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Original Research Article

A comparative study on the dependence potential of thienorphine and buprenorphine

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ABSTRACT

Background: As part of research to discover partial opioid agonists for new treatments of opioid abuse and dependency, thienorphine, a buprenorphine analogue, was synthesised and reported to be a potent, long-acting oripavine in multiple mammalian models. Thienorphine binds non-selectively to μ-, δ-, and κ-opioid receptors, and partially stimulates μ- and/or κ-opioid receptors *in vitro*. Compared with buprenorphine, thienorphine exhibits better analgesic effects and has higher oral bioavailability. Poor oral absorption and dependence have hindered the use of buprenorphine for detoxification therapy and relapse prevention in the clinic. The addiction potential of thienorphine is unknown, and is worthy of in-depth investigation.
Methods: In the present study, we conducted a comparison of thienorphine and buprenorphine with respect to their physical and psychological dependence liabilities, using a naloxone-induced withdrawal test, a conditioned place preference test, and a self-administration experiment in rats.
Results: In contrast to chronic buprenorphine administration, we failed to observe any severe abstinence syndromes in mice or rats treated with thienorphine after naloxone challenge in a physical dependence model. Compared with the dependence potentials of buprenorphine, rats treated with chronic thienorphine did not show a place conditioning response, self-administration, or psychological dependence.
Conclusions: We demonstrated that thienorphine has a lower potential than buprenorphine for physical and psychological dependence. Our results indicate that thienorphine might be a good candidate to treat opioid addiction.

Keywords: Thienorphine, Buprenorphine, Oripavine, Opioid addiction

INTRODUCTION

Opioid abuse and dependence remain serious worldwide health problems. In the clinic, the drugs used for the treatment of opioid dependence are mainly either full opioid agonists, such as methadone, the partial opioid agonist buprenorphine, or the opioid antagonist naltrexone.[1,2,3] Among these drugs, the partial opioid receptor agonist buprenorphine has advantages over full agonist and antagonist treatments of opioid addiction. Relative to full opioid receptor agonists, buprenorphine shows acceptable effectiveness and clinical compliance and has a good safety profile, particularly with respect to lower respiratory depression and dependence.[4,5] Buprenorphine, a derivative of thebaine, is a high-affinity, low-intrinsic-activity agonist of μ-opioid receptors, and also has antagonist activity against κ-opioid receptors.[6,7] However, because of its poor oral absorption and potential for dependence, buprenorphine is restricted from widespread use as an agent for detoxification therapy and relapse prevention in the clinic.[8,9] Thus, compounds that have the effectiveness of buprenorphine, but with better

oral bioavailability and lower dependence liability, would be more useful in the treatment of opioid abuse.

Thienorphine is a new compound synthesised in our institute.[10] An analogue of buprenorphine, thienorphine is also a partial agonist of the opioid receptors.[11] Thienorphine binds potently and non-selectively to μ-, δ-, and κ-opioid receptors. Stimulation by thienorphine of the G-protein-coupled μ-opioid receptor is much more effective than its stimulation of the κ-opioid receptor, and its effect on the G-protein-coupled δ-opioid receptor is the weakest. Thienorphine reacts in the same way as buprenorphine in the activation of κ- and δ-opioid receptors, and is much more effective than buprenorphine in terms of its activation of μ-opioid receptors.[12,13] *In vivo*, thienorphine exerts a potent analgesic effect in mice in a hot plate test, and its effectiveness is less potent but more efficacious than buprenorphine.[11] The analgesia caused by thienorphine treatment has been further confirmed in rhesus monkeys using tail withdrawal tests with 50 °C water.[14] Moreover, compared with buprenorphine, thienorphine shows a similar, long-lasting anti-nociceptive effect, but a much longer antagonism of morphine-induced lethality (more than 15 days).[11] In addition, the bioavailability of thienorphine is much higher than that of buprenorphine after oral administration in mice, as assessed by a hot plate test.[11] These results demonstrate that thienorphine is a potent, long-acting partial opioid agonist with relatively high oral bioavailability, and which may be a good candidate as a new treatment for opioid dependence. Thienorphine is now in a Phase II clinical study as a new treatment for opioid dependence in China. However, many pharmacological characteristics of thienorphine remain unknown. Therefore, in the present study, the physical and psychological dependence liability of chronic thienorphine administration was determined in a naloxone-induced withdrawal test, a conditioned place preference test, and a self-administration experiment. The results were compared with results from buprenorphine treatment.

METHODS

Animals

Male Wistar rats weighing either 350-400 g or 220-240 g and Kunming (KM) mice weighing 18-22 g were supplied by the Beijing Animal Center (Beijing, China). The animals were housed in clear plastic cages under standard laboratory conditions: controlled temperature 25±1 °C, 12/12 h light/dark cycle (07:00/19:00) and free access to food and water. The animals were acclimated to the laboratory environment for 3 days before entering the study. An observer who was blinded to drug treatment conducted all of the behavioural assays. All procedures were approved by the Institutional Animal Care and Use Committee, and conformed to the NIH guidelines on the ethical use of animals. All efforts were made to minimise the number of animals used and their suffering.

Drugs

Thienorphine hydrochloride (purity >99%) and buprenorphine hydrochloride (purity >99%) were synthesised in our institute.[10] Morphine hydrochloride was purchased from Qinhai Pharmaceutical Factory (Xining, China). Naloxone was obtained from Sigma-Aldrich (St. Louis, MO, USA). Morphine, buprenorphine, and naloxone were dissolved individually in saline (0.9 % NaCl), and thienorphine was dissolved in 5% dimethyl sulfoxide (DMSO) just prior to the experiment. All drugs were injected in a volume of 2 ml/kg-subcutaneous (SC) or intraperitoneal (IP) injections.

Physical dependence experiments in mice

Mice in the thienorphine group were injected subcutaneously with thienorphine (5.0 mg/kg) 3 times per day at 08:00, 14:00, and 20:00 for 7 or 14 continuous days. Mice in the saline, morphine, or buprenorphine group received saline, morphine (24.0 mg/kg), or buprenorphine (3.6 mg/kg) subcutaneously on the same schedule. Withdrawal was precipitated 4 h later by an i.p. injection of 510.0 mg/kg naloxone. Mice were then placed inside a 25 cm length, 25 cm width, and 25 cm high transparent cylinder, and the number of jumps were observed for 15 min. The weight loss were calculated after 1 h.

Physical dependence experiments in rats

Physical dependence of opioids in rats was produced by a classical regimen, consisting of three daily injections of ascending doses of opioids. Rats were treated thrice daily (08:00, 14:00, and 20:00) for 5 days with s.c. injections of escalating doses of morphine (i.e., day 1: 10 mg/kg, day 2: 20 mg/kg, day 3: 30 mg/kg, day 4: 40 mg/kg, and day 5: 50 mg/kg per injection), saline, thienorphine (3.0 mg/kg), or buprenorphine (5.0 mg/kg). On the morning of day 6 (at 08:00), rats were injected with either 50 mg/kg morphine, 3.0 mg/kg thienorphine, 5.0 mg/kg buprenorphine, or saline. Withdrawal was precipitated 6 h later by an i.p. injection of 5.0 mg/kg naloxone. Rats were then placed inside a 100 cm high, 50 cm diameter transparent cylinder and were observed for 15 min. The following somatic symptoms of withdrawal were monitored and quantified: total number of jumps, wet-dog shakes, paw-tremor bouts, sniffs, head shakes, tooth chattering, ejaculation, chewing, and irritability. At the end of the observation period, rats were removed from the observation cylinders and their weight loss during withdrawal was calculated.[15,16]

Conditioned place preference (CPP) experiments in rats

The apparatus for CPP training and testing consisted of five identical, three-chamber polyvinyl chloride (PVC) boxes. Two large-sided chambers (30.0 cm long × 30.0 cm wide × 50.0 cm high) were separated by a smaller chamber (30.0 cm long × 12.0 cm wide × 52.0 cm high, with a smooth PVC floor). The three chambers were separated using manual guillotine doors. Through a computer

interface, the time spent in each chamber was recorded by a video camera (Med Associates Inc., USA) mounted at the centre of the CPP apparatus. The camera relayed information about the rat's location to the SOF-700RA-4 software (Three compartment place preference utility, Med Associates Inc.), which was run on a PC-compatible computer in a separate room. This software can simultaneously measure the time spent in the three compartments, the distance travelled, and the number of crossings between compartments for each rat. The CPP experiment consisted of pre-conditioning, conditioning, and post-conditioning phases.[17,18]

Pre-conditioning

The pre-conditioning session was carried out on days 1 to 3. For pre-conditioning, rats were initially placed on a removable grey cylinder platform in the centre chamber, and were free to access either larger chamber through the manual guillotine doors on each side of the platform. The amount of time spent in the black or white compartment was recorded manually for 15 min. These data were used to select animals with approximately equal biases for each side. Rats with a preference for one side were excluded from further experimentation.

Conditioning

The place-conditioning session was carried out on days 4 to 9. The box was divided into two equal-sized compartments by replacing the grey cylinder platform with a sliding wall. The conditioning session was conducted twice daily, morning and afternoon, for 6 days. Rats were placed in either the black or the white compartment immediately following an SC. injection, and were left in that compartment for 45 min. In the morning session, rats were confined to one compartment after drug injection, and in the afternoon session they were confined to the opposite compartment after saline injection, and vice versa. Animals receiving saline in both sessions served as controls. Drug treatments consisted of morphine (10 mg/kg) before training, thienorphine (0.5 or 1.0 mg/kg) 30 min before training, and buprenorphine (0.5 or 1.0 mg/kg) 30 min before training.

Post-conditioning

The post-conditioning session was performed on day 10 and was identical to the pre-conditioning session. The scores for the drug-paired place were then calculated by subtracting the pre-conditioning score from the post-conditioning score. A positive score represented CPP, while a negative score represented conditioning place aversion.

Self-administration experiments in rats

Rats were anaesthetised with chloral hydrate (400 mg/kg, IP), and were implanted with indwelling venous catheters. Catheters were inserted into the right jugular vein, terminating just outside the right atrium and anchored to muscle near the point of vein entry. The distal end of the catheter was subcutaneously guided to exit above the scapulae through a Teflon shoulder harness. The harness provided a point of attachment for a spring leash connected to a single channel swivel at the opposite end. The catheter was threaded through the leash for attachment to the swivel, and the fixed end of the swivel was connected to a syringe using polyethylene tubing. Infusions were administered using a computer-controlled, motor-driven syringe pump. Infusions of saline were administered as needed to assess catheter patency. Following surgery, rats were placed in standard operant conditioning chambers and were monitored for signs of discomfort during recovery. Rats received infusions of heparinised 0.9% bacteriostatic saline (1.7 U/ml; 200 µl/30 min) via the jugular catheters for 72h after surgery. Then the self-administration procedure started.

Rats were allowed to self-administer the drug during a 4 h self-administration session under a fixed ratio-1 (FR1= 1:1) schedule of reinforcement once per day (8:30-14:30; 18:00-24:00). Once rats demonstrated independent drug-seeking behaviour, which was classified as >10 self-administrations without induction, the schedule of reinforcement was halted. If a rat failed to exhibit self-administration after 30 days of training, it was judged not to be psychologically dependent on the drug. Rats were allowed to self-administer thienorphine (0.1 or 0.5 mg/kg/ infusion) or buprenorphine (0.1 or 0.5 mg/kg/infusion), as previously described, in an alternating training schedule. The experiment lasted 34 days including the first 10-day stage of 0.1 mg/kg/infusion, the second 14-day stage of 0.5 mg/kg/infusion, and the final 10-day stage of 0.1 mg/kg/infusion.

Statistical analysis

Data are expressed as the mean±standard error of the mean (SEM). Statistical analyses to determine significant differences between two groups were performed using Student's t test, while analyses between multiple groups were performed using one-way ANOVA, followed by Dunnett's test. For the self-administration test, two-way ANOVA (dose × time) was used, followed by Bonferroni *post-hoc* tests for comparisons between different groups. Null hypotheses were rejected when $p<0.05$.

RESULTS

Physical dependence experiments in mice

Mice were divided into four groups and were treated thrice daily for 7 or 14 days with subcutaneous (SC) injections of morphine, buprenorphine, thienorphine, or saline. The doses of 5.0 mg/kg thienorphine, 24.0 mg/kg of morphine, and 3.6 mg/kg of buprenorphine were the equivalent maximum analgesic doses in mice.

Table 1: Numbers of jumps and weight loss induced by naloxone in mice.

Group	Dosing time (day)	Numbers of jumps		Weight loss (g)
		%	N	
Saline	Tid·7 d	20	0.5±1.1	0.7±0.6
Morphine	Tid·7 d	20	3.1±6.6*	0.8±0.6
Buprenorphine	Tid·7 d	10	1.4±4.4	1.0±1.0
Thienorphine	Tid·7 d	10	0.6±1.9	0.7±0.7
Saline	Tid·14d	20	2.1±3.0	0.4±0.4
Morphine	Tid·14d	100	49.5±56.0**	1.6±0.2**
Buprenorphine	Tid·14d	80	14.6±27.4*	0.8±0.2
Thienorphine	Tid·14d	0	0±0	0.5±0.2

Mice were treated with the indicated drugs for 7 or 14 days before naloxone challenge. *p<0.05, **p<0.01 versus the saline control group (n=10).

Table 2: Abstinence symptoms induced by naloxone challenge in rats.

Abstinence signs	Groups of rats treated			
	Saline	**Morphine**	**Buprenorphine**	**Thienorphine**
Jumping	0	0.3±0.4	0*	0*
Body-shake	2.5±2.5	5.8±4.4	2.1±2.7*	1.1±1.5*
Writhing	0	2.2±1.5	0.2±0.6*	0.4±1.2*
Head shaking	0.3±0.4	1.0±1.3	3.8±6.2	0.3±0.6
Standing	5.2±3.1	1.6±1.9	6.1±3.9*	9.1±5.4*
Teeth-chattering	0	13.8±9.7	4.3±2.6*	0.4±0.9*
Irritability	-	++	-	-
Blepharoptosis	-	++	+	+
Salivation	-	++	+	+
Fur Erection	-	++	-	-
Diarrhea	-	+	-	-

++ Symptom present in 100% of animals; + symptom present in 50%–99% of animals; ±symptom present in 1%–49% of animals; - symptom absent. Rats were treated with the indicated drugs for 5 days before naloxone challenge. Mean±SEM, n=10 rats per group; *p<0.05 versus the morphine-injected group.

With naloxone-induced withdrawal after 7 days of continuous administration, the number of jumps by mice in the morphine group was significantly increased compared with the control group, and no withdrawal reaction was observed in any other group. Following continuous administration of the same dose for 14 days, the number of jumps in the morphine group was 49.5 times higher than that of the control group. The withdrawal response of the buprenorphine group was also higher than that of the control group; however, there was no withdrawal response in the thienorphine group. In addition, body weight loss was significantly altered in the morphine groups compared with the saline-treated mice. The detailed results are shown in (Table 1).

Physical dependence experiments in rats

Rats were divided into four groups and were treated thrice daily for 5 days with SC injections of escalating doses of morphine, or constant doses of buprenorphine, thienorphine, or saline. The dosage of 3.0 mg/kg thienorphine and 5.0 mg/kg of buprenorphine is the equivalent maximum analgesic dose in rats.

Table 3: Abstinence symptom scores and body weight loss in rats after naloxone challenge.

Group	Abstinence signs (score)	Weight loss (g)
Saline	1.1±0.7	1.4±0.6
Morphine	8.0±2.2*	12.0±2.6*
Buprenorphine	4.0±2.0	4.2±2.5
Thienorphine	2.2±1.3	0.4±0.6

Rats were treated thrice daily for 5 days with SC injections of escalating doses of morphine, saline, or buprenorphine (5.0 mg/kg) or thienorphine (3.0 mg/kg) for the naloxone-induced abrupt withdrawal test. Abstinence symptom scores and body weight loss were observed and recorded. Mean±SEM; n=10 rats per group; *p<0.01 versus the saline-injected group.

The treated rats then underwent the naloxone-induced withdrawal test. Rats treated with morphine exhibited severe abstinence syndromes, such as jumping, writhing, head shaking, gnawing, teeth chattering, body shaking, irritability, lacrimation, salivation, diarrhea, and creeping. Abstinence symptom scores and body weight loss of the morphine-treated rats were significantly different from those of saline-treated rats (p<0.01). However, in rats

treated with buprenorphine or thienorphine, abstinence symptoms were not as markedly altered in morphine-treated rats, and there were no statistically significant differences in abstinence symptom scores or body weight loss compared with saline-treated rats. These results demonstrate that physical dependency of morphine could be detected in rats, but that thienorphine and buprenorphine treatment did not induce physical dependence symptoms. The abnormal behaviours observed in each group of rats after naloxone challenge are summarised in (Table 2), while abstinence symptom scores and body weight loss are shown in (Table 3).

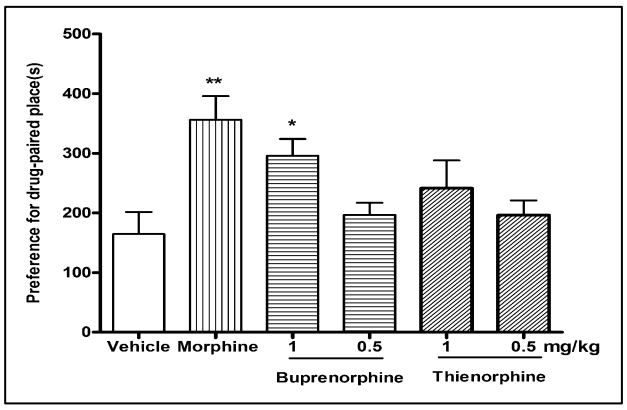

Figure 1: Conditioned place preference produced by drugs given orally in rats. Groups of rats were subcutaneously administered thienorphine (0.5/1.0 mg/kg), morphine (10 mg/kg), buprenorphine (0.5/1.0 mg/kg), or vehicle, and were placed in the conditioned place preference box for place conditioning. Each column represents the mean±standard error of the mean (n=10 rats per group); $^{*}p<0.05$, $^{**}p<0.01$ versus the vehicle-injected group.

Effect of thienorphine or buprenorphine on conditioned place preference (CPP)

Groups of rats were subcutaneously administered thienorphine (0.5 or 1.0 mg/kg), morphine (10 mg/kg), buprenorphine (0.5 or 1.0 mg/kg), or saline and were subjected to place conditioning. Morphine was used as a positive control to determine the success of the animal model. After 1 week of training, morphine significantly increased the time spent in the drug-paired place compared with that of the saline group ($p<0.01$), suggesting that morphine can strikingly induce CPP in rats. Rats administered buprenorphine at 1.0 mg/kg spent more time in the drug-paired place than the saline group ($p<0.05$), but 0.5 mg/kg buprenorphine had no effect on time spent in the drug-paired place. This demonstrates that buprenorphine has the potential to induce CPP in rats, but the effect depends on the dose. However, compared with saline treatment, thienorphine did not affect the baseline place conditioning response at doses of 0.5 or 1.0 mg/kg (Figure 1). Overall, these findings indicate that the potential for psychological dependence of thienorphine is lower than that of buprenorphine.

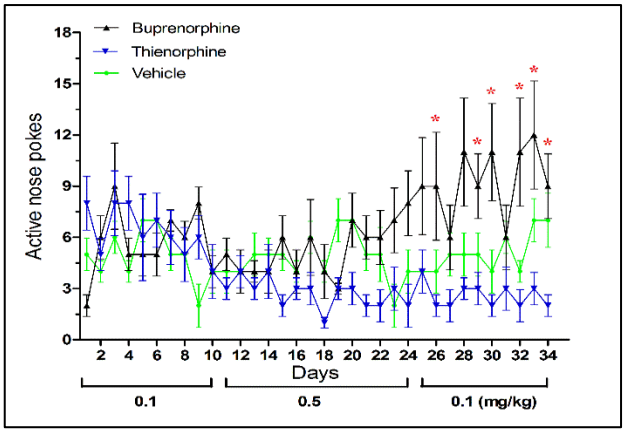

Figure 2: Effect of different doses of drugs on self-administration. Groups of rats were intravenously administered thienorphine sulfate (0.05, 0.08, 1 mg·kg-1/injection), buprenorphine (20 mg/kg), or vehicle. Groups were tested by two-way ANOVA for overall statistical differences, followed by Bonferroni post-hoc tests for individual comparisons (*p<0.05, buprenorphine vs. thienorphine). Each plotted value represents the mean±standard error of the mean (n=6 rats per group).

DISCUSSION

Thienorphine, a new compound, is a non-selective opioid receptor partial agonist and has its own pharmacological characteristics, with potent and long-acting effects and a relatively high oral bioavailability.[11-19] In the present study, we chose the equivalence dose for analgesia of thienorphine and buprenorphine. Our results indicated that, in contrast to buprenorphine, thienorphine did not induce physical and psychological dependence in rats after chronic administration, suggesting that thienorphine has a lower dependency liability than that of buprenorphine.

In this study, we applied a physical dependence model, a CPP paradigm, and a self-administration experiment to study the dependence properties of thienorphine.[19] In physical dependence experiments, equivalent aximum analgesic dose (hot plate test) in mice (5.0 mg/kg of thienorphine and 3.6 mg/kg of buprenorphine) or rat (3.0 mg/kg of thienorphine and 5.0 mg/kg of buprenorphine) was chosen. We did not observe severe abstinence syndromes in rats treated with thienorphine or buprenorphine after naloxone challenge injection in the physical dependence model. For buprenorphine, this result is in agreement with a previous study in monkeys that received chronic buprenorphine treatment for 1 month, and showed no signs of abstinence upon naloxone challenge or after abrupt withdrawal.[20] In our CPP paradigm study, rats displayed significant morphine-induced CPP, in agreement with previous data.[21] However, with the same equivalent analgesic dose (0.5 or 1.0 mg/kg of thienorphine and buprenorphine), thienorphine did not affect the baseline place conditioning response and rats failed to exhibit any CPP at two doses, while rats treated

with 1.0 mg/kg buprenorphine exhibited significantly increased CPP. In the self-administration experiment, buprenorphine induced self-administration and had potential to cause psychological dependence. However, rats treated with thienorphine failed to exhibit self-administration in the same experimental schedule. We can therefore conclude that, although thienorphine is an opioid receptor partial agonist that acts on opiate receptors in a similar way to morphine, its effects on the CPP paradigm and self-administration experiment in rats are different from the effects of morphine and buprenorphine; compared with buprenorphine, thienorphine had a lower potential for physical and psychological dependence.

There are a number of potential explanations for the lower physical and psychological dependence of thienorphine. As a typical opioid agonist, thienorphine demonstrates relatively high binding affinity to three opioid receptors, inhibiting the binding of [^{3}H] diprenorphine to μ-, δ-, and κ-opioid receptors with a K_i of 0.22±0.07 nM, 0.69±0.03 nM, and 0.14±0.06 nM, respectively.

Buprenorphine acts in a similar manner and shows no binding affinity selectivity for these three opioid receptors.[14] Nevertheless, thienorphine demonstrated a two-phase dissociation in previous studies: its dissociation to μ- and κ-opioid receptors was relatively slow. Its slow dissociation with μ- and κ-opioid receptors may therefore be a major mechanism of action in its long-lasting anti-morphine effects for 15 days. One explanation is that thienorphine may be redistributed and stored in fat tissue because of its high liposolubility and then released slowly to maintain the effective drug concentration.[11] In addition, thienorphine behaves differently in terms of κ-opioid receptor stimulation efficacy compared with buprenorphine. As a mixed partial opioid agonist, thienorphine effectively activated μ-opioid receptors and produced a maximal stimulation of 86% of κ-opioid receptors (U50488 served as the control) in a previous study.[13] Buprenorphine can also activate μ-opioid receptors, but simultaneously produces an inhibitory effect on κ-opioid receptors.[12]

Previous experiments have demonstrated that κ-opioid receptor agonists can alleviate somatic dependence triggered by μ-opioid receptor stimulation.[22,23] Compared with the possible inhibition of κ-opioid receptors by buprenorphine, thienorphine may activate κ-opioid receptors and thus reduce the symptoms of μ-opioid-receptor-stimulated opioid withdraw. This may help to explain why thienorphine did not demonstrate physical and psychological dependence liability in our study.

Several neurotransmitter systems, including the noradrenergic and dopaminergic systems, are also thought to participate in opioid dependence and withdrawal. Locus coeruleus neurons greatly increase the release of norepinephrine during naloxone-precipitated morphine withdrawal, and this increased activity correlates temporally with withdrawal behaviour at the cellular level.[24] The circuits involved in drug addiction, in the nucleus accumbens and striatum, are innervated by dopaminergic projections; modifications in these projections mediate many of the adaptations involved in drug addiction.[25]

Data that we have published previously indicate that acute or chronic thienorphine treatment with the naloxone challenge has no influence on the levels of norepinephrine in the locus coeruleus of rats, and that chronic thienorphine administration exerts no impact on dopamine levels in the nucleus accumbens or striatum.[26] Previous research demonstrated that buprenorphine treatment can progressively elevate extracellular dopamine levels in the nucleus accumbens.[27] In contrast, with repeated thienorphine treatments, there is a significant increase in the levels of monoamine oxidase and dopamine metabolites (e.g., 3,4-dihydroxyphenylacetic acid and homovanillic acid) in the nucleus accumbens and striatum.

Monoamine oxidase is a flavin adenine dinucleotide-containing enzyme that participates in the regulation of dopamine, noradrenaline, and other neurotransmitters in the central nervous system.[28] In previous research, we found that repeated administration of thienorphine significantly elevated monoamine oxidase activity in the striatum. This increased monoamine oxidase activity might accelerate the metabolism of dopamine and fail to induce the repeated rewarding effect. These findings may therefore help to explain the neurochemical mechanisms of the low dependence that thienorphine demonstrated in the current study.

CONCLUSION

In conclusion, the present study confirms that repeated thienorphine administration fails to produce CPP and self-administration and abstinence syndromes in the naloxone-induced withdrawal test, suggesting a low physical and psychological dependence of thienorphine. Although further efforts are required to discover the possible mechanisms of these effects, and to investigate the pharmacological characteristics of this compound based on the current mechanism of opioid dependence, thienorphine is a promising candidate to be developed as a new treatment for opioid dependency.

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