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The κ-Opioid Receptor in Opioid Dependence

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ABSTRACT

Opioid dependence that particularly mediates through the μ-opioid receptor remains a major concern of opioid analgesics. Drugs which interact with κ-opioid receptors are increasingly used as an alternative to μ-agonist analgesic. Several studies have reported that chronic administration of κ-opioid agonists such as U-50488H, U-69,593, and butorphanol also results in development of physical dependence/withdrawal. In addition, the ability of a highly selective κ-opioid antagonist, nor-binaltorphimine, given systemically or spinally, to precipitate withdrawal behaviors in opioid-dependent animals further demonstrates that both supraspinal and spinal sites of κ-opioid receptors play an important role in opioid dependence/withdrawal. With regard to the role of glutamate in opioid dependence/withdrawal, the κ-opioid receptor located at the presynaptic nerve terminal within the locus coeruleus crucially regulates glutamate release during the expression of opioid withdrawal. Physical dependence on κ-opioid agonists is associated with the downregulation and antagonist-sensitive state of the κ-opioid receptor in the spinal cord and specific brain areas. However, alterations of the κ-opioid receptor may not completely explain the mechanisms of dependence development. With cloned κ-opioid receptors recently available, it could be elucidated that the cellular and biological mechanisms of κ-opioid receptors for the development of dependence/withdrawal may differ from those of μ-opioid receptors.

Key words: **κ-opioid receptor, opioid dependence, glutamate locus coeruleus, spinal cord.**

Opioids are extensively used in the management of pain. Treatment of chronic pain through the use of opioids gives rise to clinical concern because of their potential for physical dependence and abuse. Physical dependence on opioids is manifested by a characteristic withdrawal syndrome following either the abrupt termination of the drug intake or precipitation by the administration of an opioid antagonist. Morphine, a prototype opioid analgesic acting mainly on the μ-opioid receptor, possesses a high abuse potential and dependence liability[(1)]. In an effort to develop drugs that are potent analgesic without the undesirable effects, much interest has focused on compounds which interact with the κ-opioid receptor. There is now substantial evidence that the κ-opioid receptor differs from the μ-opioid receptor in pharmacological, physiological, and molecular aspects and also mediates analgesia with low abuse potential[(2, 3)]. However, chronic administra-

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tion of drugs acting on the κ-opioid receptor has been reported increasingly to develop physical dependence. This article briefly reviews the experimental evidence for the involvement of the κ-opioid receptor in physical dependence/withdrawal.

KAPPA-OPIOID AGONISTS AND PHYSICAL DEPENDENCE/WITHDRAWAL

There are several compounds that interact with the κ-opioid receptor with different selectivity. These compounds include those being used in humans such as pentazocine, buprenorphine, and butorphanol, as well as others such as bremazocine, cyclazocine, ethylketocyclazocine, and ketazocine[4]. Recently, the highly selective agonists for the κ-opioid receptor are available, including U-50,488H and U-69,593. Several investigators report little or no development of physical dependence on opioid agonists acting on the κ-opioid receptor whereas others demonstrate

Table 1. Methods utilized for studying dependence on selective and preferring κ-opioid agonists in laboratory animals

Compounds	Species	Route	Dose	Duration of treatment	withdrawal signs	refs
U-50,488E	mouse	s.c.	24 mg[@]	2.5 days	–[a]	(65)
U-50,488H	rat	i.p.	25 mg/kgx2	4 days	–[b]	(47)
	monkey	s.c.	0.3 mg/kgx4 - 17.5 mg/kgx6[#]	135 days	+[c,d]	(6, 66)
	rat	i.v.	60 mg[@]	14 days	+[e]	(7)
	rat	Sylvain aqueduct	2923 nmol[@] (1.4 mg)	70 hr	–[e]	(67)
	guinea pig	s.c.	10 mg/kg	*	+[f]	(8)
U-69,593	rat	i.c.v.	26 nmol/hr (9.3 μg)	3 days	+[g]	(5, 11)
Butorphanol	mouse	s.c.	384 mg[@]	2 days	+[e]	(68)
			1324 mg	4 days	+[e]	(68)
	rat	i.c.v.	26 nmol/hr (12.4 μg)	3 days	+[g,h]	(10, 14)
	rat	i.t.	52 nmol/hr (24.9 μg)	4 days	+[i]	(16)
Cyclazocine	mouse	s.c.	35 mg[@]	2 days	+[e]	(68)
			640 mg	4 days	+[e]	(68)
Ethylketo-cyclazocine	rat	Sylvain aqueduct	3063 nmol[@] (1.2 mg)	70 hr	+[e]	(67)
Pentazocine	mouse	s.c.	384 mg[@]	2 days	+[e]	(68)
			1324 mg	4 days	+[e]	(68)
Dynorphin A	rat	Sylvain aqueduct	114 nmol[@] (0.2 mg)	70 hr	–[e]	(67)

[@]total dose, [#] increasing doses, *single injection.

[a] naloxone (NLX) (3 mg/kg, i.p.); [b] abrupt withdrawal; [c] NLX (0.1-10 mg/kg, s.c.); [d] deprivation, NLX (10 mg/kg, s.c.), naltrexone or quadazocine (1 mg/kg, s.c.); [e] NLX (3 mg/kg, s.c.); [f] NLX (15, 30 mg/kg , s.c.), nor-BNI (10 mg/kg, s.c.); [g] NLX (12, 48 nmol into LC), nor-BNI (48 nmol into LC); [h] NLX, nor-BNI (48 nmol, i.c.v.); [i] NLX, nor-BNI (48 nmol, i.t.).

physical dependence and withdrawal behaviors (Table 1). This discrepancy may be related to differences in the experimental protocols used in various laboratories, including the doses of the drugs, route of administration, duration of treatment, animal species, and selectivity of antagonists used to precipitate withdrawal.

Evaluation of selective opioid agonists shows that the dependence on κ-opioid agonists is both receptor-specific and pharmacologically unique. Several types of evidence for selective κ-opioid agonists inducing physical dependence have been documented. First, an injection of opioid antagonists produces behavioral signs of withdrawal following chronic κ-opioid agonist administration. A profile of opioid withdrawal signs, including teeth chattering, wet shakes, and locomotion, has been observed following naloxone challenge in rats given intracerebroventricular (i.c.v.) infusion of U-69,593 for 3 days[5]. In monkeys that receive chronic subcutaneous (s.c.) administration of U-50,488H, withdrawal signs (including hyperactivity, excessive grooming, and yawning) have been elicited by deprivation of the opioid agonist, or by administration of a nonselective opioid antagonist, naloxone or quadazocine[6]. In rodents, chronic intravenous (i.v.) infusion of U-50,488H also produces mild physical dependence and body weight loss after naloxone challenge[7]. Furthermore, acute physical dependence on U-50,488H has been reported. Administration of naloxone and nor-binaltorphimine (nor-BNI) induces an increase of locomotor activity in guinea pigs injected earlier with a single dose of U-50,488H [8]. Secondly, the withdrawal symptoms from dependence on U-50,488H are suppressed in a dose-dependent manner by an agonist preferring the κ-opioid receptor, ethylketazocine, but not by morphine. Finally, the μ-opioid antagonist, β-funaltrexamine, selectively precipitates withdrawal in animals treated chronically with morphine, but not in those treated chronically with the κ-opioid agonist, U-50,488H[6, 9]. A highly selective κ-opioid antagonist, nor-BNI, given directly to the brain also precipitates withdrawal behaviors in animals dependent on U-69, 593, but not those dependent on morphine[10,11].

Additional evidence of κ-opioid receptor mediating physical dependence is also documented by studying butorphanol dependence. Butorphanol is characterized as a relatively potent mixed agonist-antagonist analgesic that acts on μ-, δ-, and κ-opioid receptors with affinity ratios of 1:4:25[4, 12]. Butorphanol is considered to have a lower physical dependence liability than morphine is, within the therapeutic dose range. However, physical dependence has been reported in humans [13] and animals[14] following chronic administration of higher doses of butorphanol. Studies from our laboratory have also demonstrated that rats receiving i.c.v. or intrathecal (i.t.) infusion of high-dose butorphanol develop physical dependence and that withdrawal behaviors observed in butorphanol-dependent rats may not differ from those exhibited in morphine-dependent rats[15, 16]. Additionally, different mechanisms underlying development of dependence on butorphanol and morphine are also evident. Butorphanol dependence is mediated through κ-, and possibly δ-and μ-opioid receptors because the degree of withdrawal signs precipitated by nor-BNI is greater than those precipitated by naltrindole, a δ-opioid antagonist, and by CTOP, a μ-opioid antagonist[15,17,18]. Moreover, treatment with nor-BNI before and during i.c.v. infusion of butorphanol blocks naloxone-precipitated withdrawal sign, and thus inhibits the development of physical dependence on butorphanol[19]. On the other hand, the μ- and partially δ-opioid receptors play a major role in the development of morphine dependence.

SUPRASPINAL SITE IN κ-OPIOID DEPENDENCE/WITHDRAWAL

It has been suggested that many brain areas, including the locus coeruleus (LC), periaqueductal gray (PAG), amygdala, nucleus raphe magnus, hypothalamus, hippocampus, and neocortex are responsible for opioid dependence/withdrawal [20,21]. Using local intracerebral injections of an opioid antagonist, Maldonado *et al.*[21] has demonstrated that the LC plays a major role in the

precipitation of withdrawal signs from opioid dependence.

THE LC AND OPIOID DEPENDENCE/ WITHDRAWAL

The LC, a pontine nucleus, contains a number of noradrenergic neurons and projects noradrenergic axons to the brain and spinal cord[22]. This general innervation allows the LC to regulate the general states of arousal, attention, and autonomy. Several studies using intracerebral microinjections of methylnaloxonium (a potent hydrophilic opioid antagonist)[21] and naloxone[23] into discrete brain areas of morphine-dependent animals have demonstrated that the LC is the most sensitive region in the expression of withdrawal behaviors. Electrophysiological studies have shown that stimulation of the LC produces behavioral signs that resemble withdrawal signs in opioid dependence[24, 25]. Bilateral electrolytic lesions of the LC decrease withdrawal signs induced by i.c.v. injection of an opioid antagonist[26]. There is a marked increase in the firing of LC neurons during naloxone-precipitated withdrawal in morphine-dependent animals[27]. In addition, during opioid withdrawal, there is an increased release of noradrenaline in many brain areas and the spinal cord which are innervated from the LC[24]. Taken together, these studies suggest that the LC plays an important role in the expression of opioid dependence/withdrawal.

KAPPA-OPIOID RECEPTOR WITHIN THE LC

Autoradiographic studies have demonstrated that high-density μ- and κ-opioid receptors are present in the LC[28]. Administration of μ-opioid agonists opens K^+ channels[29] and inhibits a resting Na^+-dependent inward current in the LC neurons[30], resulting in hyperpolarization of these cells. In contrast, stimulation of the κ-opioid receptor in the LC slices does not have such direct effect on LC neurons[31]. In slice preparations, synaptic potentials in the LC neurons evoked by field stimulation are inhibited by the selective κ-opioid agonists, U-50,488H and U-69,593. These results indicate that κ-opioid receptors are located at presynaptic afferents to the LC and mediate presynaptic inhibition of LC excitation.

KAPPA-OPIOID RECEPTOR AND GLUTAMATE RELEASE IN THE LC DURING WITHDRAWAL

Absence of withdrawal-induced hyperactivity of the LC neurons is observed in isolated brain slices from morphine-dependent rats[32, 33], suggesting that the hyperactivity of the LC neurons seen in intact animals is mediated by afferents to the LC. The major excitatory input to the LC is from the nucleus paragigantocellularis (PGi) in the rostral ventrolateral medulla which releases excitatory amino acids to activate the LC neurons [34]. Lesions of the PGi decrease activation of the LC neurons during morphine withdrawal[35]. In addition, electrical stimulation of the PGi in opioid-naive rats results in voltage-dependent stereotyped behaviors. These behavioral responses are similar to withdrawal signs observed in butorphanol-dependent rats[36]. These results indicate that the PGi-LC pathway may be responsible for the expression of opioid withdrawal.

Microdialysis studies have demonstrated that an increased secretion of excitatory transmitters, particularly glutamate, from presynaptic terminals within the LC during opioid antagonist-precipitated withdrawal in opioid-dependent animals is associated with opioid withdrawal-induced behaviors[37, 38]. Injections of kynurenic acid, a nonspecific antagonist of excitatory amino acids, directly into the LC significantly inhibited the activation of the LC neurons induced by naloxone-precipitated withdrawal[35, 39]. This suggests that hyperactivity of LC neurons during naloxone-precipitated withdrawal may be mediated by an excitatory amino acid input to the LC. An increase in extracellular levels of glutamate in the LC is observed during naloxone-precipitated withdrawal from dependence on butorphanol[15] and U-69, 593, the selective κ-opioid agonist[5]. In addition, there is

convincing evidence observed in our laboratories that κ-opioid receptors within the LC regulate presynaptic release of glutamate during withdrawal from dependence on butorphanol and U-69,593 [11]. Opioid dependence is induced in rats following three days of continuous i.c.v. infusion of either butorphanol or U-69,593. Withdrawal is precipitated upon termination of the i.c.v. infusion by a discrete injection directly to the LC of a relatively selective κ-opioid antagonist, nor-BNI. Levels of the LC glutamate in both the butorphanol- or U-69,593-dependent rats increase significantly within 60 min of the LC injection of nor-BNI. Behavioral signs of withdrawal, including teeth chattering, wet shakes, and locomotion, are observed following the nor-BNI injection in butorphanol- and U-69,593-dependent rats, but not in the saline-infused controls. These results directly indicate that κ-opioid receptors within the LC play a significant role in the mediation of glutamate release and behavioral response to withdrawal from dependence on butorphanol or U-69,593.

KAPPA-OPIOID RECEPTOR AND SPINAL OPIOID DEPENDENCE/WITHDRAWAL

The spinal cord is not only a primary site of opioid analgesic action, but may also participate in withdrawal reactions in opioid dependence. The evidence for involvement of the spinal cord in the development of opioid dependence has been documented. A syndrome of withdrawal behaviors can be precipitated by i.t. naloxone injected to animals dependent on systemic morphine[40] and by intraperitoneal naloxone given to rats dependent on i.t. morphine[41]. Naloxone-precipitated withdrawal in morphine-treated animals is prevented by i.t. pretreatment of an irreversible opioid antagonist, β-chlornaltrexamine (β-CNA)[42]. The development of physical dependence on i.t. infused morphine has also been demonstrated by an i.t. naloxone challenge[43].

To investigate the role of spinal opioid receptors in opioid dependence, the responses elicited during opioid antagonist-precipitated withdrawal from dependence on i.t. butorphanol and on i.t. morphine have been evaluated in our laboratory [16]. Opioid dependence is induced by the continuous i.t. infusion of butorphanol (52 nmol/μl/h) and morphine (26 nmol/μl/h) for 4 days. Naloxone and selective opioid antagonists (48 nmol/10μl/rats) are administered i.t. to precipitate behavioral signs of withdrawal. Naloxone injected i.t. produces a significantly greater increase in the profile of withdrawal signs in morphine dependence than that in butorphanol dependence. An i.t. injection of nor-BNI elicits behavioral signs of withdrawal from butorphanol dependence, but not from morphine dependence or in the saline controls. CTOP administered i.t. precipitates greater withdrawal signs in morphine dependence than those in butorphanol dependence. An i.t. treatment with naltrindole produces equivalent signs of withdrawal in both butorphanol- and morphine-dependent rats. These results indicate that continuous i.t. butorphanol results in the development of physical dependence to a smaller extent than i.t. morphine does. Spinal κ- rather than δ- and μ-opioid receptors play a major role in the mediation of withdrawal from spinal butorphanol dependence, whereas spinal μ-opioid receptors play a more important role than δ- and κ-opioid receptors in spinal morphine dependence.

The dorsal horn of the spinal cord contains high density of μ-, δ-, and κ-opioid receptors[44] and is one potential source of afferent systems distributing to several areas of supraspinal neural networks, including the LC and PGi[45]. Opioid withdrawal in the dorsal horn of the spinal cord has been reported to associate with enhanced excitability of the supraspinal neurons[46]. Taken together, these findings indicate that the initiation and expression of withdrawal behaviors arise from neuroadaptations in the dorsal horn of the spinal cord, which directly activate the LC and/or the PGi to produce withdrawal excitation of LC neurons.

KAPPA-OPIOID RECEPTORS AND MECHANISMS IN OPIOID DEPENDENCE

The development of physical dependence seems to involve several stages from receptor occupation to inhibition of receptor synthesis. It is generally recognized that opioid dependence is initiated by opioid receptor activation. However, the relationship between physical dependence and receptor modification is still unclear. Early studies have failed to show that chronic treatment with opioid agonists consistently down-regulates and/or desensitizes opioid receptors *in vivo*. Recently, increasing evidence indicates that down-regulation of κ-opioid receptors in several brain regions and the spinal cord may occur following chronic systemic, i.c.v., or i.t. administration of κ-opioid agonists including U-50,488H[47], butorphanol[19], or bremazocine[48] (Table 2). Chronic i.c.v. administration of butorphanol also induced desensitization of κ-opioid receptors in some brain areas. In addition, treatment with nor-BNI before and during chronic i.c.v. infusion of butorphanol can prevent downregulation and desensitization of κ-opioid receptors[19]. The modification of κ-opioid receptors induced by chronic κ-opioid agonist administration appears to be consistent with that observed in cell culture. Raynor *et al.*[49] report that short-term treatment with U-50,488 in COS-7 cells containing mouse κ-opioid receptors decreases the affinity of the receptors for κ-agonists. The investigators also suggest that downregulation of cloned κ-opioid receptors may be observed with longer periods of κ-opioid agonist treatment in these cell lines.

Conformational changes in the opioid receptors have been postulated to explain changes in opioid antagonist sensitivity after chronic opioid administration[50]. A modification in the characteristics of the κ-opioid receptor during the development of physical dependence on butorphanol has been investigated in our laboratory. The results from the antagonist-precipitated withdrawal-behaviors in animals made dependent by either chronic i.c.v. or i.t. infusion of butorphanol are used to correlate findings from the competitive binding studies with nor-BNI against [^{3}H]U-

Table 2. Alterations of κ-opioid receptors following chronic treatment with selective and preferring κ-opioid agonists

		Ligand used			
		B_{max}	K_d	IC_{50} of nor-BNI against [^{3}H]U-69,593	references
whole animal					
U-50,488H		[^{3}H]ethylkocyclazocine			
(i.p.)	Medulla & pons	↓	0		(47)
	Midbrain	↓	0		(47)
	Cortex	↓	0		(47)
	Corpus striatum	↑	0		(47)
	Spinal cord	↓	0		(47)
Butorphanol		[^{3}H]U-69,593			
(i.c.v.)	Cortex	↓	↑	↓	(19)
	Corpus striatum	0	↑		(19)
(i.t.)Spinal cord		↓	0	↓	(51)
Bremazocine		[^{3}H]bremazocine			
(i.c.v.)	Cerebrum	↓			(48)
cell culture					
U-50,488		[^{3}H]U-69,593			
	COS-7		↑		(49)

↑ : increase, ↓ : decrease, 0: no change.

69,593 for κ-opioid site (Table 2). Chronic i.c.v. or i.t. administration of butorphanol induces κ-opioid receptors within the striatum and the spinal cord to become more sensitive to a selective κ-opioid antagonist, nor-BNI[19, 51]. The results suggest that the high degree of supersensitivity of the κ-opioid receptor to the antagonist may explain the important role of the κ-opioid receptor involved in the development of physical dependence on butorphanol.

At the molecular level, much less evidence exists concerning the mechanisms of physical dependence on κ-opioid agonists. Following the studies on morphine, chronic administration of the opioid agonist produces increased adenylyl cyclase activity[52], increased cyclic-AMP-dependent protein kinase (PKA) activity[53], and an upregulation of G-protein transduction systems [54]. Chronic exposure to the opioid also induces an increase in the expression of c-fos, a marker for neuronal activation, in the LC[55]. In addition, chronic treatment with opioids increases cytosolic protein kinase C (PKC) activity in the pons and medulla[56,57]. H-7 [1-(5-isoquinolinesulfonyl)-2-methylpiperazine], a PKA and PKC inhibitor, inhibits the increase in glutamate release during withdrawal and prevents withdrawal signs precipitated by the LC injection of naloxone in opioid-dependent animals[58]. Chronic morphine treatment leads to upregulation of L-type Ca^{2+} channel in many brain areas including the cortex, hippocampus, hypothalamus, brain stem, and striatum[59]. Discontinuation of the opioid causes an increase in intracellular Ca^{2+} which greatly induces an increase in neurotransmitter release and results in the expression of withdrawal behaviors. An elevation of neurotransmitter release during withdrawal can be blocked by diltiazam, an L-type Ca^{2+} channel blocker[60]. These findings indicate the possible mechanisms responsible for the development of opioid dependence/withdrawal. Actions of κ-opioid agonists may mediate through similar and/or different molecular processes compared to μ-opioid agonists. Similar to the μ-opioid agonists, agonists acting on the κ-opioid receptor inhibit the activity of adenylyl cyclase by coupling to pertussis toxin-sensitive G-protein[61, 62]. On the other hand, Cherubini and North[63] report that μ- and κ-opioid receptors mediate the agonist-inhibition of the neurotransmitter release by different mechanisms. Moreover, activation of the κ-opioid receptors may oppose some actions mediated by the μ-opioid receptor in the CNS[64]. Therefore, it is reasonable to expect that chronic activation of the κ-opioid receptor may induce physical dependence by different mechanisms, compared to the μ-opioid receptor activation.

In conclusion, increasing evidence indicates that chronic administration of agonists acting on the κ-opioid receptor leads to the development of physical dependence/withdrawal. The κ-opioid receptors located in the presynaptic LC and the dorsal horn of the spinal cord play a critical role in opioid dependence/withdrawal. Chronic treatment of κ-opioid agonists downregulates and/or desensitizes the κ-opioid receptor. The cellular mechanism in the development of physical dependence on and withdrawal from κ-opioid agonists is not well understood. Further studies are warranted to delineate the mechanisms underlying the adaptive changes resulted from chronic activation of the κ-opioid receptor. Further understanding of the mechanisms should make a significant contribution to the clinical uses of these opioids.

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κ-類鴉片受體於鴉片類藥物的依賴性所扮演的角色

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摘　要

依賴性目前仍是臨床使用作用於μ-類鴉片受體的鎮痛劑所主要關切的問題，因此使用κ-類鴉片受體的藥物以取代μ-受體致效劑作爲鎮痛劑的情形正逐漸成長中。有些研究報告指出慢性給予κ-類鴉片受體致效劑，如U-50488H，U-69,593及butorphanol也能導致身體依賴性／脫癮症狀的產生，而不論由全身或由脊髓給予nor-binaltorphimine（一種高選擇性的κ-類鴉片受體拮抗劑）均可在依賴性的動物引起催癮現象，更顯示不論在腦或脊髓的κ-類鴉片受體均在類鴉片藥物的依賴性／脫癮症狀上扮演了重要的角色。此外位於藍斑核（locus coeruleus）節前神經末端的κ-類鴉片受體調控麩氨酸（glutamate）的釋放，可能與依賴性／脫癮症狀的表現有關。對κ-類鴉片致效劑的身體依賴性與脊髓及特殊腦區κ類鴉片受體之減量和對拮抗劑敏感的狀態有關；然而κ-類鴉片受體的改變可能無法完全解釋依賴性發生的機轉。由最近κ-類鴉片受體的選殖（clone）成功及應用，未來應該能闡明其在依賴性／脫癮發生的細胞生物機轉上與μ-類鴉片受體可能不同。

關鍵詞：κ-類鴉片受體，類鴉片藥物依賴性，麩氨酸，藍斑核，脊髓。