

2-1-2012

L-Tetrahydropalamatine: A Potential New Medication for the Treatment of Cocaine Addiction

Jia Bei Wang
University of Maryland - Baltimore

John R. Mantsch
Marquette University, john.mantsch@marquette.edu

L-Tetrahydropalamatine: A Potential New Medication for the Treatment of Cocaine Addiction

Jia Bei Wang

*School of Pharmacy University of Maryland Baltimore
Baltimore, MD*

John R. Mantsch

*Department of Biomedical Sciences Marquette University
Milwaukee, WI*

Abstract: Levo-tetrahydropalamatine (*l*-THP) is an active constituent of herbal preparations containing plant species of the genera *Stephania* and *Corydalis* and has been approved and used in China for a number of clinical indications under the drug name Rotundine. The pharmacological profile of *l*-THP, which includes antagonism of dopamine D1 and D2 receptors and actions at dopamine D3, alpha adrenergic and serotonin receptors, suggests that it may have utility for treating cocaine addiction. In this review, we provide an overview of the pharmacological properties of *l*-THP and the evidence supporting its development as an anti-addiction medication. The results of preclinical work demonstrating that *l*-THP attenuates cocaine's reinforcing/rewarding effects and reinstatement in rat models of cocaine relapse are summarized, and the outcomes of studies demonstrating efficacy in human addicts are described. Finally, an overview of the safety profile of *l*-THP is provided and challenges associated with FDA approval of *l*-THP are discussed.

Introduction

Despite intense drug development efforts, the treatment of cocaine addiction persists as an unmet medical need for which there is no currently available FDA-approved medication. The impact of cocaine addiction on society is tremendous, with costs likely in the tens of billions of dollars [1]. While sizable, the monetary cost of cocaine addiction is overshadowed by the enormous toll that it takes on the individual, family, and community. The complexity of cocaine's neuropharmacological actions (as a monoamine uptake blocker, cocaine acutely promotes the actions of dopamine, norepinephrine and serotonin leading to widespread effects in the brain) and the multi-faceted nature of addiction make treatment a significant challenge. Current treatment strategies consist primarily of cognitive/behavioral-based interventions and have limited efficacy. It is generally recognized that any significant therapeutic advances will likely stem from the identification and/or development of medications that target the neuropathological consequences of long-term cocaine abuse.

Traditionally, drug development approaches aimed at treating cocaine addiction have been based on the ability of candidate compounds to attenuate the subjective or positive reinforcing/rewarding effects of cocaine. However, while mitigating these effects of cocaine may curb its use, it has become clear that a critical attribute of any effective treatment will be its ability to prevent the sudden onset of drug craving and resultant relapse that emerges, often unpredictably, even after extended periods of abstinence from drug use. Since it appears that the neurobiological processes that underlie craving and relapse are largely distinct from those that mediate cocaine's reinforcing/subjective effects, it can be argued that optimal treatment may require a "cocktail approach" involving multi-drug therapy or medications with pharmacological profiles that include actions at multiple receptor targets.

Pharmacology of *L*-Tetrahydropalmatine

Drug Properties

Tetrahydropalmatine (THP; C₂₁H₂₅NO₄; Chemical name: (13aS)-2,3,9,10-tetramethoxy-6,8,13,13a-tetrahydro-5H-isoquinolino[2,1-b]isoquinoline; Molecular Weight: 355.43) is a tetrahydroprotoberberine (THPB) diisoquinoline alkaloid and a primary active constituent of the herbal plant species *Stephania rotunda* Lour (Qianjinteng) and *Corydalis ambigua* (Yanhusuo). Preparations of these plants have been used traditionally for their sedative, neuroleptic and analgesic properties [2]. In particular, the levo isomer of THP (*l*-THP; structure shown in Figure 1) appears to contribute to many of the therapeutic effects of these herbs [3]. Notably, the dextro isomer of THP has distinct pharmacological actions that include depletion of monoamines and may contribute to the toxicology profile of THP-containing preparations or racemic mixtures of the compound [4, 5]. In addition to serving as an active constituent in traditional Chinese herbal preparations, purified or synthetic *l*-THP is approved for use and available as Rotundine or Rotundin in China [6] where *l*-THP has been used as an analgesic and sedative for more than 40 years.

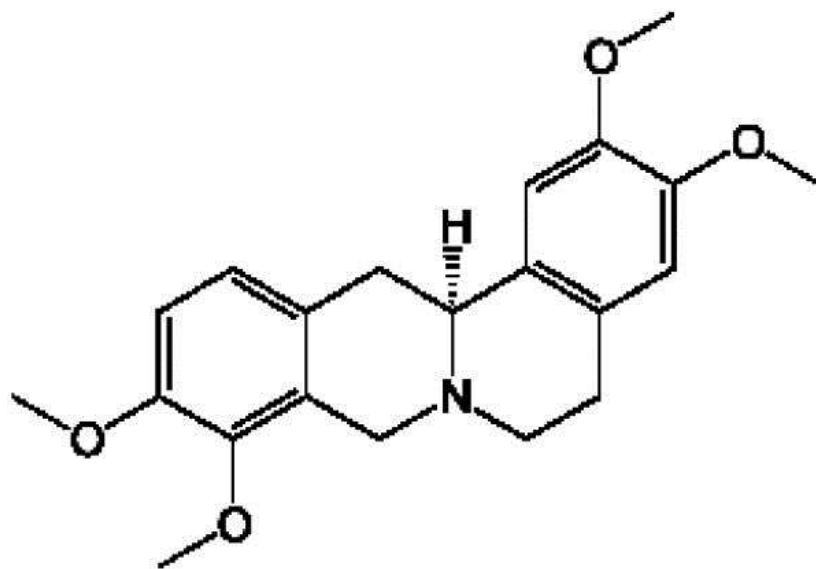


Figure 1 Chemical structure of *l*-THP

Metabolism

The metabolism of *l*-THP involves demethylation at several sites, with a number of demethylated metabolites identified in urine and feces [7, 8]. Notably, several of these metabolites can be found in *Corydalis* Yanhusuo and may themselves have actions at dopaminergic receptors and other putative *l*-THP targets [9], thereby contributing to the therapeutic effects of *l*-THP. Further investigation of the pharmacological profiles of *l*-THP metabolites will likely be important to fully understanding the mechanisms that contribute to its apparent clinical efficacy.

Pharmacological actions at D1, D2, D3 dopamine and other receptors

Primarily through the efforts of Chinese scientists, most notably led by Dr. Jin Guozhang, a researcher at the Shanghai Medical Institute, much has been learned about the pharmacological profile of *l*-THP. A large body of evidence suggests that *l*-THP binds to D1 and D2 dopamine receptors [10-12]. In contrast to other THPB derivatives, which have partial agonist effects at the D1 dopamine receptor, *l*-THP is an antagonist at both of these receptors as defined according to its minimal stimulation of cAMP production in D1 receptor-expressing HEK cells relative to dopamine ([13] and Mantsch, unpublished results) and lack of D2 receptor-mediated mitogenic effects. The K_i values for *l*-THP at D1 and D2 dopamine receptors are approximately 124 nM (D1) and 388 nM (D2), while the IC_{50} values are 166 nM (D1) and 1.4 μ M (D2), respectively (Table 1). The relatively high affinity of *l*-THP at D1 vs. D2 receptors, distinguishes it from other available dopamine receptor antagonist drugs (e.g., haloperidol). Although *l*-THP lacks high affinity for these receptors, pharmacokinetic data suggest that brain concentrations of *l*-THP that are reached following administration of clinically relevant doses are more than sufficient for occupancy [14]. *l*-THP also binds to the D3 dopamine receptor ([13] and see Table 1). Considering that the D3 receptor has been identified as a target of interest for medications aimed at preventing relapse, blockade of D3 receptors could contribute to the putative utility of *l*-THP as an anti-addiction agent [15]. However, the affinity of *l*-THP for the D3 receptor is considerably lower (1.4 μ M) than for D1 and D2 receptors, and the

IC₅₀ is close to 3.3 μM. Thus, the ability of *l*-THP to antagonize D3 receptors at clinically relevant doses is unclear. In addition to the antagonism of post-synaptic dopamine receptors, the blockade of pre-synaptic autoreceptors by *l*-THP results in increased dopamine release [16], and it has been suggested that lower affinity of *l*-THP for D2 receptors may confer some degree of autoreceptor selectivity [16, 17].

Table 1 *l*-THP binding profile at monoaminergic receptors*

Receptor	IC ₅₀ (nM ±SEM)	K _i (nM ±SEM)	Hill Slope ± SEM
Dopamine D1	166 ± 8	124 ± 6	-0.84 ± 0.003
Dopamine D2	1470 ± 270	388 ± 78	-1.14 ± 0.13
Dopamine D3	3250 ± 540	1420 ± 220	-1.09 ± 0.14
5-HT _{1A}	374 ± 69	340 ± 63	-0.86 ± 0.12
**Adrenergic, α 1	ND	ND	ND
***Adrenergic, α 2A	ND	ND	ND

*Data from NIDA sponsored drug screening report (to JBW), except noted.

** shows more than 50% inhibition non-selective binding assay at 10μM [7].

*** shows more than 50% inhibition binding assay at 10μM [7].

ND not determined; SEM standard error of mean

Along with dopamine receptors, *l*-THP has been reported to interact with a number of other receptor types, including alpha-1 adrenergic receptors, at which it functions as an antagonist [18], and gamma-aminobutyric acid (GABA)_A receptors, at which it facilitates GABA binding through positive allosteric effects [19]. Additionally, *l*-THP displays significant binding to 5-HT_{1A} and alpha-2 adrenergic receptors (Table 1). In the case of 5-HT_{1A} receptors, *l*-THP binds with a K_i of approximately 340 nM and has an IC₅₀ of approximately 370 nM, concentrations that are likely exceeded in the brain following administration of *l*-THP doses that are active in animal models.

Rationale for the Use of l-THP for the Treatment of Addiction

The contribution of dopamine to cocaine-seeking behavior is well-characterized [20-22]. As a blocker of dopamine uptake [23], cocaine increases dopaminergic activity in brain regions critical for reinforcement, such as the nucleus accumbens, resulting in stimulation

of post-synaptic dopamine receptors and modulation of behavioral output from the motive circuit (i.e., drug seeking). Interference with the activation of dopamine receptors following cocaine administration has long been thought to represent a promising approach for the management of cocaine addiction [24]. However, drugs that act as pure antagonists at D1 and D2 dopamine receptors have proven to be largely ineffective for treating cocaine addicts, due to the high incidence of side effects such as sedation and anhedonia and the ability of drug users to overcome receptor antagonism by self-administering greater amounts of cocaine [24]. Like other dopamine receptor antagonists, *l*-THP attenuates locomotor activity [13, 25], reduces response rates and breakpoints for sucrose pellet self-administration [13, 26] and increases thresholds for intracranial self-stimulation [25] – effects that are highly suggestive of sedative and anhedonic properties. However, it has been suggested that, in contrast to many other dopamine receptor antagonist drugs, there is separation between the doses at which *l*-THP produces these sedative/anhedonic effects and those that are active in preclinical addiction/abuse models, suggesting that the pharmacological properties of *l*-THP may extend beyond simple D1/D2 receptor antagonism. Validation of this claim will require additional research directly comparing *l*-THP with other dopamine receptor antagonists previously tested for the treatment of cocaine addiction (e.g., alpha-flupenthixol) and is critical for demonstration that *l*-THP does not suffer from the same shortcomings of these drugs.

Recent investigation of drugs that target dopaminergic neurotransmission has focused on agents that function as partial agonists [27, 28], interfere with the activation of D3 dopamine receptors [29], or have more complex pharmacological profiles with differential actions at multiple receptor types and locations [30, 31]). Although other THPB analogs, e.g., levo-stepholidine (*l*-SPD), have been shown to be partial agonists at D1 dopamine receptors [32] it has been demonstrated that *l*-THP has no intrinsic efficacy at D1 dopamine receptors and therefore likely functions as a D1 receptor antagonist [13]. Further, despite some indications that D3 receptor antagonism may contribute to the effects of *l*-THP in preclinical abuse models [26] the affinity of *l*-THP for D3 dopamine receptors is very low. Thus, it is possible that actions at non-dopaminergic receptors may account for the effects of *l*-THP.

In addition to blocking dopamine clearance through inhibition of the dopamine transporter, cocaine prevents uptake of both norepinephrine and serotonin, thereby augmenting noradrenergic and serotonergic neurotransmission and increasing activation of adrenergic and serotonergic receptors [33]. Considering the widespread effects of cocaine on monoaminergic neurotransmission, it should not be surprising that cocaine addiction is a complex disorder that involves actions on and dysregulation of multiple receptors, cell types, and neurobiological systems. Implicit in this understanding is the possibility that medications that target a single receptor type may not be adequate for the management of cocaine addiction. Thus, effective pharmacotherapy may require a “cocktail” approach that involves the use of more than one medication or drugs such as *l*-THP with more complex pharmacological profiles involving action at multiple receptors. An added benefit of such an approach is that it may permit additive therapeutic effects while reducing the risk for unwanted side effects by minimizing occupation of any single receptor.

Although there has been much focus on dopamine receptors as targets for the development of addiction medications, there is considerable evidence that serotonin [34] and norepinephrine [35] can also contribute to cocaine's effects and influence cocaine-seeking behavior. For this reason, the ability of *l*-THP to antagonize cocaine-induced activation of serotonergic (5-HT), adrenergic *and* dopaminergic receptors may distinguish it from agents with a more limited range of action. In particular, secondary effects at alpha-1 and 5-HT_{1A} receptors, or agonist effects at alpha-2 receptors could contribute to the beneficial effects of *l*-THP against drug relapse. Alpha-1 adrenergic [363 Zhang, X.Y. 2005] and 5-HT_{1A} [37] receptor antagonists and alpha-2 agonists [38] have been previously reported to attenuate cocaine seeking in rats. Secondary actions of *l*-THP at 5-HT_{1A} and alpha adrenergic receptors could also minimize the extrapyramidal effects associated with dopamine receptor antagonism by *l*-THP [39-41]. The contribution of these mechanisms to the effects of *l*-THP will require further investigation. Despite its use as an analgesic agent, no interaction of *l*-THP with opioid receptors has been documented, and its analgesic effects are naloxone-independent [42].

Preclinical Studies Of *L*-Thp

The idea that *l*-THP may represent an effective medication for treating drug addiction is well-supported by the preclinical animal literature (see [Table 2](#) for an overview). A variety of experimental approaches are available for examining different aspects of abuse/addiction using rodents. Importantly, different assays can be used to assess the ability of potential treatments to attenuate the positive reinforcing/rewarding effects of cocaine and cocaine relapse. One potential issue for interpretation of the actions of *l*-THP in behavioral assays, and a concern about its clinical use, is that the drug has known sedative effects that can interfere with behaviors required for assessment of drug-seeking behavior. In fact, *l*-THP has been widely used in China for its sedative properties. Accordingly, it has been found that *l*-THP produces dose-dependent reductions in locomotor activity and operant responding for non-drug reinforcers in rats [[13](#), [26](#), [43](#)]. For this reason, a critical goal of preclinical testing has been to separate non-specific motor suppressive effects of *l*-THP from reductions in drug responsiveness and drug-seeking behavior.

[Table 2](#)

Effects of *l*-THP in preclinical behavioral models of cocaine abuse/addiction

Preclinical Model	Effects of <i>l</i> -THP	References
FR Cocaine Self-Administration	Rightward/downward shift in dose-response curve for self-administration	[14][26]
PR Cocaine Self-Administration	Decreased breakpoints	[26][27]
Drug Discrimination	Rightward shift in dose-response curve	[27]
Intracranial Self-Stimulation	Attenuation of cocaine-induced decreases in reward threshold	[26]
Cocaine-Induced Reinstatement	Decreased reinstatement in response to an intraperitoneal cocaine injection	[14][44]
Cue-Induced Reinstatement	Decreased reinstatement during response-contingent presentation of cocaine-associated cues	[44]
Stress-Induced Reinstatement	Decreased reinstatement in response to footshock stress	[44]

Actions of l-THP on Cocaine Reward/Reinforcement

The study of the acute positive reinforcing effects of drugs has relied heavily on preclinical drug self-administration procedures in which rats are surgically implanted with intravenous catheters and required to press a lever (or engage in a similar task) in order to receive drug infusions. The validity of such procedures arises from the observation that, with few exceptions, drugs that are abused by humans are also self-administered by rats, while drugs that are not abused by people (including *l*-THP) are not. Compounds that alter drug self-administration by rats often do so by reducing the positive reinforcing/rewarding effects of drugs and therefore may curb drug use by human addicts [44][45]. The most basic self-administration approach involves the use of fixed ratio (FR) schedules under which drug is delivered every time a rat presses a lever a fixed number of times. Two studies by different research groups have demonstrated that, in rats trained to self-administer cocaine under FR schedules, *l*-THP alters self-administration in a manner that is consistent with a reduction in the reinforcing effects of cocaine [13, 25]. Mantsch and colleagues reported that, when the effects of *l*-THP were tested across a range of cocaine doses using an approach that involved variation of cocaine doses during 30-min components within a single self-administration session, the dose-response curve for self-administration (0.031 – 1 mg/kg/infusion) was shifted downward and to the right by *l*-THP [13]. In the second study by Xi and colleagues [25], it was found that, when rats were tested for self-administration at a single higher cocaine dose (0.5 mg/kg/infusion) in the absence of prior variation in the self-administered cocaine dose, *l*-THP dose-dependently increased responding, a behavioral pattern that is associated with a reduction in the reinforcing effects of cocaine when observed under these conditions. Notably, in these studies, *l*-THP was effective at doses that failed to alter concurrently-measured [13] or independently-measured [25] food-reinforced responding under identical schedules of reinforcement.

A second protocol for examining treatment effects on positive reinforcement by cocaine involves the use of progressive ratio (PR) schedules of cocaine self-administration, under which the response requirement for cocaine delivery progressively increases with each

successive cocaine infusion. Using this approach, the ability of a medication to reduce cocaine's reinforcing efficacy and/or the motivation to acquire cocaine can be assessed according to changes in the breakpoint for self-administration, defined as the maximal amount of work (i.e., lever presses or nose pokes) that the subject will perform in order to receive the drug [46][47]. Increases and decreases in breakpoints (i.e., a greater or lesser amount of work performed to receive the drug) are interpreted as elevations and reductions in reinforcing efficacy and/or motivation to take the drug, respectively. It has been suggested that PR schedules offer an advantage over FR schedules for the determination of changes in reinforcing efficacy, due to reduced susceptibility to the rate-decreasing (e.g., sedative) effects of drugs and relative ease of interpretation of findings. *L*-THP has been reported by two separate research groups to reduce breakpoints for cocaine self-administration in rats at doses that fail to alter PR self-administration of a food reinforcer [25, 26]. When combined with the findings from studies investigating the effects of *l*-THP on cocaine self-administration under FR schedules of reinforcement, these data suggest that *l*-THP effectively reduces the reinforcing properties of cocaine, thus potentially curbing use.

Alterations in the rewarding effects of cocaine can also be studied using an intracranial self-stimulation (ICSS) approach [48]. With this method, an electrode is implanted into the brain to permit stimulation of neural pathways subserving reward/reinforcement. Implanted rats will repeatedly press a lever in order to receive stimulation. Drugs of abuse such as cocaine will increase sensitivity of rats to stimulation, as demonstrated by a reduction in the threshold current for ICSS. *L*-THP blocks cocaine-induced decreases in ICSS thresholds at doses that alone fail to increase threshold in a manner indicative of anhedonic effects [25]. Although these findings suggest that *l*-THP does not produce anhedonic effects at doses that can mitigate cocaine's effects, it should be noted that effects on ICSS thresholds in rats with a history of cocaine self-administration have not been assessed.

Yet another common method for the examining the ability of treatments to interfere with abuse-related drug effects is the drug discrimination protocol [49]. Using this approach, rats learn to

recognize the interoceptive, subjective state (i.e., discriminative stimulus) produced by cocaine and are trained to emit distinct response patterns in the presence and absence of cocaine delivery. As is the case with the reinforcing effects of cocaine, *l*-THP blocks cocaine's discriminative stimulus effects, as observed as a rightward shift in the dose response curve for cocaine substitution for the training dose [8]. Also as is observed with the reinforcing effects of cocaine, *l*-THP attenuates cocaine discrimination at doses that fail to produce suppression of response rate [26].

Effects of l-THP in Preclinical Models of Relapse

Although the ability to competitively block cocaine's acute subjective and positive reinforcing/rewarding effects may alter use patterns, it is unlikely that this, by itself, will lead to sustained drug abstinence. Many addicts enter into treatment during periods of abstinence in order to prevent drug relapse, which is typically preceded by craving, or the intense desire to use a drug. A variation of the self-administration protocol, the reinstatement paradigm, can be used to study stimuli that induce drug relapse [50]. Using this approach, relapse can be examined based on the ability of stimuli to reinstate or restore extinguished drug-seeking behavior after it has been extinguished. Notably, the same stimuli that produce craving and relapse in humans (drug re-exposure, stress, and exposure to drug-associated cues) also reinstate extinguished cocaine-seeking behavior in rats [51]. Importantly, the neurobiological substrates that underlie reinstatement appear to be distinct from those that mediate the subjective and positive reinforcing/rewarding effects of cocaine. *l*-THP, administered ip [13] or orally [43] attenuates reinstatement of extinguished cocaine seeking in rats in response to a cocaine challenge, a stressful stimulus (uncontrollable electric footshock), or response-contingent exposure to a stimulus (tone and light complex) previously associated with drug delivery in rats. This attenuation was observed at *l*-THP doses that failed to alter lever-pressing for a non-drug (i.e., food) reinforcer when tested either concurrently with reinstatement or in separate groups of rats.

Clinical Use and Studies Of *L*-Thp

Pharmacokinetics of l-THP

The pharmacokinetic properties of *l*-THP are favorable for its development as an anti-addiction medication. Plasma and tissue levels of *l*-THP can be quantified using HPLC. It is well absorbed following oral administration in both rat and man [14, 52]. In rats, following oral administration of racemic THP or *l*-THP, blood levels of *l*-THP show a rapid peak within the first hour, followed by a gradual decline, resulting in a $t_{1/2}$ of approximately 5 hours [14]. The half-life for *l*-THP in man appears to be about 10 hours [53][54], permitting once daily dosing. *L*-THP also readily enters the brain [14] with peak levels within the first hour followed by stable concentrations measured in a number of brain regions, including the striatum, for the next 4-6 hrs. The effects of *l*-THP on cytochrome P450 mediated metabolism of other drugs appears to be minimal and primarily involve low affinity inhibition of CYP2D6 [55].

Clinical Uses in China

It has long been recognized that *l*-THP has therapeutic value for treating a number of CNS-related conditions. The effectiveness of *l*-THP as a non-opioid analgesic and sedative/anxiolytic agent resulted in the approval of purified *l*-THP for this indication by the Chinese SFDA (FDA equivalent) and has led to extensive investigation of the pharmacological properties of *l*-THP. The suggestion that the therapeutic effects of *l*-THP may be partly attributable to dopamine receptor antagonism [42, 56] has led to the investigation of the potential utility of *l*-THP for other disorders known to be associated with dopaminergic dysfunction, particularly drug addiction. Interest in *l*-THP as a medication for treating addiction has peaked with recent preliminary clinical trials in China that found that *l*-THP reduces drug craving and relapse [15] and promotes detoxification [16] in recovering heroin addicts.

Clinical Studies in Heroin-Dependent Populations

Although clinical trials examining the potential utility of *l*-THP for cocaine addiction have not been conducted, the results of studies testing for effectiveness in heroin-dependent populations have been promising. A pilot study testing for the effects of *l*-THP in heroin users [57] examined the efficacy of *l*-THP in reducing craving and relapse rate in 120 heroin addicts (average of 2-3 heroin uses per day for about 3 years). In this randomized, double-blind, placebo-controlled study, patients received 4 weeks of *l*-THP treatment and three months follow-up after *l*-THP treatment during which the severity of the protracted abstinence (a.k.a., post-acute) withdrawal syndrome (PAWS), as measured using a Heroin Withdrawal Scale (HWC) questionnaire, and abstinence rate, determined based on drug-positive urine tested, were assessed. The HWC questionnaire consisted of self-rating on a 5-point scale of 30 different symptoms in four different categories: mood, craving, insomnia, and somatic symptoms. The treatment group had significantly lower overall PAWS scores, with reductions in somatic symptoms and insomnia and, especially, in craving (3.5 for treatment group vs. 7.0 for placebo group) as well as a three-fold higher abstinence rate (47.8%) relative to the placebo control group (15.2%). No hepatic toxicity was reported.

A second human study [58] examined the therapeutic effect of *l*-THP combined with methadone for heroin detoxification. Sixty patients were randomly divided into two groups: one received methadone plus *l*-THP; the other received methadone only. The primary outcome measures were total amount of methadone used during detoxification and days of detoxification. The combined treatment group achieved a 96% rate of successful detoxification, compared to 73% for the methadone alone group. The combined group also used significantly less total methadone (275 mg vs. 415 mg) and needed less days for the detoxification treatment (8 days vs. 12 days).

Although the effects of *l*-THP in cocaine-addicted populations has not yet been studied, due primarily to the lack of approval for testing in the U.S., these human studies, when considered along with our preclinical studies, provide compelling evidence to support the use

of *l*-THP as an effective new medication for the treatment of drug addiction with a non-opioid mechanism and anti-craving efficacy.

Safety Profile

The availability of *l*-THP on the Chinese market since the early 1960's and its widespread use in a variety of patient populations, as well as its regulation by the Chinese SFDA, should position *l*-THP as a safe medication rather than as an unregulated and potentially dangerous botanical product. According to the Chinese pharmacopeia [6] and drug labeling, *l*-THP is safe at the recommended therapeutic dosage range (60-180 mg). At higher doses, adverse effects include sleepiness, dizziness, and nausea. Overdose can cause respiratory inhibition and, consistent with other drugs with dopamine receptor antagonist properties, extrapyramidal symptoms. There appears to be only a few reported cases of allergic reactions upon the use of *l*-THP. Despite its longstanding safety record in China, some *l*-THP containing preparations, most notably Jin Bu Huan, an adulterated herbal product, are currently banned by the FDA for human consumption in the US due to concerns about toxicity [59, 60]. However, reports of hepatitis [60, 61] and CNS depression [59] related to the *l*-THP containing preparation, Jin Bu Huan, were likely related, in part, to contamination and improper use issues common to many unregulated herbal products. Final determination of the safety of *l*-THP awaits more methodical testing of the effects of standardized doses of purified *l*-THP. Accordingly, there has been a recent push towards re-evaluation of *l*-THP by the FDA.

Future Perspective

Although the results from preclinical experiments and preliminary Chinese clinical trials suggest that *l*-THP has great potential for the treatment of cocaine addiction, there are a number of obstacles that must be overcome before *l*-THP can be considered for approved use in cocaine-dependent populations in the United States. Foremost among these are concerns about the safety of *l*-THP, which are largely secondary to issues with *l*-THP containing botanical preparations and known problems with previously evaluated dopamine antagonist drugs. In the former case, distancing the safety profile of *l*-

THP from those of unregulated botanical preparations while leveraging the large body of available evidence that has been accumulated across years of approved and regulated use of Rotundine in China is critical. Notably, while the clinical data from China provide important “proof of concept” of *l*-THP’s efficacy and indication of its safety, additional testing in man consistent with FDA standards will be essential. This will, of course, require the approval of *l*-THP as a new investigational drug by FDA. With regards to concerns about dopamine antagonist drugs that have been previously advanced as potential anti-addiction medications, further evidence to support the claim that *l*-THP is distinct from and superior to these drugs (e.g., alpha-flupenthixol) is needed. Although there are some indications that the pharmacological profile of *l*-THP is unique and positively distinguishes it from other dopamine antagonist drugs in terms of safety and efficacy, our understanding of the mechanisms of action of *l*-THP remains somewhat limited. In particular, side-by-side comparison with other dopamine antagonist drugs is needed in order to more convincingly make the case that *l*-THP does not share the shortcomings (e.g., extrapyramidal effects, sedation) that have prevented their approval as anti-addiction medications.

In the event that *l*-THP does not receive FDA approval, there is still much to be learned from its unique pharmacological mechanisms. At minimum, the demonstrated efficacy of *l*-THP in preclinical models and clinical studies suggests that the development or identification of compounds with more complex pharmacological effects that include actions at multiple monoamine receptors (not just D1 and D2 dopamine receptors) or the formulation of “drug cocktail” approaches may represent promising new strategies for the treatment of addiction. Interestingly, *l*-THP represents just one of series of naturally-occurring tetrahydroprotoberberine compounds with similar pharmacological profiles. Compounds such as *l*-SPD, which has a similar binding profile as *l*-THP but functions as a partial agonist at D1 dopamine receptors [32] may serve as provocative new platforms for development as anti-addiction medications and, along with *l*-THP, could provide starting points for targeted redesign using medicinal chemistry.

Finally, the extant data supporting the use of *l*-THP (and related compounds) for the treatment of cocaine addiction suggest potential utility for the pharmacological management of addiction to other drugs

of abuse. Indeed, clinical trials demonstrating efficacy in recovering heroin addicts [57, 58] along with studies showing efficacy in preclinical models of opiate abuse [62] suggest that *l*-THP may be effective for treating addiction to heroin. Studies examining its potential use in other addiction populations (alcohol, nicotine) are currently ongoing and should provide additional understanding about the therapeutic utility of *l*-THP in the near future.

Executive Summary

Treatment of Cocaine Addiction

- Despite its societal impact, cocaine addiction persists as a serious medical condition for which no FDA-approved medication exists.
- An ideal medication for treating addiction should attenuate cocaine's rewarding effects and at the same time reduce drug craving, thus preventing relapse.
- The multifaceted nature of cocaine addiction and its underlying neurobiology suggests that multiple-drug ("cocktail") therapy or compounds with more complex pharmacological profiles will be necessary for effective treatment.

Pharmacology of L-Tetrahydropalmatine

- The tetrahydroprotoberberine, *l*-THP, has a pharmacokinetic and pharmacological profile that may be optimal for treating cocaine addiction.
- The pharmacological profile of *l*-THP includes antagonism of dopamine D1, and D2 receptors as well as actions at dopamine D3, alpha adrenergic and serotonin receptors.

Preclinical Studies of L-THP

- *l*-THP is effective in preclinical models that examine effects on the reinforcing/rewarding/subjective effects of cocaine as well as in models of relapse.
- In these preclinical models, *l*-THP is effective at doses that fail to produce non-specific motor impairment and/or sedation.

Clinical Use and Studies Of L-THP

- L-THP has a pharmacokinetic profile that is favorable for clinical use.
- /-THP has a long-standing record of safe use in China for a number of indications under the trade-name Rotundine.
- Concerns about liver toxicity and sedation associated with the use of some /-THP containing herbal preparations in the US are likely due to poor quality and improper use of these unregulated products.
- Preliminary clinical studies investigating the effects of /-THP in human heroin addict populations have yielded promising results.
- Additional clinical examination of the efficacy of /-THP in human cocaine addict populations is needed.
- Testing in human populations in the US awaits further demonstration to the FDA that /-THP is safe for human consumption at doses that effectively manage addiction.

Acknowledgements: The authors wish to thank the National Institute of Health (NIDA grant 1DP1DA031401 to JBW and NCCAM grant AT004736 to JRM) for financial support.

References

1. Anonymous Office of National Drug Control Policy . The Economic Costs of Drug Abuse in the United States, 1992-2002. Executive Office of the President; Washington, DC: 2004. (Publication No. 207303)
2. Anonymous Yanhusuo Pharmacopoeia of the People's Republic of China. 2000;I:108-108.
3. Chu H, Jin G, Friedman E, Zhen X. Recent development in studies of tetrahydroprotoberberines: mechanism in antinociception and drug addiction. *Cellular and molecular neurobiology*. 2008;28:491-499.
4. Xu SX, Jin GZ, Yu LP, Liu GX, Lu WW, Fang SD. Brain dopamine depleted by d-tetrahydropalmatine. *Zhongguo yao li xue bao = Acta pharmacologica Sinica*. 1987;8:207-212.
5. Liu GQ, Algeri S, Garattini S. D-L-tetrahydropalmatine as monoamine depletor. *Archives Internationales de Pharmacodynamie et de Therapie*. 1982;258:39-50.
6. Anonymous Rotundine Pharmacopoeia of the People's Republic of China. 2010;II:338-339.

7. Li L, Ye M, Bi K, Guo D. Liquid chromatography-tandem mass spectrometry for the identification of L-tetrahydropalmatine metabolites in *Penicillium janthinellum* and rats. *Biomedical chromatography : BMC*. 2006;20:95-100.
8. Lai CK, Chan AY. Tetrahydropalmatine poisoning: diagnoses of nine adult overdoses based on toxicology screens by HPLC with diode-array detection and gas chromatography-mass spectrometry. *Clinical chemistry*. 1999;45:229-236.
9. Ma ZZ, Xu W, Jensen NH, Roth BL, Liu-Chen LY, Lee DY. Isoquinoline alkaloids isolated from *Corydalis yanhusuo* and their binding affinities at the dopamine D1 receptor. *Molecules (Basel, Switzerland)* 2008;13:2303-2312.
10. Jin GZ. Progress in studies of the pharmacology of l-tetrahydropalmatine and l-stepholidine. *Yao xue xue bao = Acta pharmaceutica Sinica*. 1987;22:472-480.
11. Jin GZ, Xu J, Zhang FT, Yu LP, Li JH, Wang XL. Relevance of the sedative-tranquilizing effect of l-tetrahydropalmatine to brain monoaminergic neurotransmitters. *Zhongguo yao li xue bao = Acta pharmacologica Sinica*. 1983;4:4-10.
12. Huang K, Dai GZ, Li XH, Fan Q, Cheng L, Feng YB, Xia GJ, Yao WX. Blocking L-calcium current by l-tetrahydropalmatine in single ventricular myocyte of guinea pigs. *Zhongguo yao li xue bao = Acta pharmacologica Sinica*. 1999;20:907-911.
13. Mantsch JR, Li SJ, Risinger R, Awad S, Katz E, Baker DA, Yang Z. Levo-tetrahydropalmatine attenuates cocaine self-administration and cocaine-induced reinstatement in rats. *Psychopharmacology*. 2007;192:581-591.
14. Hong Z, Fan G, Le J, Chai Y, Yin X, Wu Y. Brain pharmacokinetics and tissue distribution of tetrahydropalmatine enantiomers in rats after oral administration of the racemate. *Biopharmaceutics & drug disposition*. 2006;27:111-117.
15. Xi ZX, Gilbert J, Campos AC, Kline N, Ashby CR, Jr, Hagan JJ, Heidbreder CA, Gardner EL. Blockade of mesolimbic dopamine D3 receptors inhibits stress-induced reinstatement of cocaine-seeking in rats. *Psychopharmacology*. 2004;176:57-65.
16. Marcenac F, Jin GZ, Gonon F. Effect of l-tetrahydropalmatine on dopamine release and metabolism in the rat striatum. *Psychopharmacology*. 1986;89:89-93.
17. Jin GZ, Wang XL, Shi WX. Tetrahydroprotoberberine--a new chemical type of antagonist of dopamine receptors. *Scientia Sinica. Series B, Chemical, biological, agricultural, medical & earth sciences / Chung-kuo k'o hsueh yuan, chu pan*. 1986;29:527-534.

18. Lu ZZ, Wei X, Jin GZ, Han QD. Antagonistic effect of tetrahydroproberberine homologues on alpha 1-adrenoceptor. *Yao xue xue bao = Acta pharmaceutica Sinica*. 1996;31:652–656.
19. Halbsguth C, Meissner O, Haberlein H. Positive cooperation of protoberberine type 2 alkaloids from *Corydalis cava* on the GABA(A) binding site. *Planta Medica*. 2003;69:305–309.
20. Anderson SM, Pierce RC. Cocaine-induced alterations in dopamine receptor signaling: implications for reinforcement and reinstatement. *Pharmacology & therapeutics*. 2005;106:389–403.
21. Self DW. Regulation of drug-taking and -seeking behaviors by neuroadaptations in the mesolimbic dopamine system. *Neuropharmacology*. 2004;47(Suppl 1):242–255.
22. Volkow ND, Fowler JS, Wang GJ. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology*. 2004;47(Suppl 1):3–13.
23. Kuhar MJ, Ritz MC, Boja JW. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends in neurosciences*. 1991;14:299–302.
24. Platt DM, Rowlett JK, Spealman RD. Behavioral effects of cocaine and dopaminergic strategies for preclinical medication development. *Psychopharmacology*. 2002;163:265–282.
25. Xi ZX, Yang Z, Li SJ, Li X, Dillon C, Peng XQ, Spiller K, Gardner EL. Levo-tetrahydropalmatine inhibits cocaine's rewarding effects: experiments with self-administration and brain-stimulation reward in rats. *Neuropharmacology*. 2007;53:771–782.
26. Mantsch JR, Wisniewski S, Vranjkovic O, Peters C, Becker A, Valentine A, Li SJ, Baker DA, Yang Z. Levo-tetrahydropalmatine attenuates cocaine self-administration under a progressive-ratio schedule and cocaine discrimination in rats. *Pharmacology, biochemistry, and behavior*. 2010;97:310–316.
27. Childress AR, O'Brien CP. Dopamine receptor partial agonists could address the duality of cocaine craving. *Trends in pharmacological sciences*. 2000;21:6–9.
28. Pulvirenti L, Koob GF. Dopamine receptor agonists, partial agonists and psychostimulant addiction. *Trends in pharmacological sciences*. 1994;15:374–379.
29. Heidbreder CA, Gardner EL, Xi ZX, Thanos PK, Mugnaini M, Hagan JJ, Ashby CR., Jr. The role of central dopamine D3 receptors in drug addiction: a review of pharmacological evidence. *Brain research. Brain research reviews*. 2005;49:77–105.
30. Gorelick DA, Gardner EL, Xi ZX. Agents in development for the management of cocaine abuse. *Drugs*. 2004;64:1547–1573.

31. Vocci FJ, Acri J, Elkashef A. Medication development for addictive disorders: the state of the science. *The American Journal of Psychiatry*. 2005;162:1432–1440.
32. Jin GZ, Zhu ZT, Fu Y. (-)-Stepholidine: a potential novel antipsychotic drug with dual D1 receptor agonist and D2 receptor antagonist actions. *Trends in pharmacological sciences*. 2002;23:4–7.
33. Fleckenstein AE, Gibb JW, Hanson GR. Differential effects of stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. *European journal of pharmacology*. 2000;406:1–13.
34. Filip M, Alenina N, Bader M, Przegalinski E. Behavioral evidence for the significance of serotonergic (5-HT) receptors in cocaine addiction. *Addiction Biology*. 2010;15:227–249.
35. Weinschenker D, Schroeder JP. There and back again: a tale of norepinephrine and drug addiction. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2007;32:1433–1451.
36. Zhang ZM, Jiang B, Zheng XX. Effect of l-tetrahydropalmatine on expression of adhesion molecules induced by lipopolysaccharides in human umbilical vein endothelium cell. *Zhongguo zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica*. 2005;30:861–864.
37. Burmeister JJ, Lungren EM, Kirschner KF, Neisewander JL. Differential roles of 5-HT receptor subtypes in cue and cocaine reinstatement of cocaine-seeking behavior in rats. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2004;29:660–668.
38. Erb S, Hitchcott PK, Rajabi H, Mueller D, Shaham Y, Stewart J. Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine seeking. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2000;23:138–150.
39. Imaki J, Mae Y, Shimizu S, Ohno Y. Therapeutic potential of alpha2 adrenoceptor antagonism for antipsychotic-induced extrapyramidal motor disorders. *Neuroscience letters*. 2009;454:143–147.
40. Wadenberg ML. Serotonergic mechanisms in neuroleptic-induced catalepsy in the rat. *Neuroscience and biobehavioral reviews*. 1996;20:325–339.
41. Kalkman HO, Neumann V, Hoyer D, Tricklebank MD. The role of alpha2-adrenoceptor antagonism in the anti-cataleptic properties of the atypical neuroleptic agent, clozapine, in the rat. *British journal of pharmacology*. 1998;124:1550–1556.

42. Hu JY, Jin GZ. Supraspinal D2 receptor involved in antinociception induced by l-tetrahydropalmatine. *Zhongguo yao li xue bao = Acta pharmacologica Sinica*. 1999;20:715–719.
43. Figueroa-Guzman Y, Mueller C, Vranjkovic O, Wisniewski S, Yang Z, Li SJ, Bohr C, Graf EN, Baker DA, Mantsch JR. Oral administration of l-tetrahydropalmatine attenuates reinstatement of extinguished cocaine seeking by cocaine, stress or drug-associated cues in rats. *Drug and alcohol dependence*. 2011;116:72–79.
44. Mello NK, Negus SS. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 1996;14:375–424.
45. Haney M, Spealman R. Controversies in translational research: drug self-administration. *Psychopharmacology*. 2008;199:403–419.
46. Stafford D, LeSage MG, Glowa JR. Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: a review. *Psychopharmacology*. 1998;139:169–184.
47. Richardson NRRD. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. *Journal Neuroscience Methods*. 1996;66:1–11.
48. Kornetsky C, Bain G. Brain-stimulation reward: a model for the study of the rewarding effects of abused drugs. *NIDA research monograph*. 1992;124:73–93.
49. Spealman RD. Use of cocaine-discrimination techniques for preclinical evaluation of candidate therapeutics for cocaine dependence. *NIDA research monograph*. 1992;119:175–179.
50. Shaham Y, Shalev U, Lu L, De Wit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology*. 2003;168:3–20.
51. Shalev U, Grimm JW, Shaham Y. Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacological reviews*. 2002;54:1–42.
52. Chao-Wu L, Shuo Z, Hai-Qing G, Xiu-Mei Z. Determination of L- tetrahydropalmatine in human plasma by HPLC and pharmacokinetics of its disintegrating tablets in healthy Chinese. *European journal of drug metabolism and pharmacokinetics*. 2011.
53. Zhang J, Tan L, Zhou J, Lu X, Yuan Y. Determination of Rotundine in Human Plasma by HPLC and Pharmacokinetic Studies. *journal of China Pharnaceutical University*. 1998;29:67–70.
54. Li C, Zhang S, Gao H, Zhang X. Determination of L-tetrahydropalmatine in human plasma by HPLC and pharmacokinetics of its disintegrating tablets in healthy Chinese. *Eur J Drug Metab Pharmacokinet*. 2011.

55. Zhao Y, Hellum BH, Liang A, Nilsen OG. The In Vitro Inhibition of Human CYP1A2, CYP2D6 and CYP3A4 by Tetrahydropalmatine, Neferine and Berberine. *Phytotherapy Research : PTR*. 2011
56. Wu G, Jiang JW, Wu GC, Cao XD. Effects of four dopamine agonists on l-tetrahydropalmatine-induced analgesia and electroacupuncture analgesia in rabbits. *Zhongguo yao li xue bao = Acta pharmacologica Sinica*. 1990;11:196–200.
57. Yang Z, Shao YC, Li SJ, Qi JL, Zhang MJ, Hao W, Jin GZ. Medication of l-tetrahydropalmatine significantly ameliorates opiate craving and increases the abstinence rate in heroin users: a pilot study. *Acta Pharmacologica Sinica*. 2008;29:781–788.
58. Hu Y, Qiu Y, Zhong Y, He H. Therapeutic Effects of Rotundine Combined with Methadone in Treatment of Heroin Dependence. *Chinese Journal of Drug Abuse Prevention and Treatment*. 2006;12:270–271.
59. Horowitz RS, Feldhaus K, Dart RC, Stermitz FR, Beck JJ. The clinical spectrum of Jin Bu Huan toxicity. *Archives of Internal Medicine*. 1996;156:899–903.
60. Woolf GM, Petrovic LM, Rojter SE, Wainwright S, Villamil FG, Katkov WN, Michieletti P, Wanless IR, Stermitz FR, Beck JJ, Vierling JM. Acute hepatitis associated with the Chinese herbal product jin bu huan. *Annals of Internal Medicine*. 1994;121:729–735.
61. Picciotto A, Campo N, Brizzolara R, Giusto R, Guido G, Sinelli N, Lapertosa G, Celle G. Chronic hepatitis induced by Jin Bu Huan. *Journal of hepatology*. 1998;28:165–167.
62. Liu YL, Yan LD, Zhou PL, Wu CF, Gong ZH. Levo-tetrahydropalmatine attenuates oxycodone-induced conditioned place preference in rats. *European journal of pharmacology*. 2009;602:321–327.