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Opioid Receptors and Butorphanol Dependence

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ABSTRACT

Butorphanol, a mixed opioid agonist/antagonist, is considered to be a relatively safe drug when used within the therapeutic dose range. However, diversional uses of butorphanol involving high doses have been documented. In the present review, the relative involvement of μ-, δ-, and κ-opioid receptors in butorphanol physical dependence in rats is discussed. Physical dependence was produced by continuous intracerebroventricular (icv) infusion of butorphanol (26 nmol/h) for 72 h in male Sprague-Dawley rats. Multiple icv injections of β-funaltrexaimne (β-FNA, a μ-antagonist, 12, 24, or 48 nmol/5 μl), naltrindole (NTI, a δ-antagonist, 0.1, 1, or 10 nmol/5 μl), or nor-binaltorphimine (nor-BNI, a κ-antagonist, 12, 24, or 48 nmol/5 μl) significantly attenuated the development of butorphanol dependence. Furthermore, icv administration of both NTI (24, 48, or 100 nmol/5 μl) and nor-BNI (3, 10, 20, 48, or 100 nmol/5 μl) precipitated withdrawal behaviors, whereas, β-FNA (12, 24, 48, or 100 nmol/5 μl) was unable to elicit withdrawal signs in butorphanol-dependent rats. The results indicate that the development of butorphanol dependence is due to effects of butorphanol on central μ-, δ-, and κ-opioid receptors.

Key words : Butorphanol, β-funaltrexamine, naltrindole, nor-binaltorphimine, physical dependence, μ-, δ-, and κ-opioid receptors.

INTRODUCTION

Butorphanol is thought to possess a low abuse potential, when given within the therapeutic dose range. However, abuse of butorphanol with diphenhydramine[17] via intravenous injection has been reported among teenagers. Evans et al.[3] reported that after eight months of butorphanol use, a patient showed opioid withdrawal symptoms including tachycardia, diaphoresis, generalized malaise, myalgia, rhinorrhea, nausea, abdominal cramping and diarrhea. Brown[2] reported that a case of butorphanol dependence which involved intramuscular use of the drug. Hoover and Williams[5] carried out a survey of butorphanol diversion in U.S. hospitals and concluded that the diversion of butorphanol for purposes of abuse may be a more serious problem than is generally known. Jasinski et al.[9] administered butorphanol 48 mg/day subcutaneously to former narcotic addicts who subsequ-

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ently developed typical opiate-like withdrawal symptoms. Finally, Horan and Ho[6,8] reported that butorphanol may precipitate abstinence in morphine dependent rats and produce morphine -like withdrawal signs. Since potential abuse exits for the drug, studies are warrented to clarify the mechanisms of the butorphanol dependence.

OPIOID RECEPTORS AND BUTORPHANOL

Butorphanol is known to act on μ-, δ-, and κ-opioid receptors[7]. Mu (main receptors)[4] -, δ-(positive modulatory role)[1,14] -, and κ (negative modulatory role)[18] -opioid receptors have been implicated in mediation or modulating morphine dependence in mice. Relative to morphine, butorphanol has higher affinities for μ-, δ-, and κ-opioid receptors[7]. However, due to the presence of the cyclobutylmethyl group in the N position and the 14-hydroxyl group, butorphanol is also a partial agonist (agonist/antagonist) at opioid receptors. Since butorphanol has actions on μ-, δ-, and κ-opioid receptors, we therefore hypothesize that these same receptors may be involved in mediating butorphanol dependence in rats.

PHARMACOLOGICAL MANIPULATION OF OPIOID RECEPTORS

Opioid receptor subtypes were selectively blocked by antagonists administered icv before and during butorphanol infusion in rats, so as to determine relative involvement of μ-, δ-, as well as κ-opioid receptors in the development of physical dependence upon butorphanol. The finding of these studies are shown in Table 1[11,12,15]. The results indicate that μ-, δ-, as well as κ-opioid receptors are all involved in the development of physical dependence upon butorphanol.

PRECIPITATED WITHDRAWAL STUDIES WITH ANTAGONISTS

Opioid receptor subtype selective antagonists were administered icv to precipitate with

Table 1. Effects of pretreatment with β-FNA, NTI, or nor-BNI on naloxone-precipitated withdrawal behaviors (all or none) in butorphanol-infused rats.

	β-FNA	NTI	Nor-BNI	Receptors
Escape behavior	−	−	−	μ,δ,κ
Teeth-chattering	−	−	−	μ,δ,κ
Wet shakes	±	−	−	δ,κ
Forepaw tremors	−	−	−	μ,δ,κ
Yawning	±	±	±	
Ptosis	±	−	−	δ,κ
Ejaculation	+[a]	−	±	μ,δ
Urination	−	±	±	μ
Diarrhea	−	−	−	μ,δ,κ
Weight loss(>3%)	−	−	−	μ,δ,κ
Rectal temp.	−	+[b]	+[b]	μ,δ,κ

−, Antagonist-pretreated rats showed withdrawal behaviors significantly inhibited from the saline control at dose(s) tested as determined by the chi-square test.

±, Pretreatment with antagonists showed no significantly different effect from the saline control.

[a], Significantly increased from the saline control as determined by the chi-square test.

[b], Significantly increased from the saline control as determined by two-tailed Student's t-test.

Table 2. Withdrawal behaviors (all or none) precipitated by β-FNA, NTI, nor-BNI, or naloxone in butorphanol-dependent rats.

	β-FNA	NTI	Nor-BNI	NLX	Receptors
Escape behavior	±	±	±	±	
Teeth-chattering	±	+	+	+	δ,κ
Wet shakes	±	+	+	+	δ,κ
Forepaw tremors	±	+	+	+	δ,κ
Yawning	±	+	+	+	δ,κ
Ptosis	±	±	+	±	κ
Ejaculation	±	+	+	+	δ,κ
Urination	±	+	±	+	δ
Diarrhea	±	±	±	±	
Weight loss (>3%)	±	±	±	±	
Rectal temp.	+	+	+	+	μ,δ,κ

+, Antagonists elicited significant effects at dose(s) tested compared with the saline control as determined by the chi-square test or Fisher's exact test.

±, Antagonists had no significant effect as determined by the chi-square test or Fisher's exact test.

drawal in butorphanol-dependent rats, so as to determine the relative potency of antagonists to elicit each withdrawal sign. The findings are shown in Table 2[10,13]. The potency of antagonists to precipitate withdrawal in butorphanol-dependent rats is as follows: nor-BNI (κ) > naloxone (nonspecific) > NTI (δ) >>> β-FNA (μ). These data suggest that butorphanol acts more potently on κ-opioid receptors than μ- and δ-opioid receptors in the rat brain. The κ-opioid receptors are the main opioid receptor subtype involved, whereas μ- and δ-opioid receptors have a permissive (positive modulatory) role in the development of butorphanol dependence in rats. In contrast, κ-opioid receptors were determined to have a negative modulatory role on the development of morphine (acting mainly on μ-opioid receptor system) tolerance and dependence in mice[12,18].

OPIOID RECEPTORS AND WITHDRAWAL BEHAVIORS

I. *Escape Behavior*

Since pretreatment with β-FNA, NTI, or nor-BNI blocked this particular withdrawal behavior (Table 1), it is concluded that μ-, δ-, and κ-opioid receptors are all involved in mediating escape behavior in butorphanol-dependent rats following naloxone challenge. However, icv antagonists failed to produce escape behavior in butorphanol-dependent rats (Table 2). These results indicate that butorphanol has less efficacy on μ-opioid receptors. Therefore, escape behavior, a μ-receptor-related withdrawal sign, was not apparent in butorphanol-dependent rats.

II. *Teeth-chattering*

Mu-, δ-, and κ-opioid receptors are all involved (Tables 1 and 2). However, β—FNA failed to elicit teeth-chattering in butorphanol-dependent rats (Table 2). This may be due to acute κ agonist effect of β-FNA.

III. *Wet Shakes*

Delta- and κ-opioid receptors are involved in mediating wet shakes (Tables 1 and 2).

IV. *Forepaw Tremors*

Mu-, δ-, and κ-opioid receptors are all involved (Tables 1 and 2). However, β-FNA failed to elicit forepaw tremors in butorphanol-dependent rats (Table 2). This may be due to acute κ agonist effect of β-FNA.

V. *Yawning*

Pretreatment with selective antagonists had no effect on the expression of yawning, indicating non-involvement of all three opioid receptor subtypes or these receptors are involved non-inclusively, i. e., any one of these subtypes may mediate yawning alone (Table 1). Therefore, when one receptor subtype is blocked, the other two may mediate yawning. Results from the antagonist-precipitated withdrawal study supported the latter view (Table 2). However, β-FNA failed to elicit yawning in butorphanol-dependent rats (Tbale 2). This may be due to acute κ agonist effect of β-FNA.

VI. *Ptosis*

Delta- and κ-opioid receptors are involved (Table 1). However, up to 100 nmol of NTI failed to elicit ptosis in butorphanol-dependent rats (Table 2). This indicates that δ-opioid receptors have a permissive role for the expression of ptosis, while κ-opioid receptors are the main subtype mediating this particular sign.

VII. *Ejaculation*

Antagonism of μ-opioid receptors facilitated ejaculatory behaviors in rats (Table 1). Both NTI pretreatment studies and NTI-precipitated withdrawal studies indicate the involvement of δ-opioid receptors in mediating this particular withdrawal sign (Tables 1 and 2). In contrast, pretreatment studies with nor-BNI suggest κ-opioid receptors are involved in the occurrence of ejaculations[11]. However, nor-BNI pretreatment did not affect significantly the number of butorphanol-infused rats expressing ejaculatory behaviors upon naloxone challenge (Table 1). These results indicate that κ-opioid receptors facilitate ejaculatory behaviors initiated spontaneously or by drugs in male rats. This is the reason that nor-BNI pretreatment (blocking κ-opioid receptors) reduced the occurrence of ejaculations elicited by naloxone (acting on δ-opioid receptors to initiate ejaculations) in butorphanol-infused rats, but the number of rats expressing this particular behavior was not affected by such pretreatment. On the other hand, nor-BNI elicited ejaculations in butorphanol-dependent rats (Table 2). These results indicate that antagonism of κ-opioid receptors unleashes compensatory mechanisms, e.g., increases in neurotransmitter(s) release, for effects of butorphanol infusion on κ-opioid receptors. These compensatory mechanisms then mediate increases in ejaculations in butorphanol-dependent rats.

VIII. *Urination*

Increases in urination is mediated mainly by μ-opioid receptors in butorphanol-dependent rats undergoing withdrawal (Table 1). However, β-FNA failed to elicit urination in butorphanol-dependent rats, this may be due to the acute κ-agonist effect of β-FNA (Table 2). At the dose of 100 nmol, NTI increased urination significantly in butorphanol-dependent rats (Table 2). This may indicate that NTI interacts with both δ- and μ-opioid receptors at this high concentration, since at lower doses, NTI had no significant effect (Table 2).

IX. *Diarrhea*

Central μ-, δ-, and κ-opioid receptors are involved (Table 1). However, icv selective antagonists failed to elicit diarrhea in butorphanol-dependent rats (Table 2). About 40% of butorphanol-infused rats showed diarrhea when challenged by sc naloxone indicating the involvement of peripheral opioid receptors in mediating diarrhea, i. e., antagonism of central opioid receptors alone was not sufficient to elicit diarrhea in butorphanol-dependent rats[15].

X. *Weight Loss*

Mu-, δ-, and κ-opioid receptors are involved (Table 1). However, icv selective antagonists failed to elicit weight loss in butorphanol-dependent rats (Table 2). At the same time, icv antagonists failed to elicit urination and diarrhea (Table 2). Both urination and diarrhea may have contributed to weight loss, thus weight loss was not evident in butorphanol-dependent rats when challenged with icv antagonists.

XI. *Rectal Temperature*

Mu-opioid receptors are involved quantitatively, while δ- and κ-opioid receptors are involved qualitatively in the expression of temperature changes in butorphanol-infused rats challenged by sc naloxone (Table 1). Mechanisms of increased rectal temperatures following icv antagonists treatment awaits further study.

BINDING CHARACTERISTICS OF OPIOID RECEPTORS

Butorphanol acted as a partial agonist at μ- and δ-opioid receptors and increased both the K_D and B_{max} of ^{3}H-DAGO and ^{3}H-DPDPE binding in frontal cortices and striata of rats (Table 3). However, butorphanol acts as a full κ-agonist to desensitize and downregulate κ-opioid receptors labeled by ^{3}H-U69,593 in frontal cortices of rats (Table 3). These results indicate that high concentrations of butorphanol may act as a full agonist at κ-opioid receptors and decrease the number of κ-opioid receptors in the rat brain. Furthermore, butorphanol acts more potently at central κ-opioid receptors than at μ- or δ-opioid receptors.

With β-FNA (12 nmol) pretreatment, the increase in B_{max} was prevented, whereas the increase in K_D was not (Table 3). These results indicate that a complex mode of interactions among antagonists, butorphanol, and opioid receptors, and the desensitization and up-regulation of μ-opioid receptors are subject to separate mechanisms of regulation, one of which is susceptible to β-FNA, while the other is not.

β-FNA, an alkylation agent, prevented the

Table 3. Changes in μ-, δ-, or κ-opioid receptor binding parameters in frontal cortices and striata of rats

Treatment	μ-receptor		δ-repeptor		κ-receptor	
	K_D	B_{max}	K_D	B_{max}	K_D	B_{max}
I. Frontal Cortices:						
Saline	1	1	1	1	1	1
Butorphanol	1.73[a]	1.19	1.53	1.44	1.5	0.55
β-FNA[b]+Buto	1.67	0.99				
NTI[c]+Buto			1.09	1.53		
Nor-BNI[b]+Buto					0.96	0.97
II. Striata:						
Saline	1	1	1	1	1	1
Butorphanol	1.72	1.58	1.43	1.64	1.58	0.91
β-FNA[b]+Buto	1.72	1				
NTI[c]+Buto			1.09	1.28		
Nor-BNI[b]+Buto					1.05	0.94

[a] Ratio of value obtained from the experimental group over that of the saline control.

[b] Doses in 12 nmol/5 μl, [c]Doses in 0.1 nmol/5 μl.

increased number of μ-opioid receptors induced by butorphanol infusion. These results suggest that butorphanol infusion increased a sub-population of μ-opioid receptors which were sensitive to β-FNA, i.e., blocking this β-FNA sensitive sub-species of μ-opioid receptor prevented increase in B_{max} by butorphanol infusion. On the other hand, μ-opioid receptors that were unalkylated by β-FNA were exposed to butorphanol and desensitized by it. This may be the reason why β-FNA pretreatment had no effect on K_D changes caused by butorphanol infusion.

The desensitization of δ-opioid receptors by butorphanol infusion was prevented by 3 injections of NTI. However, up-regulation of δ-opioid receptors was unopposed. These seemingly paradoxical phenomena can be explained by consideration of the model proposed by Rothman et al.[16].

Rothman et al.[16] suggested that ^{3}H-DADLE labels two binding sites: the low and high affinity sites. The lower affinity site is the δ-binding sites with a characteristic of an 'opioid receptor complex', in which μ-agonists non-competitively inhibit this complex through an adjacent μ-binding site. These two binding sub-sites were called δ_{cx}-and μ_{cx}-binding sites ($_{cx}$ indicating 'in the complex')[16]. The high affinity site is named δ_{ncx} for the δ-binding sites 'not in the complex'.

Our current results (Table 3) indicate that butorphanol may act as a δ agonist to desensitize δ-opioid receptors, and this process can be prevented by the NTI pretreatment; at the same time, butorphanol may also act as a partial μ agonist or μ antagonist and thus up-regulate both μ-and δ-opioid receptors through interacting μ_{cx}-and δ_{cx}-binding sites. This process is not reversed by NTI (a δ selective antagonist). Indeed, ^{3}H-DAGO binding capacity was found to be increased after three days of butorphanol infusion (Table 3). In other words, NTI competed with butorphanol for interactions with central δ-opioid receptors and thus prevented the desensitization of δ-opioid receptors by butorphanol infusion. Increases in the number of δ-opioid receptors was unopposed by NTI pretreatment. This result may be due to actions of butorphanol on μ_{cx} and δ_{cx} interacting binding sites.

Pretreatment with nor-BNI prevented actions of butorphanol infusion on κ-opioid receptor binding parameters (Table 3). It is thus postulated that nor-BNI competed with butorphanol for interactions with κ-opioid receptors and blocked effects of butorphanol upon κ-opioid receptors in the rat brain.

PERSPECTIVES

When used within the therapeutic dose range (e.g., 4 mg), butorphanol is considered to be of low abuse potential. However, when used in high doses, the dependence liability can be very grave. Teenagers have been reoprted to self-administer up to 80 mg[17]. Therefore, the problem of butorpahnol dependence is related to high dose uses. The clinical implication derived from results of the pretreatment study with antagonists in rats is that effective prevention in the development of butorphanol dependence or therapy for butorphanol addicts must target δ- and/or κ-opioid receptors.

Changes of binding characteristics of opioid receptors were associated with the induction of butorphanol dependence in rats, i.e., these changes were found in butorphanol infused rats but not in saline-infused controls (Table 3). Futhermore, pretreatment with selective antagonists blocked some actions of butorphanol on opioid receptor subtypes, e.g., up-regulation of μ-opioid receptors, desensitization of δ-opioid receptors and both down-regulation and desensitization of κ-opioid receptors, and attenuated some withdrawal signs (Table 1 and 3). These results indicate that the induction of butorphanol dependence in rats is, indeed, related to the effects of butorphanol on opioid receptors, i.e., blocking the actions of butorphanol on opioid receptors blocked the induction of butorphanol dependence.

Our current results indicate that κ-opioid

receptors in addition to μ- and δ-opioid receptors may play important roles in the development of opioid dependence.

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類鴉片受體與Butorphanol藥物依賴性

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摘　　要

Butorphanol是一種兼具有催動和拮抗類鴉片受體之藥物，當Butorphanol使用劑量在治療範圍內時係屬於一種較安全的藥劑。然而，各種不同的使用量，甚至高劑量的使用亦已經被報導。本研究係探討在butorphanol生理依賴性的灰鼠中μ,δ,和κ類鴉片受體相對參與程度。藉著對雄性Sprague-Dawley灰鼠腦室連續注射butorphanol (26 nmol/h)達72小時，可使灰鼠對butorphanol產生生理的依賴性。然而，若對灰鼠腦室分別注射不同劑量的β-funaltrexaimne (β-FNA，一種μ類鴉片受體拮抗劑，注射量分別爲12, 24,或48 nmol/5 μl)、naltrindole (NTI，一種δ類鴉片受體拮抗劑，注射量分別爲0.1, 1,或10 nmol/5 μl)或nor-binaltorphimine (nor-BNI，一種κ類鴉片受體拮抗劑，注射量分別爲12, 24,或48 nmol/5 μl)將顯著減緩灰鼠對butorphanol生理依賴性的產生。此外，若同時對灰鼠腦室注射不同劑量的NTI(24, 48,或100 nmol/5 μl)和nor-BNI(3, 10, 20, 48, 或100 nmol/5 μl)將迅速促使斷癮徵狀發生，然而，若投與β-FNA (12, 24, 48 或100 nmol/5 μl)則無法促使butorphanol生理依賴性的灰鼠產生斷癮徵狀。本結果顯示butorphanol生理依賴性的產生係butorphanol影響到腦部μ,δ,和κ類鴉片受體所導致。

鍵詞：Butorphanol, β-Funaltrexaimne, Naltrindole, Nor-binaltorphimine，生理依賴性，μ,δ,和κ類鴉片受體。