotine. Thus, the role of the KORs appears to be opposite to the role played by other opioid receptors such as the MORs and DORs in the rewarding effects of nicotine.

Although dynorphin blocks nAChR-mediated effects in PC12 cells, the precise mechanism by which KOR activation decreases the rewarding effects of nicotine is not fully understood (Itoh et al. 2000). KOR activation on its own has been shown to decrease both firing of VTA dopaminergic neurons and release of dopamine in the NAcc (Di Chiara and Imperato 1988b; Margolis et al. 2003). However, the effects of KOR activation on nicotine-induced increases in NAcc dopamine have not yet been addressed. Further, future studies may need to explore the effects of direct injections of KOR agonists and antagonists in specific brain regions such as the NAcc and VTA on nicotine self-administration and nicotine-induced increases in dopamine in these brain regions.

First-time smokers often report unpleasant experiences such as vomiting, headache, tachycardia, and gastric discomfort (DiFranza et al. 2004). Based on the role of KORs and dynorphin in dysphoria, it is hypothesized that the dynorphin-KOR system is potentially involved in mediating the aversive effects of nicotine experienced by first-time smokers (Fowler and Kenny 2014). However, the role of KORs in the aversive effects of nicotine has not been directly explored. The rewarding and aversive effects of nicotine are mediated by distinct but overlapping circuits (D'Souza and Markou 2011; Laviolette and van der Kooy 2004). Therefore, future studies must focus on identifying the role of KORs in specific brain regions in the aversive and rewarding effects of nicotine. In summary, activation of KORs using low doses of a KOR agonist can decrease the reinforcing effects of nicotine either by decreasing the rewarding effects of nicotine and/or by increasing the aversive effects of nicotine.

Activation of KORs is also associated with a stress-like state and can thus increase motivation for drugs of abuse. Consistent with this hypothesis, activation of KORs using high doses of the KOR agonist (±)U-50,488H (5 or 10 mg/kg, i.p.) increased expression of nicotine-induced CPP compared to controls (Smith et al. 2012). This increase in nicotine-induced CPP was mediated by activation of the KORs in the amygdala. Smith et al. (2012) administered the KOR agonist only once, and this administration was done 1 h prior to testing for CPP (i.e., on the test day) and not during conditioning with nicotine. Compared to Ismayilova and Shoaib (2010) (described above), Smith et al. (2012) not only used a different model and protocol (self-administration vs. CPP) to assess the effects of KOR activation on the reinforcing effects of nicotine but also used higher doses of the KOR agonist (±)U-50,488H (1–3 vs. 5–10 mg/kg). The dose of KOR agonist used by Smith et al. produces a stress-like state (Wee and Koob 2010). Based on the above findings, one can conclude that increased recruitment of KORs using high doses of a KOR agonist can induce stress and indirectly increase motivation for nicotine. Further studies are required to determine the specific brain regions that are involved during the excessive recruitment of KORs by high doses of a KOR agonist.

KORs and chronic nicotine exposure

Chronic nicotine treatment in adult rats decreased prodynorphin mRNA levels in the NAcc, but increased prodynorphin mRNA levels in the prefrontal cortex and caudate putamen (Carboni et al. 2016) (see Table 3). Importantly, these changes in prodynorphin mRNA levels were accompanied by nicotine-induced locomotor sensitization. However, no changes in KOR mRNA were observed after chronic nicotine treatment in any of the above described regions. Taken together, these data suggest that chronic nicotine treatment differentially affects dynorphin synthesis in the different brain regions. The precise role of these changes in dynorphin levels and/or prodynorphin mRNA in specific brain regions on nicotine-induced behaviors is not fully understood. Future studies need to identify the role of dynorphin in specific brain regions on nicotine-induced behavioral effects by altering dynorphin levels in specific brain regions using viral-mediated overexpression and siRNA techniques.

Age of the animals influenced KOR-mediated behavioral and neurochemical effects after chronic nicotine treatment using osmotic minipumps. For example, administration of KOR agonist (±)U-50,488H after chronic nicotine treatment increased anxiety-like behavior, induced CPA, and decreased NAcc dopamine levels in adult, but not adolescent rats compared to respective controls (Tejeda et al. 2012). Together, the data suggest that KORs are more sensitive after chronic nicotine treatment in adult, but not in adolescent rats. This could be protective mechanism to limit nicotine intake in adults. These data also suggest that the KOR-dependent protective mechanism is absent in adolescents making them more vulnerable to nicotine addiction.

Withdrawal from nicotine after chronic nicotine treatment altered dynorphin and prodynorphin mRNA levels, and these molecular changes were dependent on the time elapsed since the last dose of nicotine. For example, a decrease in striatal dynorphin levels was reported after nicotine withdrawal when brain tissue was collected between from 4 to 72 h. Additionally, there was an increase in striatal prodynorphin mRNA between 8 and 96 h (Isola et al. 2008) (see Table 3). These data suggest that nicotine withdrawal-induced decrease in dynorphin levels was followed by a compensatory increase in dynorphin synthesis as suggested by an increase in prodynorphin mRNA. Interestingly, withdrawal from nicotine after chronic nicotine administration was

accompanied by desensitization of KORs in the NAcc (McCarthy et al. 2010). The desensitization of KORs was first observed at 24-48 h after withdrawal of nicotine and lasted for over 72 h. This decrease in KOR signaling coincides with aversive affective effects associated with nicotine withdrawal as described above in the section on DORs. It is not clear if this decrease in KOR signaling is directly due to nicotine withdrawal or a compensatory mechanism to counter the increase in dynorphin synthesis described above.

Pharmacological manipulation of KORs influenced both somatic and affective aversive effects associated with nicotine withdrawal. Administration of high doses of the KOR agonist (±)U-50,488H (5 mg/kg, s.c.) enhanced spontaneous nicotine withdrawal-induced aversive somatic effects in adult rats, suggesting increased sensitivity of the KORs during nicotine withdrawal (Tejeda et al. 2012). In this study, somatic signs of nicotine withdrawal were assessed 24 h after removal of nicotine pumps, while the KOR agonist was administered 25 min before recording of somatic withdrawal signs. Interestingly, the same study reported that the increased sensitivity of the dynorphin-KOR system during nicotine withdrawal was observed in adult rats and not in adolescent rats despite receiving similar nicotine treatment as adult rats. This suggests that the KORs do not mediate nicotine withdrawal-induced aversive effects in adolescent rats. In contrast, activation of the KORs using low doses of the KOR agonist (±)U-50,488H (0.01–1 mg/kg) 30 min prior to induction of mecamylamine-precipitated nicotine withdrawal, attenuated nicotine withdrawal-induced CPA (Ise et al. 2002). These data suggest that KOR activation attenuated nicotine withdrawal-associated aversive affective effects. It is not clear if the differences in the role of the KORs between those reported by Tejeda et al. (2012) vs. Ise et al. (2002) are due to the fact that different withdrawal effects were measured in the two studies (somatic vs. affective) or because nicotine withdrawal was induced differently in the two studies (spontaneous vs. precipitated). Besides, there were also methodological differences between Tejeda et al. (2012) and Ise et al. (2002) such as the dose of the KOR agonist used (5 vs. 0.01–1 mg/kg), dose of nicotine used (3.2 mg/kg/day, base vs. 10 mg/kg, base) and duration of nicotine treatment (14 vs. 7 days). Further investigation is required to determine if KORs are differentially regulated by differences in nicotine treatment and/or by spontaneous vs. precipitated nicotine withdrawal. Finally, activation of peripheral KORs using a compound (ICI204, 448) that does not cross the blood-brain barrier inhibited nicotine withdrawal induced increases in feeding, metabolism, and locomotor activity in rats (Sudakov et al. 2014). These data suggest that peripheral and central KORs may be mediating different aspects of nicotine withdrawal and possibly play a differential role in these effects. In summary, the above data support a role for the KORs in somatic and affective aversive effects associated with nicotine withdrawal.

Long-acting KOR antagonist nor-BNI (5 and 15 mg/kg, s.c.) attenuated aversive somatic effects associated with spontaneous nicotine withdrawal in adult rats (Tejeda et al. 2012). Consistent with these findings, KOR antagonists nor-BNI and JDTic attenuated nicotine withdrawal-induced aversive somatic and affective symptoms in mice (Jackson et al. 2010). However, KOR antagonists such as nor-BNI and JDTic have several pharmacokinetic limitations such as that they are both long-acting (approx. 21 days) and have delayed onset of action (Munro et al. 2012). This complicates study design and to counter these limitations, studies have evaluated the effect of a short acting KOR antagonist LY2456302 on nicotine withdrawal-induced affective and somatic effects (Jackson et al. 2015). LY2456302 alleviated nicotine withdrawal-induced aversive somatic and affective effects in a manner similar to JDTic and nor-BNI. In summary, although further work is required to understand the role of KORs in nicotine withdrawal, to date a majority of the literature supports the hypothesis that activation of KORs worsens the aversive somatic and affective effects associated with nicotine withdrawal. Further, blockade of KORs attenuated nicotine withdrawal-induced aversive effects and can be utilized to facilitate smoking cessation in smokers.

KORs and nicotine-seeking behavior

A few studies have investigated the role of KORs in reinstatement of nicotine seeking. For example, it is known that footshock-induced stress facilitates reinstatement of nicotine seeking (Buczek et al. 1999). Notably, blockade of the KORs with the KOR antagonist nor-BNI attenuated stress-induced, but not cue-induced reinstatement of nicotine seeking (Grella et al. 2014). Further, KOR antagonist nor-BNI attenuated reinstatement of stress-induced nicotine CPP, but did not have any effect on nicotine-induced reinstatement of CPP (Jackson et al. 2013). Consistent with these findings, KOR antagonists attenuated stress-induced reinstatement of cocaine-seeking behavior (Redila and Chavkin 2008).

Exposure to chronic mild stress can lead to tolerance-like effects of KOR activation. For example, exposure to chronic stress attenuated KOR activation-induced reinstatement of nicotine-CPP, possibly due to either downregulation or desensitization of KORs (Al-Hasani et al. 2013). Future studies will need to explore alterations in the dynorphin-KOR system after repeated stress and its possible impact on reinstatement of drug seeking including nicotine seeking. In summary, data to date demonstrate that blockade of KOR-mediated neurotransmission attenuated reinstatement of nicotine seeking and that KORs may be useful targets to prevent relapse amongst abstinent smokers.

KORs: therapeutic potential and future directions

Currently, there are no FDA approved medications that exclusively target the KORs. KOR antagonists have recently been tested in humans (Buda et al. 2015; Lowe et al. 2014). Based on the studies described above, we hypothesize that KOR

antagonists will promote smoking cessation by attenuating both nicotine withdrawal-induced aversive effects and reinstatement of nicotine seeking amongst abstinent smokers.

Further, we hypothesize that low doses of the KOR agonists may have a role in promoting smoking cessation by increasing the aversive effects of nicotine or decreasing the rewarding effects of nicotine. A major challenge in utilizing KOR agonists clinically has been the occurrence of dysphoria upon activation of KORs. In the future, it may be possible to dissociate dysphoric effects from activation of KORs. Currently, efforts are on to develop novel KOR agonists/positive allosteric modulators with minimal dysphoric effects (Burford et al. 2013; Zhou et al. 2013). Such KOR ligands may have greater clinical utility and allow for a more complete exploitation of the KORs as a possible therapeutic target for smoking cessation treatment.

Several single nucleotide polymorphisms in dynorphin-KOR system genes have been reported in humans (Clarke et al. 2012; Huang et al. 2008; Wang et al. 2014). Some of these polymorphisms in the KOR genes increase vulnerability to drug dependence in humans (Li and Zhang 2013). Exactly how these polymorphisms alter dynorphin release or dynorphin-KOR signaling is unknown. Do some of these genetic variations in dynorphin-KOR system genes alter aversive effects of nicotine and increase potential to develop nicotine addiction? Moreover, do these genetic variations in the dynorphin-KOR system alter aversive effects associated with nicotine withdrawal? In summary, further work is required to understand the influence polymorphisms in genes related to the KORs in the development of nicotine dependence.

Both animal and human studies have reported gender-dependent differences following pharmacological manipulation of the dynorphin-KOR system (Gear et al. 1996, 1999; Russell et al. 2014; Zacny and Beckman 2004). To date, the focus of these gender-dependent differences in the dynorphin-KOR system has largely been restricted to the role of dynorphin-KOR system in pain (Rasakham and Liu-Chen 2011). However, considering the distribution of KORs in several brain regions involved in addiction, there is growing interest in understanding the interaction of gender and the dynorphin-KOR system in drug addiction (Chartoff and Mavrikaki 2015). In keeping with the focus of this review, it will be of great interest to see if gender and dynorphin-KOR system interactions seen in pain extend to acute and chronic effects of nicotine. Furthermore, if there are gender-dependent differential effects of nicotine on the dynorphin-KOR system, it will be interesting to investigate if these differential effects impact manifestations of nicotine withdrawal and/or response to currently available smoking cessation treatments?

It is well known that activation of KORs produces a negative aversive state in both animals and humans (Bruijnzeel 2009). However, the cellular mechanism of this KOR-mediated negative aversive effect is not completely understood. Increased expression of serotonin reuptake transporters in mesolimbic brain regions such as the NAcc, resulting in decreased synaptic serotonin levels, has been suggested as one possible mechanism (Schindler et al. 2012). Another possible cellular mechanism that may mediate KOR-mediated aversive effects is the activation of the p38 mitogen-activated protein kinase (MAPK) pathway (Bruchas et al. 2007). In support of this mechanism, phosphorylation of the p38 MAPK pathway in the VTA dopaminergic neurons was shown to mediate the aversive effects of the KOR agonist (±)U-50,488H (Ehrich et al. 2015). Interestingly, microglial p38 MAPK pathway plays a role in nicotine withdrawal-induced hyperalgesia (Ding et al. 2015). Future studies must identify exactly what downstream KOR-associated pathways are activated by acute and chronic nicotine exposure. Understanding these downstream pathways will help in effectively manipulating the KORs and make them a more viable therapeutic target for future smoking cessation medications.

Conclusions

The endogenous opioid system, which was originally conceived as an endogenous response system to painful stimuli, is now seen as an important mediator in drug addiction. Several FDA-approved medications currently used to treat alcohol and heroin addiction target the MORs. In this review, we focused on the effects of nicotine on the endogenous opioid system and the possible role of the different opioid receptors as potential targets to promote smoking cessation. Amongst the three opioid receptors discussed in this review, the role of the MORs in nicotine-dependent behaviors has been extensively investigated in both animals and humans. This is primarily because of a better understanding of the MOR structure and the availability of clinically viable medications targeting the MORs. Moreover, identification of the OPRM1 A118G polymorphism continues to make the MORs an exciting target with the highest potential for the development of smoking cessation medications. MOR antagonists attenuated nicotine seeking in animal models and reduced craving in human smokers. Thus, MOR antagonists and/or negative allosteric modulators would help promote smoking cessation. However, future studies need to identify patient subpopulations that may be more responsive to MOR-based smoking cessation medications.

The role of the DORs in nicotine dependence has been explored the least amongst the three opioid receptors. This is partly because of incomplete understanding of the structure of the DORs and the limited availability of clinically viable medications/compounds selectively targeting the DORs. Preclinical research has shown that DOR antagonists decreased nicotine seeking, while the DOR agonists attenuated the aversive effects associated with nicotine withdrawal. Thus, both DOR agonists and antagonists have the potential to promote smoking cessation. However, based on the literature

reviewed above, the likelihood of seeing a successful smoking cessation medication targeting the DORs in the near future appears to be comparatively low. The development of clinically viable selective compounds targeting the DORs will go a long way in facilitating the process of exploiting the DORs as a potential target for future smoking cessation medications.

In contrast to the MORs and DORs, the KORs appear to have an inhibitory role in the rewarding effects of drugs of abuse including nicotine. Interesting work conducted in adolescent animals suggests a limited role for KORs in nicotine-dependent behaviors in adolescents, which possibly makes them more vulnerable to nicotine addiction. Preclinical research has shown that KOR antagonists attenuated both the aversive effects of nicotine withdrawal and reinstatement of nicotine seeking. Therefore, KOR antagonists and/or negative allosteric modulators would be useful as smoking cessation medications. The availability of clinically viable KOR antagonists has greatly increased the potential of the KORs as a target for future smoking cessation medications.

However, despite the extensive investigation of the endogenous opioid system in nicotine dependence over the last two decades, much work still needs to be accomplished. For example, little is known about the role of the different opioid receptors in specific brain regions in nicotine seeking and nicotine withdrawal. Therefore, future work must focus on identifying the role of the different opioid receptors in specific brain regions and neural circuits in nicotine-dependent behaviors using a combination of pharmacological, molecular, and genetic approaches. Additionally, the influence of age and gender on the role of opioid receptors in nicotine-dependent behaviors needs to be evaluated. Finally, genetic studies in humans must continue to assess the influence of polymorphisms in opioid receptor-linked genes in nicotine dependence. Identification of such polymorphisms will help in both identifying individuals vulnerable to develop nicotine addiction and patient subpopulations who may be more responsive to opioid-based smoking cessation medications. In conclusion, the opioid receptors are promising targets and it is our belief that continued focus on the endogenous opioid system will provide efficacious smoking cessation medications in the near future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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