

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Antagonism of Opioid μ Receptors for Smoking Cessation

Xiu Liu

Abstract

Opioid neurotransmission plays a role in rewarding process including the reinforcing actions of nicotine. In the past four decades, a great effort has been exercised to test the effectiveness of nonselective opioid antagonists (mainly naloxone and naltrexone) for smoking cessation. However, both clinical and animal researches have yielded equivocal results. That may be attributable to the fact that opioid receptors have three distinctive subtypes (μ , δ , and κ), functions of which are from complimentary to opposite. Our laboratory studies have used animal models of nicotine self-administration to examine involvement of individual opioid receptor subtypes in the reinforcement of nicotine. Specifically, rats were trained in daily 1-h sessions to press a lever to intravenously self-administer nicotine, and antagonists selective for the three subtypes of opioid receptors were administered prior to the test sessions. Results showed that selective blockade of the μ , but not δ or κ , opioid receptors effectively reduced nicotine self-administration, whereas it produced no effect on food self-administration. These results indicate that activation of the opioid μ , but not δ or κ , receptors is specifically involved in nicotine reinforcement. It is suggested that opioid μ receptor-mediated neurotransmission would be a promising target for developing smoking cessation medication.

Keywords: nicotine self-administration, opioid receptors, smoking cessation

1. Introduction

Tobacco-related diseases are a major problem in many perspectives from human health to social economics [1]. For example, in the United States, tobacco smoking becomes a leading cause of death, accounting for the loss of 480,000 lives each year. Alarmingly, every day more than 3200 youth aged 18 years or younger smoke their first cigarette, and 2100 young people become daily cigarette smokers. The prevalence rates of smoking are 7.2% in middle and 20.2% in high school, accounting for a total young smokers being about 4 million [2]. Although almost all smokers want to quit smoking and make attempts, up to 97% of them relapse to tobacco smoking [3–6]. Unfortunately, the currently available medications, i.e., nicotine replacement, bupropion, and varenicline, show low clinical effectiveness [7–11].

Opioid neurotransmission has been implicated in mediating rewarding actions and dependence of drugs of abuse including nicotine [12–16]. For instance, nicotine

administration has been found to increase expression and release of opioid peptides in mesolimbic regions [17–22]. Opioid receptor antagonists have been reported to decrease nicotine-induced dopamine release in the nucleus accumbens, an important terminal region of the mesolimbic dopamine circuitry [23], reduce nicotine reward [24, 25], and precipitate withdrawal symptoms in rats treated chronically with nicotine [26].

Over the past four decades or so, however, clinical effort to test the potential of opioid antagonists (mainly naloxone and naltrexone) for smoking cessation has yielded equivocal results: some trials reported that these antagonists reduced consumption of cigarettes, while others failed to find any benefit [27–37]. Similarly, laboratory animal research has also produced mixed findings. In our own studies, neither acute nor chronic pretreatment with naltrexone across seven daily nicotine self-administration test sessions altered nicotine intake in the rats trained to steadily self-administer nicotine [38]. That is consistent with previous reports showing that naloxone and naltrexone did not produce an effect on nicotine self-administration [39, 40]. However, intracranial manipulation studies have found that a μ -opioid agonist, DAMGO, microinjected into the ventral tegmental area [41] or the pedunculo-pontine tegmental nucleus [42] effectively reduced nicotine self-administration in rats. Studies using knockout mice showed that deletion of the μ -opioid receptors or their endogenous ligand β -endorphin resulted in decreased rewarding properties of nicotine as measured by the conditioned place preference paradigm [43, 44]. Moreover, a recent rat study reported that naloxone reduced nicotine self-administration [45].

These inconsistent results in both clinical and animal research may be attributable to the existence of different subtypes of the opioid receptors. There are three main subtypes of the opioid receptors: μ , δ , and κ [46–48]. These receptors have quite divergent and in some cases even opposite actions. In the drug rewarding processes, for instance, activation of the μ and κ receptors may have opposite actions with the κ receptors opposing rewarding actions and/or enhancing aversive effects of drugs [49–52]. In knockout mice, animals deficient in μ receptors showed decreased level of anxiety, whereas the δ receptor knockout mice had higher anxiety [53], suggesting these two subtypes have an opposite role in regulating anxiety states. In the tests measuring the anxiety states induced by nicotine, the μ and δ receptor antagonism produced opposite effects, whereas the κ receptor antagonist showed no effect [54]. Therefore, due to their broad spectrum of actions, the nonselective receptor antagonists such as naloxone and naltrexone can block different opioid receptors, and unfortunately the effects of blocking individual types of receptors might have offset one another.

2. Research purposes

In light of the facts that nonselective antagonism of opioid receptors produced inconclusive results for smoking cessation, that three subtypes of opioid receptors exist with distinct and even opposing functions, and that effects of antagonizing these individual receptor subtypes have received little experimental attention, it is imperative to elucidate the involvement of the opioid receptor subtypes in mediating nicotine reinforcement. Thus, our laboratory used animal models of tobacco smoking and the currently available antagonists that are highly selective for the different subtypes of the opioid receptors to examine the roles of the μ , δ , and κ receptors in nicotine consumption behavior [55].

3. Experimental procedures

Male Sprague-Dawley rats ($n = 26$) were trained in daily 1-h sessions to intravenously self-administer nicotine (0.03 mg/kg/infusion, free base) after implantation of an indwelling intravenous catheter under isoflurane anesthesia. In each session, animals were placed in the standard operant conditioning chambers and connected to the drug delivery system. The sessions were initiated by introduction of two levers. Once responses on the active lever met a fixed-ratio 5 requirement, an infusion of nicotine was dispensed with a presentation of an auditory/visual stimulus consisting of a 5 s tone and 20 s turn-on of the lever light. All rats received 25 daily self-administration training sessions before any pharmacological tests because our work showed that rats readily developed stable nicotine self-administration behavior within 25 sessions [56].

4. Main research findings

Blockade of the μ opioid receptors by a selective antagonist naloxonazine dose-dependently reduced lever-press responses and correspondingly the number of nicotine infusions rats willingly self-administered. However, naloxonazine did not alter food self-administering responses, which was tested in the same set of rats that were retrained for food self-administration after completion of nicotine test. In contrast, neither did blockade of the δ receptors via administration of the selective antagonist naltrindole nor the κ -selective antagonist 5'-guanidinonaltrindole (GNTI) change nicotine self-administration behavior (**Figure 1**).

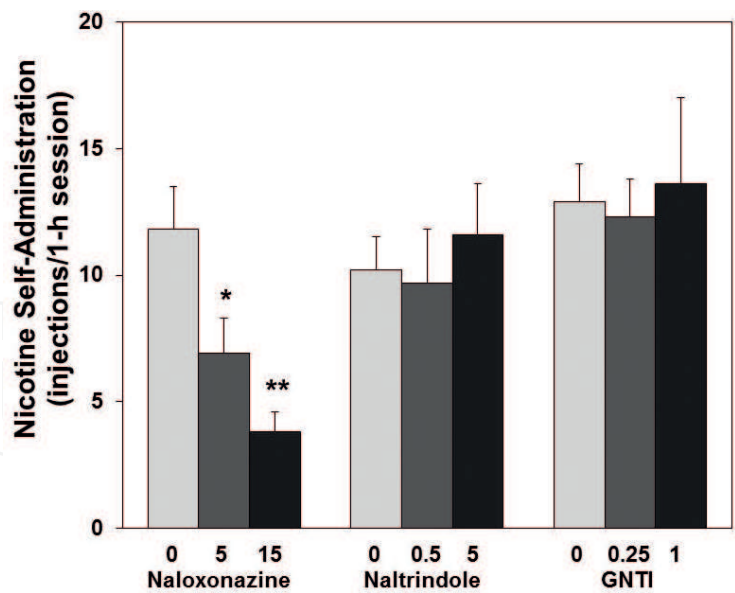


Figure 1.
Effects of antagonists selective for μ (naloxonazine), δ (naltrindole), and κ (GNTI) receptors on nicotine self-administration in rats. The doses of these antagonists are in mg/kg. Nicotine self-administration data are expressed as mean (\pm SEM). * $p < 0.05$, ** $P < 0.01$ significant difference from respective 0 (vehicle) condition.

5. Discussion

The significant finding is that naloxonazine produced a specific suppressant effect on the lever-press responses maintained by nicotine self-administration, i.e.,

the primary reinforcement of nicotine. Given that naloxonazine did not change food self-administering responses, indicating no nonspecific interference with operant behavior directed to get natural reward, the results indicate the critical involvement of opioid neurotransmission via the μ receptors in the nicotine rewarding process. The underlying mechanism may involve the μ modulation of dopamine neurons in the mesolimbic circuitry, which mediates the rewarding properties of drug of abuse including nicotine. For example, in the ventral tegmental area, opioid peptides modulate dopamine neurotransmission predominantly via activation of the μ receptors [23], and in the nucleus accumbens, μ agonist inhibited dopamine overflow, and this effect was reversed by naloxonazine [57]. The suppressant effect of naloxonazine on nicotine intake is in line with previous research suggesting a role of the μ receptors in mediating the reinforcement of nicotine and tobacco smoking [27, 31, 35, 43–45]. Of significance is that our results further pinpoint the μ subtype of the opioid receptors in mediating reinforcement of nicotine. Therefore, these findings lend support for the continued clinical effort to test the effectiveness of opioid antagonists for smoking cessation and further instructively suggest that the effort focus should be shifted to targeting at the μ receptors.

The finding that naltrindole produced no effect on nicotine intake indicates that opioid neurotransmission via the δ receptors may not mediate the reinforcing actions of nicotine as measured by the operant nicotine self-administration paradigm. It is in line with evidence showing that this agent produced no change in nicotine-induced sensitization [58] and consistent with another report showing unaltered nicotine intake after naltrindole pretreatment using similar nicotine self-administration procedures [45]. However, these negative results seem to be at odds with a previous study using knockout mice that were deficient of preproenkephalin gene (producing enkephalin, the endogenous agonist for the δ receptors). These knockout mice showed a significant decrease in nicotine-induced conditioned place preference, indicating a reduction of the rewarding effects of nicotine [59]. This discrepancy regarding involvement of the δ receptors in nicotine reward may be attributable to the significant differences in subjects (rats versus gene knockout mice) and the methods of measuring nicotine reward (self-administration versus conditioned place preference). Besides, it is interesting to note the evidence showing that the δ receptors have been implicated in other actions of nicotine. For instance, the δ receptor antagonists were reported to change nicotine-induced antinociception [60] and anxiogenic response [54]. Nevertheless, an alternative explanation of the knockout mouse data exists. Due to the fact that in addition to preferentially activating the δ receptors enkephalin also acts at the μ receptors [61], it is argued that the reduced rewarding actions of nicotine in these knockout mice may result at least to some extent from the diminished μ receptor activities. Thus, the results obtained from these knockout mice in fact reconcile with the suppression of nicotine self-administration by naloxonazine observed in our study.

There was no effect of κ -selective antagonist 5'-guanidinonaltrindole (GNTI) on nicotine self-administration. This finding is consistent with results obtained from gene knockout mice. In the mice deficient of prodynorphin genes, which produce dynorphin, the endogenous agonist for κ receptors, the conditioned place preference induced by nicotine (and ethanol and cocaine as well) was comparable to that observed in their wild-type counterparts [51, 62, 63]. In another report [45], however, the elevated activation of the κ receptors by experimenter administered agonist seemed to interfere with operant behavior for nicotine intake. In that study [45], the selective κ receptor agonist U50,488 changed nicotine self-administering behavior in opposing directions depending on the doses administered. An increase of nicotine self-administration was observed after pretreatment with a low dose of 0.3 mg/kg, whereas rats decreased their nicotine self-administration after

administration of higher doses (1 and 3 mg/kg). It should be noted that U50,488 was found to produce “abnormal” behaviors (such as biting the edge of behavioral testing arena) at doses above 0.9 mg/kg [64] and that the κ agonists may bind to other opioid receptors and thereby to produce opposing actions [65]. Furthermore, it is interesting to note that activation of the κ receptors may play a role in the increased drug self-administration in drug-dependent but not non-dependent subjects [66, 67]. For instance, nor-BNI (a κ receptor antagonist) has been found to effectively reduce the escalated cocaine self-administration in rats with a prolonged access to cocaine and the increased ethanol intake in rats that became ethanol dependent by an ethanol vapor inhalation procedure [67, 68].

6. Conclusions

These research results demonstrate that nicotine self-administration behavior is sensitive to pharmacological antagonism of the μ , but not the δ or the κ , opioid receptors. Together with the evidence showing that nicotine administration enhances release of the endogenous μ receptor ligand endorphin [19, 69–71], these data indicate a critical role of opioid neurotransmission via the μ receptors in the rewarding properties of nicotine. On one hand, these results help understand the inconsistent outcomes obtained from both clinical trials and animal tests using the nonselective antagonists naloxone and naltrexone. On the other hand, the findings suggest that focusing on manipulation of the μ receptor-mediated pathways within the opioid system might prove to be a fruitful strategy for the development of medication for nicotine addiction and smoking cessation.

Acknowledgements


The research work reviewed in this chapter was supported by NIH grants R01 DA017288 and R01 DA037277 from the National Institute on Drug Abuse as well as the State of California Tobacco-Related Disease Research Program grant #12KT-0188. The authors would like to thank Courtney Jernigan, Lisa Biswas, Erin Harrison, Ramachandram Avusula, Thomas Rousselle, and Thuy Tran for their excellent technical assistance.

Author details

Xiu Liu
Department of Pathology, University of Mississippi Medical Center,
Jackson, MS, USA

*Address all correspondence to: xliu@umc.edu

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] WHO. 2015. Available from: <https://www.who.int/news-room/fact-sheets/detail/tobacco>
- [2] CDC. Tobacco use among middle and high school students—United States, 2011-2016. *Morbidity and Mortality Weekly Report*. 2017;**66**(23): 597-603
- [3] Benowitz NL. Nicotine addiction. *The New England Journal of Medicine*. 2010;**362**(24):2295-2303
- [4] Shiffman S, Mason KM, Henningfield JE. Tobacco dependence treatments: Review and prospectus. *Annual Review of Public Health*. 1998;**19**:335-358
- [5] Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction*. 2004;**99**(1):29-38
- [6] CDC. Current cigarette smoking among adults—United States. *Morbidity and Mortality Weekly Report*. 2014;**63**:29-34
- [7] Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an $\alpha 4 \beta 2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. *JAMA*. 2006;**296**(1):56-63
- [8] Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an $\alpha 4 \beta 2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. *JAMA*. 2006;**296**(1):47-55
- [9] Aubin HJ, Bobak A, Britton JR, Oncken C, Billing CB Jr, Gong J, et al. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial. *Thorax*. 2008;**63**(8):717-724
- [10] Vogeler T, McClain C, Evoy KE. Combination bupropion sr and varenicline for smoking cessation: A systematic review. *The American Journal of Drug and Alcohol Abuse*. 2016;**42**(2):129-139
- [11] Rose JE, Behm FM. Combination treatment with varenicline and bupropion in an adaptive smoking cessation paradigm. *The American Journal of Psychiatry*. 2014;**171**(11):1199-1205
- [12] Gianoulakis C. Endogenous opioids and addiction to alcohol and other drugs of abuse. *Current Topics in Medicinal Chemistry*. 2004;**4**(1):39-50
- [13] Pomerleau OF. Endogenous opioids and smoking: A review of progress and problems. *Psychoneuroendocrinology*. 1998;**23**(2):115-130
- [14] Xue Y, Domino EF. Tobacco/ nicotine and endogenous brain opioids. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2008;**32**(5): 1131-1138
- [15] Le Merrer J, Becker JA, Befort K, Kieffer BL. Reward processing by the opioid system in the brain. *Physiological Reviews*. 2009;**89**(4):1379-1412
- [16] Berrendero F, Robledo P, Trigo JM, Martin-Garcia E, Maldonado R. Neurobiological mechanisms involved in nicotine dependence and reward: Participation of the endogenous opioid system. *Neuroscience and Biobehavioral Reviews*. 2010;**35**(2):220-231
- [17] Houdi AA, Dasgupta R, Kindy MS. Effect of nicotine use and

- withdrawal on brain preproenkephalin a mRNA. *Brain Research*. 1998;**799**(2): 257-263
- [18] Houdi AA, Pierzchala K, Marson L, Palkovits M, Van Loon GR. Nicotine-induced alteration in Tyr-Gly-Gly and Met-enkephalin in discrete brain nuclei reflects altered enkephalin neuron activity. *Peptides*. 1991;**12**(1):161-166
- [19] Boyadjieva NI, Sarkar DK. The secretory response of hypothalamic beta-endorphin neurons to acute and chronic nicotine treatments and following nicotine withdrawal. *Life Sciences*. 1997;**61**(6):PL59-PL66
- [20] Davenport KE, Houdi AA, Van Loon GR. Nicotine protects against mu-opioid receptor antagonism by beta-funaltrexamine: Evidence for nicotine-induced release of endogenous opioids in brain. *Neuroscience Letters*. 1990;**113**(1):40-46
- [21] Dhatt RK, Gudehithlu KP, Wemlinger TA, Tejwani GA, Neff NH, Hadjiconstantinou M. Preproenkephalin mRNA and methionine-enkephalin content are increased in mouse striatum after treatment with nicotine. *Journal of Neurochemistry*. 1995;**64**(4):1878-1883
- [22] Pierzchala K, Houdi AA, Van Loon GR. Nicotine-induced alterations in brain regional concentrations of native and cryptic Met- and Leu-enkephalin. *Peptides*. 1987;**8**(6):1035-1043
- [23] Tanda G, Di Chiara G. A dopamine-mu1 opioid link in the rat ventral tegmentum shared by palatable food (Fonzies) and non-psychostimulant drugs of abuse. *The European Journal of Neuroscience*. 1998;**10**(3):1179-1187
- [24] Walters CL, Cleck JN, Kuo YC, Blendy JA. Mu-opioid receptor and creb activation are required for nicotine reward. *Neuron*. 2005;**46**(6):933-943
- [25] Zarrindast MR, Faraji N, Rostami P, Sahraei H, Ghoshouni H. Cross-tolerance between morphine- and nicotine-induced conditioned place preference in mice. *Pharmacology, Biochemistry, and Behavior*. 2003;**74**(2):363-369
- [26] Malin DH, Lake JR, Carter VA, Cunningham JS, Wilson OB. Naloxone precipitates nicotine abstinence syndrome in the rat. *Psychopharmacology*. 1993;**112**(2-3):339-342
- [27] Karras A, Kane JM. Naloxone reduces cigarette smoking. *Life Sciences*. 1980;**27**(17):1541-1545
- [28] Nemeth-Coslett R, Griffiths RR. Naloxone does not affect cigarette smoking. *Psychopharmacology*. 1986;**89**(3):261-264
- [29] Gorelick DA, Rose J, Jarvik ME. Effect of naloxone on cigarette smoking. *Journal of Substance Abuse*. 1988;**1**(2):153-159
- [30] Krishnan-Sarin S, Rosen MI, O'Malley SS. Naloxone challenge in smokers. Preliminary evidence of an opioid component in nicotine dependence. *Archives of General Psychiatry*. 1999;**56**(7):663-668
- [31] King AC, Meyer PJ. Naltrexone alteration of acute smoking response in nicotine-dependent subjects. *Pharmacology, Biochemistry, and Behavior*. 2000;**66**(3):563-572
- [32] Sutherland G, Stapleton JA, Russell MA, Feyerabend C. Naltrexone, smoking behaviour and cigarette withdrawal. *Psychopharmacology*. 1995;**120**(4):418-425
- [33] Wong GY, Wolter TD, Croghan GA, Croghan IT, Offord KP, Hurt RD. A randomized trial of naltrexone for smoking cessation. *Addiction*. 1999;**94**(8):1227-1237

- [34] King A, de Wit H, Riley RC, Cao D, Niaura R, Hatsukami D. Efficacy of naltrexone in smoking cessation: A preliminary study and an examination of sex differences. *Nicotine & Tobacco Research*. 2006;**8**(5):671-682
- [35] Rukstalis M, Jepson C, Strasser A, Lynch KG, Perkins K, Patterson F, et al. Naltrexone reduces the relative reinforcing value of nicotine in a cigarette smoking choice paradigm. *Psychopharmacology*. 2005;**180**(1):41-48
- [36] Ray R, Jepson C, Patterson F, Strasser A, Rukstalis M, Perkins K, et al. Association of OPRM1 A118G variant with the relative reinforcing value of nicotine. *Psychopharmacology*. 2006;**188**(3):355-363
- [37] Wewers ME, Dhatt R, Tejawani GA. Naltrexone administration affects ad libitum smoking behavior. *Psychopharmacology*. 1998;**140**(2):185-190
- [38] Liu X, Palmatier MI, Caggiula AR, Sved AF, Donny EC, Gharib M, et al. Naltrexone attenuation of conditioned but not primary reinforcement of nicotine in rats. *Psychopharmacology*. 2009;**202**(4):589-598
- [39] Corrigall WA, Coen KM. Opiate antagonists reduce cocaine but not nicotine self-administration. *Psychopharmacology*. 1991;**104**(2):167-170
- [40] DeNoble VJ, Mele PC. Intravenous nicotine self-administration in rats: Effects of mecamylamine, hexamethonium and naloxone. *Psychopharmacology*. 2006;**184**(3-4):266-272
- [41] Corrigall WA, Coen KM, Adamson KL, Chow BL, Zhang J. Response of nicotine self-administration in the rat to manipulations of mu-opioid and gamma-aminobutyric acid receptors in the ventral tegmental area. *Psychopharmacology*. 2000;**149**(2):107-114
- [42] Corrigall WA, Coen KM, Zhang J, Adamson L. Pharmacological manipulations of the pedunculopontine tegmental nucleus in the rat reduce self-administration of both nicotine and cocaine. *Psychopharmacology*. 2002;**160**(2):198-205
- [43] Berrendero F, Kieffer BL, Maldonado R. Attenuation of nicotine-induced antinociception, rewarding effects, and dependence in mu-opioid receptor knock-out mice. *The Journal of Neuroscience*. 2002;**22**(24):10935-10940
- [44] Trigo JM, Zimmer A, Maldonado R. Nicotine anxiogenic and rewarding effects are decreased in mice lacking beta-endorphin. *Neuropharmacology*. 2009;**56**(8):1147-1153
- [45] Ismayilova N, Shoaib M. Alteration of intravenous nicotine self-administration by opioid receptor agonist and antagonists in rats. *Psychopharmacology*. 2010;**210**(2):211-220
- [46] Snyder SH, Pasternak GW. Historical review: Opioid receptors. *Trends in Pharmacological Sciences*. 2003;**24**(4):198-205
- [47] Dhawan BN, Cesselin F, Raghubir R, Reisine T, Bradley PB, Portoghese PS, et al. International Union of Pharmacology. XII. Classification of opioid receptors. *Pharmacological Reviews*. 1996;**48**(4):567-592
- [48] Mansour A, Fox CA, Akil H, Watson SJ. Opioid-receptor mRNA expression in the rat CNS: Anatomical and functional implications. *Trends in Neurosciences*. 1995;**18**(1):22-29
- [49] Shippenberg TS, Zapata A, Chefer VI. Dynorphin and the pathophysiology of drug addiction. *Pharmacology & Therapeutics*. 2007;**116**(2):306-321

- [50] Hasebe K, Kawai K, Suzuki T, Kawamura K, Tanaka T, Narita M, et al. Possible pharmacotherapy of the opioid kappa receptor agonist for drug dependence. *Annals of the New York Academy of Sciences*. 2004;**1025**:404-413
- [51] Galeote L, Berrendero F, Bura SA, Zimmer A, Maldonado R. Prodynorphin gene disruption increases the sensitivity to nicotine self-administration in mice. *International Journal of Neuropsychopharmacology*. 2009;**12**(5):615-625
- [52] Matsuzawa S, Suzuki T, Misawa M, Nagase H. Different roles of mu-, delta- and kappa-opioid receptors in ethanol-associated place preference in rats exposed to conditioned fear stress. *European Journal of Pharmacology*. 1999;**368**(1):9-16
- [53] Filliol D, Ghozland S, Chluba J, Martin M, Matthes HW, Simonin F, et al. Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. *Nature Genetics*. 2000;**25**(2):195-200
- [54] Balerio GN, Aso E, Maldonado R. Involvement of the opioid system in the effects induced by nicotine on anxiety-like behaviour in mice. *Psychopharmacology*. 2005;**181**(2):260-269
- [55] Liu X, Jernigan C. Activation of the opioid μ 1, but not delta or kappa, receptors is required for nicotine reinforcement in a rat model of drug self-administration. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2011;**35**(1):146-153
- [56] Liu X, Caggiula AR, Yee SK, Nobuta H, Poland RE, Pechnick RN. Reinstatement of nicotine-seeking behavior by drug-associated stimuli after extinction in rats. *Psychopharmacology*. 2006;**184**(3-4):417-425
- [57] Britt JP, McGehee DS. Presynaptic opioid and nicotinic receptor modulation of dopamine overflow in the nucleus accumbens. *The Journal of Neuroscience*. 2008;**28**(7):1672-1681
- [58] Heidbreder C, Shoaib M, Shippenberg TS. Differential role of delta-opioid receptors in the development and expression of behavioral sensitization to cocaine. *European Journal of Pharmacology*. 1996;**298**(3):207-216
- [59] Berrendero F, Mendizabal V, Robledo P, Galeote L, Bilkei-Gorzo A, Zimmer A, et al. Nicotine-induced antinociception, rewarding effects, and physical dependence are decreased in mice lacking the preproenkephalin gene. *The Journal of Neuroscience*. 2005;**25**(5):1103-1112
- [60] Campbell VC, Taylor RE, Tizabi Y. Effects of selective opioid receptor antagonists on alcohol-induced and nicotine-induced antinociception. *Alcoholism, Clinical and Experimental Research*. 2007;**31**(8):1435-1440
- [61] Drake CT, Chavkin C, Milner TA. Opioid systems in the dentate gyrus. *Progress in Brain Research*. 2007;**163**:245-263
- [62] Blednov YA, Walker D, Martinez M, Harris RA. Reduced alcohol consumption in mice lacking prodynorphin. *Alcohol*. 2006;**40**(2):73-86
- [63] McLaughlin JP, Marton-Popovici M, Chavkin C. Kappa opioid receptor antagonism and prodynorphin gene disruption block stress-induced behavioral responses. *The Journal of Neuroscience*. 2003;**23**(13):5674-5683
- [64] Kitamura T, Ogawa M, Yamada Y. The individual and combined effects of U50,488, and flurbiprofen axetil on visceral pain in conscious rats. *Anesthesia and Analgesia*. 2009;**108**(6):1964-1966

[65] Heidbreder CA, Babovic-Vuksanovic D, Shoaib M, Shippenberg TS. Development of behavioral sensitization to cocaine: Influence of kappa opioid receptor agonists. *The Journal of Pharmacology and Experimental Therapeutics*. 1995;275(1):150-163

[66] Glick S, Maisonneuve I, Raucci J, Archer S. Kappa opioid inhibition on morphine and cocaine self-administration on rats. *Brain Research*. 1995;681(1-2):147-152

[67] Wee S, Orio L, Ghirmai S, Cashman JR, Koob GF. Inhibition of kappa opioid receptors attenuated increased cocaine intake in rats with extended access to cocaine. *Psychopharmacology*. 2009;205(4):565-575

[68] Walker BM, Zorrilla EP, Koob GF. Systemic kappa-opioid receptor antagonism by nor-binaltorphimine reduces dependence-induced excessive alcohol self-administration in rats. *Addiction Biology*. 2010;16(1):116-119

[69] Conte-Devolx B, Oliver C, Giraud P, Gillioz P, Castanas E, Lissitzky JC, et al. Effect of nicotine on in vivo secretion of melanocorticotrophic hormones in the rat. *Life Sciences*. 1981;28(9):1067-1073

[70] Rosecrans JA, Hendry JS, Hong JS. Biphasic effects of chronic nicotine treatment on hypothalamic immunoreactive beta-endorphin in the mouse. *Pharmacology, Biochemistry, and Behavior*. 1985;23(1):141-143

[71] Marty MA, Erwin VG, Cornell K, Zgombick JM. Effects of nicotine on beta-endorphin, alpha MSH, and ACTH secretion by isolated perfused mouse brains and pituitary glands, in vitro. *Pharmacology, Biochemistry, and Behavior*. 1985;22(2):317-325