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Recent Development in Studies of Tetrahydroprotoberberines: Mechanism in Antinociception and Drug Addiction

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Abstract The tetrahydroprotoberberines (THPBs) are compounds isolated from Chinese herbs that possess a unique pharmacological profile as D2 dopamine receptor antagonists and D1 receptor agonists. *l*-Tetrahydropalmatine (*l*-THP) and *l*-stepholidine (SPD), members of the THPB family, were shown to have potential clinical use in the treatment of pain. However, their mechanism of action is not clear. In the past decades, Chinese scientists have made a great deal of effort to explore the mechanisms by which the THPBs and its analogues elicit antinociception and their potential utility in treating drug abuse. It is now clear that the antinociception produced by *l*-THP is related to inhibition of D_2 dopamine receptors. The present review focuses on the recent progress made in understanding the mechanisms of *l*-THP- and *l*-SPD-mediated antinociception and the sequel of drug addiction.

Keywords Tetrahydroprotoberberines · *l*-Tetrahydropalmatine · *l*-Stepholidine · Dopamine receptor · Antinociception · Drug addiction

Abbreviations

str	Striatum
ac	Nucleus accumbens
sc	Somatosensory cortex
th	Thalamus
PAG	Periaqueductal gray
dh	Dorsal horn

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Introduction

Tetrahydroprotoberberines(THPBs), a series of alkaloids isolated from the famous Chinese analgesic medicine *Corydalis yanhusuo W T Wang*, was recently found to elicit profound effects on the dopaminergic system in the central nervous system (CNS) (Jin 1987, 2001; Xu et al. 1989). *l*-Tetrahydropalmatine (*l*-THP, Fig. 1), one of the main active ingredients of *Corydalis* (Jin 2001; Kin et al. 1964), was demonstrated to have excellent analgesic effects and has been in use in clinical practice for years in China. In the passed decades, many Chinese scientists have made a great deal of effort to explore the antinociceptive mechanism of *Corydalis* (Hu and Jin 1999a, b, 2000; Xu et al. 1982; Zhang et al. 1986). In addition to *l*-THP, *l*-stepholidine (*l*-SPD, Fig. 1), which is a THPB extracted from *Stephanie intermedi*, has attracted a great deal of attention since it displays a unique pharmacological profile toward dopamine (DA) receptors. *l*-SPD acts as a D_1 DA receptor agonist while it elicits antagonistic activity at the D_2 DA receptor (Guo et al. 1997). This compound was described to possess the highest affinity for D_1-and D_2-like DA receptors among all known THPBs. Up to date, the THPBs are the only compounds extracted from herbs with dual actions on D_1 and D_2 DA receptors. This unique pharmacological profile makes them not only useful tools in studies of DA receptors and dopaminergic functions, but also as potential candidates for drug discovery targeted at neuropsychiatric disorders (Huang et al. 1992; Jin et al. 1992; Jin and Sun 1995; Jin et al. 2002). In the present review, we will focus on recent progress made with regard to the mechanism of action of THPBs (*l*-THP and *l*-SPD) induced analgesia and their potential role in treating drug addiction.

The Antinociceptive Action of *l*-THP and its Analogues

Dopaminergic Systems in Regulating Nociception

The importance of the central dopaminergic systems in regulating nociception has been well documented. For instance, administration of the dopamine precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), or DA reuptake blockers were shown to elicit antinociception. In addition, some DA receptor antagonists (Bittencourt and Takahashi 1997; Gilbert and Franklin 2001; Pelissier et al. 2006; Shimizu et al. 2004; Zarrindast et al. 1999) have also been described to produce nociception; although other studies have reported either no effect or hyperalgesia with DA receptor agents

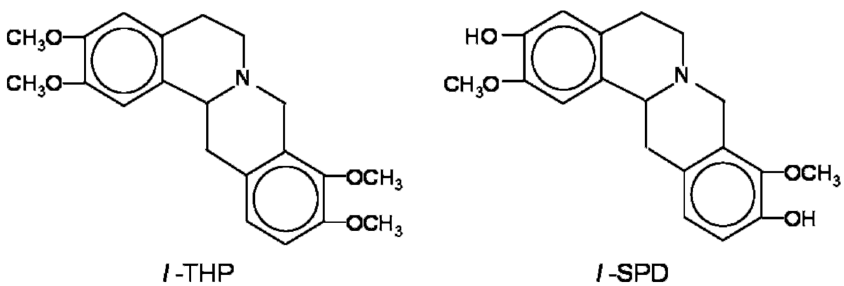

Fig. 1 The chemical structures of *l*-THP and *l*-SPD. *l*-THP and *l*-SPD belong to tetrahydroprotoberberines (THPBs), sharing the common structure of isoquinoline ring

(Malhotra et al. 2000; Michael et al. 1998). Distinct DA receptors appear to differentially modulate nociception (Frussa-Filho et al. 1996; Magnusson and Fisher 2000; Roane et al. 1998; Taylor et al. 2003).

Antinociceptive Effect of *l*-THP is Mediated via Antagonism of D_2 DA Receptors

Early efforts aimed at exploring the antinociceptive mechanism of action of *l*-THP indicated that the drug is unlikely to have either antipyretic or narcotic effects since *l*-THP did not induce a significant change in the level of prostaglandins (PGs) (Xu et al. 1982). Furthermore, pharmacological experiments demonstrated that *l*-THP exhibited no affinity for the opiate receptors (Zhang et al. 1986). However, the finding of the dual properties of *l*-THP and its analogs at DA receptors has shed light on our understanding of the mechanism of their antinociceptive actions (Huang and Jin 1992; Xu et al. 1989).

Recent studies have described that intraperitoneal injections of the D_2 dopamine receptor antagonist, spiperone produced a dose-dependent antinociceptive effect in the tail-flick test; and *l*-THP mimicked the effect of spiperone. However, neither SKF38393, SCH23390 nor a D_2 receptor agonist produced antinociceptive effects (Table 1), suggesting that the antagonistic activity of *l*-THP at the D_2 DA receptor is likely contributing to its antinociceptive action. This is supported by the fact that the D_2 dopamine receptor agonist, quinpirole, but not a D_1 dopamine receptor agonist, dose-dependently antagonized *l*-THP-induced antinociception (Table 1) (Hu and Jin 1999b). It is thus clear that the antinociceptive action of *l*-THP is dependent on its antagonistic effect at the D_2 dopamine receptor without directly interacting with the opioid receptors. Furthermore, intrathecal injections of the D_2 agonist, quinpirole, produced a dose-dependent antinociceptive effect. However, *l*-THP, spiperone, SKF38393 or SCH23390 produced no effect on nociception when they were administered intrathecally (Table 1) (Hu and Jin 1999b). Thus, it appears that the analgesic action of *l*-THP is mediated by blocking supraspinal D_2 receptors and not at the spinal level.

In addition, *l*-SPD, an analogue of *l*-THP, also produced a similar analgesic action in the hot-plate test (Chen et al. 1986; Zhang et al. 1986), indicating that THPBs share a common analgesic property.

Potential Molecular Mechanism

In order to understand the molecular mechanism for the analgesic action of *l*-THP, Hu et al. carried out a set of experiments to address the role of c-fos protein expression in the analgesic action of *l*-THP in an animal model of formalin-induced pain. The results indicated that *l*-THP-induced c-fos immunoreactive protein mainly in striatal and nucleus accumbens (NAc), and to a lesser extent in sensorimotor cortical neurons. This expression pattern is similar to that obtained in D_2 receptor antagonist-treated animals in the formalin- pain test. Moreover, in the formalin-pain tested animals, c-fos-positive neurons were mainly located in ascending pain afferent systems (APAS) and in the descending pain modulation system (DPMS) (Fig. 2). Following *l*-THP treatment, the number of c-fos-positive neurons in the APAS (such as dorsal horn) was increased, while a decrease in expression was noted in the DPMS (such as periaqueductal gray (PAG) (Fig. 2). This pattern suggests that an altered c-fos expression may be involved in the drug's analgesic action. It appears that *l*-THP and its analogs enhance activity in

Table 1 Effect of *l*-THP on tail-flick latency (TFL) in rats

Drugs	Dose	%change of TFL
i.p.		
D1 agonist SKF38393	2,3 mg/kg	–
D1 antagonist SCH23390	2,3 mg/kg	–
D2 agonist quinpirole	2,3 mg/kg	–
D2 antagonist spiperone	1,2,3 mg/kg	↑
NS	0.4 ml	–
l-THP	10,20,40 mg/kg	↑
Vehicle	0.4 ml	–
i.p.		
l-THP 40 mg/kg		
+quinpirole	2,3 mg/kg	⊙
+NS	0.4 ml	+
+SKF38393	2,3 mg/kg	+
+Naloxone	2,4 mg/kg	+
i.th.		
D1 agonist SKF38393	20,40 μg/kg	–
D1 antagonist SCH23390	20,40 μg/kg	–
D2 agonist quinpirole	20,30,40 μg/kg	↑
D2 antagonist spiperone	20,40 μg/kg	–
NS	10 μl	–
l-THP	100,200,300 μg/kg	–
Vehicle	10 μl	–
i.th.		
Quinpirole 40μg/kg		
+spiperone	20,30,40 μg/kg	⊙
+NS	10 μl	+
+*l*-THP	200,300 μg/kg	⊙
+Vehicle	10 μl	+
+SCH23390	20,40 μg/kg	+

Injection of D2 receptor antagonist spiperone (i.p.) dose-dependently increased TFL of rats in tail flick test. *l*-THP mimicked the effect of spiperone; Implicating that antagonistic activity to D2 DA receptor is likely contributed to antinociceptive effectiveness of *l*-THP. This was supported by the fact that only D2 agonist quinpirole dose-dependently antagonized the *l*-THP-induced antinociception. Furthermore, i.th. administration of D2 agonist quinpirole produced a significant and dose-dependent antinociception. Thus, it appears that the analgesic action of l-THP is mediated by blocking the supraspinal D2 receptors and not at spinal level

↑: significant increase of TFL; -: no change of TFL; ⊙: significant antagnistic effect; +: no antagonistic effect

brainstem DPMS neurons by blocking D_2 dopamine receptors in striatum and NAc, and subsequently inhibit inputs from peripheral pain afferent in the spinal cord (Hu and Jin 1999a).

It was found that arcuate nucleus (Ar) and habenula are the relay nuclei between striatum/NAc and DPMS, and that the β-endorphin(β-END) neurons in the Ar send a major projection to PAG as demonstrated by horseradish peroxidase (HRP) retrograde tracing and immuno-histochemistry (Hu and Jin 2000). However, only the striatum/NAc- Ar -PAG pathway is involved in the analgesic action of *l*-THP, since the analgesic effect of *l*-THP disappeared after an Ar lesion.

While *l*-THP does not exhibit any binding affinity for opioid receptors, it is interesting to note that *l*-THP releases endogenous opioid peptides such as END, enkephalin (ENK) and dynorphin (DYN) in brain (Jin 2001) and END or ENK in spinal or supraspinal levels. Moreover, DYN at the level of the spinal cord is known to

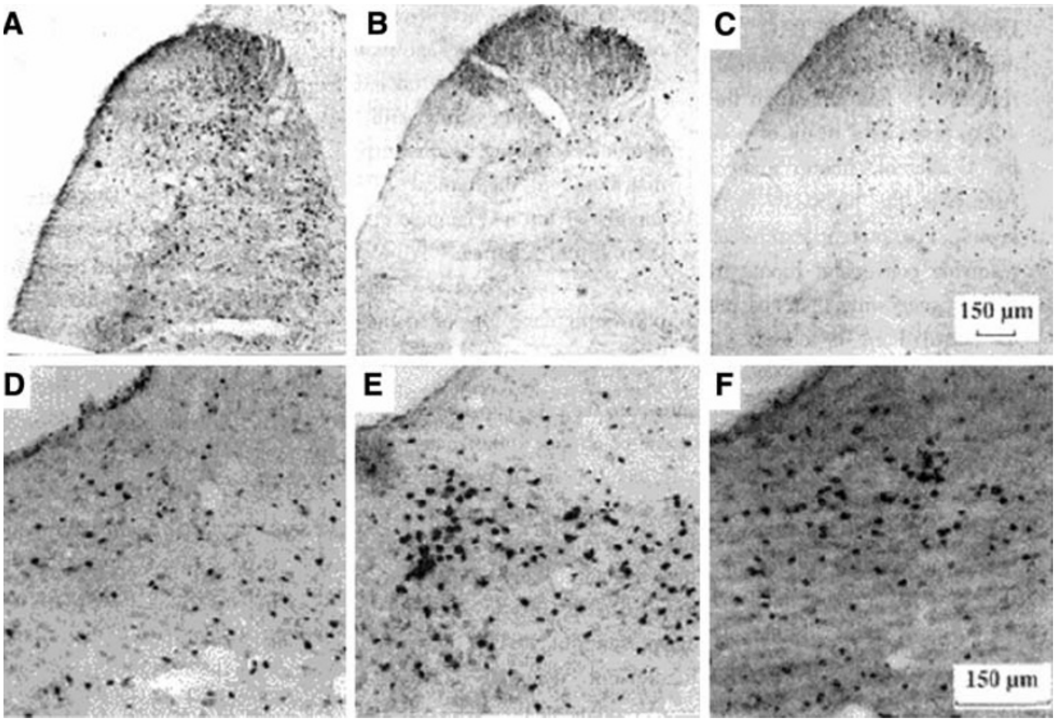

Fig. 2 Effect of *l*-THP on brain c-fos expression induced by formalin. Rats with formalin-induced pain (10 min of formalin stimuli) were administrated *i.p.* 60 mg/kg of *dl*-THP or *l*-THP for 2 h. After perfusion, immunohistochemistry was then performed in spinal cord or brain sections with anti-c-fos antibody. A–C: dorsal horn; D–F: PAG. *left*): formalin-pain; *middle*): formalin-pain+*dl*-THP; *right*): formalin-pain +*l*-THP

be associated with the antinociceptive effects of analgesic drugs (Herz and Millan 1990; Yoshimura and North 1983). Thus, it appears that endogenous opioid peptides, may at least in part, contribute to the antinociceptive action of *l*-THP. Yet, *l*-THP elicits neither physical nor psychological dependence (Jin 2001; Zhang et al. 1986).

In summary, *l*-THP and its analogues are potent antinociceptive agents and this action is mediated through blockade of D_2 dopamine receptors. Furthermore, the striatum/NAc- Ar- PAG pathway appears to be the main pathway that mediates this action of *l*-THP (Fig. 3).

l-SPD and Drug Addiction

Addiction is a chronic, relapsing brain disease characterized by persistent and uncontrolled drug seeking behavior despite negative consequence (Adinoff 2004; Leshner 1997; Pierce and Kumaresan 2006). It is believed that mesolimbic DA system may be the principal anatomical circuit that is responsible for the reward effects produced by drugs such as cocaine (Adinoff 2004; McBride et al. 1999; Pierce and Kumaresan 2006; Wise 1998, 2002). Although it has been demonstrated that both D1 and D2 DA receptors play an essential role in drug addiction, agents targeting dopamine receptors have rarely been found to be clinically useful (Berger et al. 1996; Haney et al. 1999; Platt et al. 2000; Warner et al. 1997). The main disadvantage of

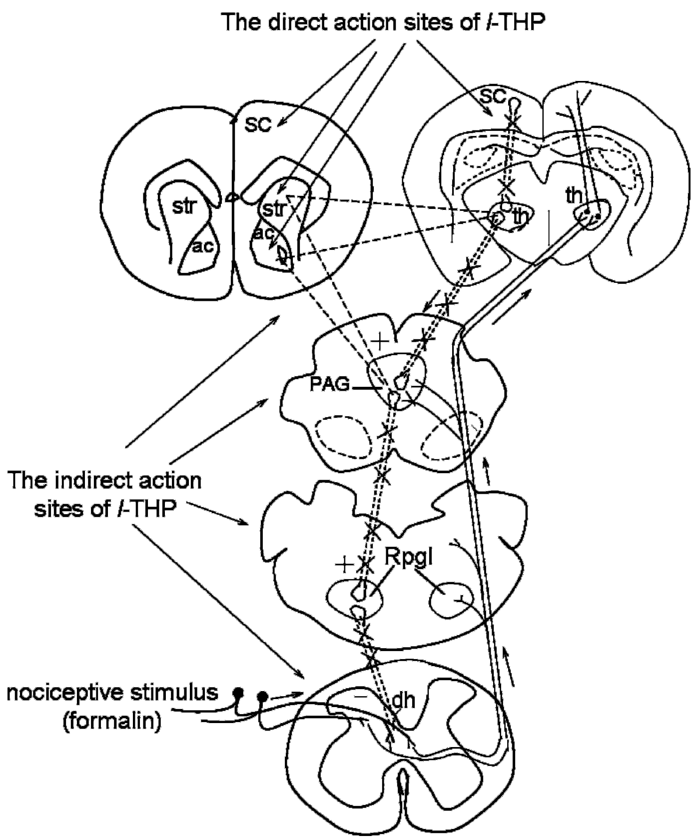

Fig. 3 Putative mechanism of analgesic effect of *l*-THP. In formalin-pain models, the c-fos-positive neurons were mainly located at ascending pain afferent system (APAS, double line) and descending pain modulation system (DPMS, double dashed line). Following the *l*-THP treatment, the number of c-fos-positive neurons in APAS (such as dorsal horn) was increased (+), but was decreased (–) in DPMS (such as PAG and Rpgl). Therefore, it appears that *l*-THP and its analogs enhanced the activity of brainstem DPMS by the blockade of D_2 receptors in the striatum and NAc, and sequentially inhibited the inputs of peripheral pain afferent information at spinal level through PAG-Rpgl-spinal cord dorsal horn pathway

specific D_1 receptor agonists as potential therapeutic agents is their potential reinforcing and abuse potential (Weed et al. 1997), whereas D_2 receptor antagonists are frequently accompanied with severe adverse extrapyramidal motor effects (Coffin et al. 1989; Grech et al. 1996). It should be noted that some partial agonists of the DA receptors were found to be of potential use in treating psychostimulants abuse (Pulvirenti and Koob 1994; Spealman et al. 1997).

l-SPD possesses dual actions on brain DA receptors eliciting partial D_1 receptor agonistic activity while antagonising D_2 dopamine receptors (Jin et al. 2002; Zou et al. 1997). The potential role of *l*-SPD in the treatment of drug abuse has recently received some attention, since theoretically, an agent with partial D_1 receptor agonistic and D_2 antagonistic properties may reduce drug abuse liability with diminished potential to induce extrapyramidal motor deficits (Jin et al. 2002). Interestingly, a preliminary clinical trial conducted in China has shown that *l*-SPD alleviates the protracted withdrawal syndrome that follows opioid abuse, and attenuates craving for addictive drugs, thus, implicating *l*-SPD as a potential candidate for the treatment of drug abuse.

In support of this possibility, a recent study in animals showed that *l*-SPD inhibits acquisition, maintenance, and re-acquisition of morphine conditioned place preference (CPP) (Wang et al. 2007). This is also in agreement with an earlier study, which showed that *l*-12-chloroscoulerine, a modified *l*-SPD compound that exhibits the dual properties of D_1 dopamine receptor agonist and D_2 receptor antagonist suppressed acquisition of morphine-induced CPP, an action that appears to be mediated via blockade of D_2 dopamine receptors (Liu et al. 2003). We have recently found that *l*-SPD inhibits amphetamine-induced DA neuron firing in the VTA (unpublished observation).

As mentioned above, *l*-THP was also found to increase the synthesis and release of endogenous opioid peptides (END, ENK and DYN) in CNS (Jin 2001)- an action which may contribute to the anti-dependence potential of drugs of abuse. Supporting this possibility, a recent clinical trial conducted in heroin addicts in China found that, *l*-THP significantly reduced drug craving and withdrawal syndromes during treatment and resulting in a three-fold higher abstinent rate compared to placebo controls, when assessed 3 months after subjects were discharged (Yang et al. 2006). In addition, a recent report indicated that *l*-THP attenuated cocaine self-administration and cocaine-induced reinstatement in rats, suggesting that *l*-THP has potential role in the treatment of cocaine addiction (Mantsch et al. 2007).

In summary, clinical trial and animal studies demonstrated that THPBs including *l*-SPD and *l*-THP are potential candidates for the treatment of drug abuse. The underlying mechanism may involve THPBs-stimulated the synthesis and release of endogenous opioid peptides.

Conclusion Remark

Considering the existing evidence, *l*-SPD, with its dual properties toward the D_1 and D_2 DA receptors, appears to lower liability for dependence to psychostimulants, while at the same time also reducing the likelihood of producing extrapyramidal motor deficits that exists with other D_2 dopamine receptor antagonists. Although many questions regarding the mechanism of *l*-SPD, *l*-THP and its analogues remain to be addressed, it appears that agents with dual actions toward DA receptors may represent a new and potent drug class for the treatment of pain and for use in reducing the addictive potential of drugs of abuse.

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