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Bidirectional role of acupuncture in the treatment of drug addiction

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ABSTRACT

Drug addiction is a chronically relapsing disorder, affecting people from all walks of life. Studies of acupuncture effects on drug addiction are intriguing in light of the fact that acupuncture can be used as a convenient therapeutic intervention for treating drug addiction by direct activation of brain pathway. The current review aims to discuss the neurobiological mechanisms underlying acupuncture's effectiveness in the treatment of drug addiction, on the basis of two different theories (the incentive sensitization theory and the opponent process theory) that have seemingly opposite view on the role of the mesolimbic reward pathways in mediating compulsive drug-seeking behavior. This review provides evidence that acupuncture may reduce relapse to drug-seeking behavior by regulating neurotransmitters involved in drug craving modulation via somatosensory afferent mechanisms. Also, acupuncture normalizes hyper-reactivity or hypoactivity of the mesolimbic dopamine system in these opposed processes in drug addiction, suggesting bidirectional role of acupuncture in regulation of drug addiction. This proposes that acupuncture may reduce drug craving by correcting both dysfunctions of the mesolimbic dopamine pathway.

1. Introduction

Drug addiction is a chronic, relapsing disorder characterized by a compulsive pattern of drug-seeking and drug-taking behavior despite severe harms, negative emotional state during abstinence, and deficits in control over drug consumption (Koob and Volkow, 2016; Robinson and Berridge, 2003), which remains one of the most critical public health problems in the world. The successful therapeutic intervention for the treatment of drug addiction is believed by many to reduce the high rate of craving and relapse. Many therapeutic approaches have been employed in the treatment of drug addiction, and yet, there is still no satisfactory medical intervention to treat the high rates of relapse.

The question of addiction is concerned with how addicts develop important features of addiction that are characterized by the compulsive use of drugs and relapse. It is widely accepted that there are two major theories of addiction to address this question: the incentive sensitization theory and the opponent process theory. The incentive sensitization theory of addiction emphasizes a particular phenomenon: excessive incentive motivation for drugs triggered by cues, leading to compulsive drug-seeking and drug-taking behavior and relapse. This theory addresses that repeated administration of drugs produces long-lasting changes in the mesolimbic dopamine system that mediates a basic incentive-motivational function, the attribution of incentive salience. Consequently, these neural pathways can become enduringly sensitized to drugs and drug-associated stimuli, causing intense craving and wanting (Robinson and Berridge, 2003). On the contrary, the opponent process theory is based on the negative reinforcement of addiction; drugs are administered continuously to alleviate negative emotional states that accompany drug use withdrawal and potentially cause intense drug craving. The neurobiological substrates that contribute towards compulsion to drug seeking and relapse involve a decrement of reward neurotransmission in the mesolimbic dopamine system and activation of the brain stress system (Koob and Le Moal, 2008b).

Acupuncture as a traditional therapeutic intervention is popularly practiced in East Asian countries and is en route to gaining acceptance in Europe and the Americas. With growing public interest regarding acupuncture therapy, considerable research has been done to investigate acupuncture analgesia after the introduction of acupuncture to the scientific community. The discovery of the endogenous opioid system was a remarkable step toward understanding the analgesic mechanism of acupuncture (Han and Terenius, 1982; Mayer et al., 1977). Studies using animal models have especially brought the search for a neurobiological mechanism for drug addiction since the National Institutes of Health Consensus Development Panel issued a report that acupuncture may be

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an effective adjunct or acceptable alternative therapy for the treatment of functional disorders including drug addiction (Anonymous, 1998).

Acupuncture produces therapeutic effects by stimulating specific acupuncture points on the skin and muscle through the insertion of the metallic needles (Stux et al., 2003). The acupuncture stimulation can be delivered by manual twisting of acupuncture needles or finely controlled electrical stimulation of acupuncture needles (electroacupuncture, or EA). Needling of acupuncture points produces unique sensations of swelling and numbness (*Deqi*) which many acupuncturists believe to be crucial for achieving the therapeutic effects of acupuncture (Zhou and Benharash, 2014). Neuroimaging studies have indicated that acupuncture elicits a significant positive correlation between the intensity of *Deqi* sensations and neural activity in the brain regions associated with particular behavioral function, which suggests that acupuncture exerts its effects via the brain (Hui et al., 2005, 2009). Previous work established that acupuncture-mediated simulation of peripheral afferent nerve fibers gives rise to *Deqi* sensations, which in turn transmit acupuncture afferent signals to the brain to produce the central effects of acupuncture (Zhao, 2008). As acupuncture points, with enriched mechanoreceptors in the skin and muscle, are thought to be the loci of afferent fibers (Li et al., 2004), it can be speculated that somatosensory nerve fibers may mediate the generation of *Deqi* in acupuncture.

Although few experiments are investigating the effect of acupuncture on mental illness, the results of some animal studies provide evidence for acupuncture's role in suppressing stress response via reduced hippocampal neuroinflammation (Yue et al., 2018) and increased hippocampal protein synthesis required for synaptic plasticity (Oh et al., 2018). In addition, acupuncture influences behavioral states and imbalances in several brain neurotransmitter systems implicated in psychiatric disorders, such as anxiety, depression, and drug abuse (Pilkington, 2013). Thus, it is not unexpected that acupuncture-initiated impulses restore the biochemical balance by regulating neurotransmitters that control addictive behavior and thus act to modulate reward neuronal pathways in the brain. Indeed, many studies provide evidence for the role of acupuncture in effectively suppressing the compulsive use of abused drugs by directly affecting the mesolimbic dopamine system and the brain stress system (Chen et al., 2019; Kim et al., 2020; Lin et al., 2012; Roh et al., 2018). Studies involving humans have also demonstrated acupuncture as a compelling drug addiction care modality (Chen et al., 2018; Cui et al., 2008; Motlagh et al., 2016).

The mesolimbic dopamine pathways, especially those originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc), are believed to mediate the acute reinforcing effects of addictive drugs and the motivational effects of drug withdrawal (Koob, 1992; Koob et al., 1994; Porrino, 1993). The amygdala is well situated to integrate brain arousal-stress systems and processing systems to mediate the reinforcing effects of drugs of abuse (Edwards and Koob, 2010). The activation of the brain stress system may be particularly important for the negative motivational state during acute drug withdrawal, which makes an addicted person more vulnerable to relapse (Becker, 2008). We will review some of the evidence for the role of acupuncture in modulating the brain reward and stress systems and suppressing drug craving and relapse.

2. Drug reward pursuit in animal models

Many studies assess the degree of effort by laboratory animals to forage drugs of abuse during withdrawal of drug reward as an index of drug-seeking behavior, which is considered to reflect a wanting or craving that eventually leads to drug relapse (Koob and Le Moal, 2001; Robinson and Berridge, 1993). Animal models for drug reward pursuit include intravenous drug self-administration, conditioned place preference (CPP), and brain stimulation reward (Sanchis-Segura and Spanagel, 2006). Studies using these animal models have evaluated the motivational significance of sensitization and opponent processes in drug addiction (Koob and Le Moal, 2008b; Vezina, 2004).

2.1. A role for the mesolimbic dopamine pathway in drug sensitization

Importantly, these animal model studies have suggested that drug-induced neural sensitization in the mesolimbic dopamine system, which shows that drug-evoked dopamine release in the NAc is augmented in sensitized animals, is intimately implicated in enhanced drug reward-seeking behavior and relapse (Kawa et al., 2019; Robinson and Berridge, 2003). In studies involving direct self-administration of amphetamine, dopamine receptor antagonist inhibits the development of facilitated amphetamine self-administration in animals sensitized to amphetamine (Pierre and Vezina, 1998). In agreement with these findings, it was suggested that neural sensitization of the mesolimbic dopamine pathway mediates the lowering of the reward threshold that animals need to learn to self-administer drugs, making it easier to administer the drugs (Robinson and Berridge, 2003). Supporting evidence for the hypothesis that sensitization of VTA dopamine neurons underlies compulsive drug taking and seeking behaviors have been observed during the administration of abused drugs. Sensitization of VTA dopamine neurons in animals sensitized to amphetamine caused significant increases in breakpoint under a progressive ratio schedule in amphetamine self-administration studies, suggesting a functional role for VTA dopamine neurons in their increased motivation to obtain amphetamine reward (Vezina et al., 2002). Similar research using a CPP test found the positive correlation between cocaine-induced changes in extracellular dopamine levels in the NAc and cocaine-conditioned behaviors, indicating that cocaine-induced CPP might be mediated through increased dopamine neurotransmission in the NAc (Duvauchelle et al., 2000). These results, combined with the finding that administration of dopamine receptor antagonists suppressed the sensitized response to cocaine-paired environment (Shippenberg and Heidbreder, 1995), provide further support for the role of the mesolimbic dopamine pathway in mediating the heightened motivation for rewards.

Behavioral sensitization induced by repeated administration of drugs, commonly assessed by monitoring locomotor activity, is to some extent considered incentive-sensitization of drugs and thought to play a role in the reinstatement of drug-seeking (Robinson and Berridge, 2003). Moreover, prolonged cocaine self-administration under an intermittent-access schedule induces escalation of intake, sensitized motivation for cocaine, and robust reinstatement of cocaine-seeking, suggesting behavioral relationships between incentive-sensitization and drug craving (Kawa et al., 2016). In support of this, recent studies have reported that intermittent access cocaine self-administration leads to behavioral sensitization, higher motivation for cocaine seeking and taking, and increased the ability of cocaine at the dopamine transporter in the NAc, suggesting the involvement of sensitization of dopamine neurotransmission in the NAc in cocaine-induced incentive-sensitization (Allain et al., 2021, 2017; Calipari et al., 2013; Carr et al., 2020). Behavioral sensitization appears to offer the neuroplasticity underlying the reinstatement of extinguished drug-self administration behavior. An earlier study has implied that sensitization of the mesolimbic dopamine pathway induced by repeated administration of psychostimulant drugs may be involved in both behavioral sensitization and drug-induced reinstatement of drug-seeking behavior (Vezina, 2004). The implication of sensitization in the mediation of reinstatement of drug-seeking is still controversial. However, sensitization is likely to play a role in the reinstatement of drug-seeking behavior as there is a common neural circuit that includes the mesolimbic dopamine system for sensitization and reinstatement response (Steketee and Kalivas, 2011).

Drug self-administration studies have demonstrated that the potentiation of dopaminergic neurotransmission in the mesolimbic pathway may be responsible for the reinstatement of drug-seeking behavior induced by the drug itself, drug-associated environmental cue, and the stressor after extinction in animals (Mantsch et al., 2016). The reinstatement of drug-seeking is also observed in the CPP paradigm. In the reinstatement of extinguished CPP, the mesolimbic dopamine pathway appears to be activated by a priming injection of drugs or exposure to stressful stimuli (Aguilar et al., 2009). Animal models of drug relapse based on operant self-administration and CPP procedures measure the reinstatement of drug-seeking after the acquisition and subsequent extinction of the drug-reinforced behavior (Shaham et al., 2003; Spanagel, 2017).

2.2. Roles for the mesolimbic dopamine pathway and brain stress system in opponent motivational process

Studies using animals of drug addiction provide evidence for the involvement of decreases in reward transmission such as dopamine and opioid peptides in the NAc and brain stress systems such as corticotropin-releasing factor (CRF) and noradrenaline in the extended amygdala in the opponent motivational process (George et al., 2012). A microdialysis study in ethanol-dependent rats found the role of accumbal dopamine in ethanol-drinking behavior during withdrawal from chronic ethanol administration. This study showed a reduction in extracellular dopamine levels in the NAc and an increase in ethanol self-administration in dependent rats compared to non-dependent rats, suggesting that withdrawal-associated reduction in the dopamine release in the NAc may represent the mechanism underlying the negative affective state during withdrawal that might contribute to the motivation of ethanol-seeking behavior (Weiss et al., 1996). A similar motivational effect of withdrawal in dependent animals relevant to the opponent process has been observed with commonly abused drugs such as heroin and psychostimulants (Koob and Le Moal, 2008a; Negus and Banks, 2018). Ethanol self-administration in the animal models of dependence has been also used to evaluate the role of the brain stress system in motivating ethanol-seeking behavior. Neuropharmacological studies on the negative reinforcing effects of ethanol have established an important role for CRF in the extended amygdala (Koob, 2015). Activation of central CRF_2 receptor has been shown to increase ethanol self-administration rates and anxiety-like behavior in ethanol-dependent rats, suggesting that the stress response such as anxiety mediated via activation of the endogenous brain CRF system is likely a driving factor for relapse to ethanol-seeking behavior in ethanol dependence (Valdez et al., 2002, 2004).

As opposed to animal models used in psychiatric research that lack applicable clinical value, animal models of addiction described above can be more readily translated to a valuable reference for the clinical situation (Spanagel, 2017). A few experiments using animal models of addiction have revealed the neurobiological mechanisms underlying acupuncture's effectiveness in the treatment of drug addiction. Thus, the results from these animal studies will provide crucial and highly informative data for clinical trials to determine the effectiveness of acupuncture.

3. Acupuncture as a modality to reduce drug sensitization

3.1. Modulation of the mesolimbic dopamine pathway by acupuncture

According to the incentive sensitization theory, the neural changes underlying sensitization induced by repeated administration of psychostimulants may be responsible for the enhancement of subsequent motivation for psychostimulants associated with behavioral sensitization (Robinson and Berridge, 2008). Moreover, psychomotor sensitization has been linked to the sensitization of the mesolimbic dopamine system (Vezina, 2004). Evidence from the microdialysis study suggests that a neurochemical mechanism likely involved in behavioral sensitization would be the enhanced response of mesolimbic dopamine neurons to the cocaine challenge in rats treated with repeated cocaine administration (Chefer et al., 2003).

Many studies have been designed to investigate the effects of manual acupuncture or EA on behavioral and neurochemical changes in rodent models of drug addiction. Generally, in studies on the effectiveness of manual acupuncture, rats were treated acutely with manual acupuncture. On the other hand, in studies on the effectiveness of EA, rats were treated chronically with EA. Both manual acupuncture and EA were carried out under unanesthetized condition.

A recent study has shown that acupuncture at Shenmen (HT7) points attenuated sensitization of extracellular dopamine levels within the NAc of rats treated with repeated cocaine (Jin et al., 2018). In a manner consistent with this finding, HT7 acupuncture reduced locomotor sensitization and increased the expression of tyrosine hydroxylase in the VTA of rats given repeated injections of cocaine (Lee et al., 2009). Together, these results indicate that acupuncture may reduce sensitization to the motor response by inhibiting an enhancement in VTA dopamine neuron activity in rats sensitized to cocaine. As sensitization of the mesolimbic dopamine pathway has been implicated in excessive drug-craving (Vanderschuren and Pierce, 2010; Vezina, 2004), it can be hypothesized that acupuncture may reduce cocaine-seeking behavior via inhibition of VTA dopamine neurons.

Acupuncture-induced inhibition of neuronal and behavioral sensitization of the mesolimbic dopamine pathway has been confirmed considerably in previous studies. HT7 stimulation inhibited the sensitization of dopamine release in the NAc and behavioral sensitization in rats treated with repeated morphine administration (Kim et al., 2005). Additionally, EA at Zhubin (KI9) and Taichong (LR3) decreased locomotor activity and dopamine levels and tyrosine hydroxylase expression in the NAc induced by a systemic methamphetamine challenge after exposure to repeated methamphetamine administration (Ho et al., 2017). Acupuncture at Zusanli (ST36) reduced the expected nicotine-induced elevation in c-Fos expression in the NAc and striatum and also decreased the amount of nicotine-induced hyperactivity (Chae et al., 2004). Given the behavioral relationship between sensitization and relapse (Steketee and Kalivas, 2011), these results raise the possibility that acupuncture may reduce relapse towards cocaine-seeking behavior.

Supporting this hypothesis, results from cocaine self-administration study demonstrated that HT7 acupuncture decreased cocaine-induced reinstatement of cocaine-seeking behavior after cocaine self-administration behavior was extinguished (Jin et al., 2018). Although the role of neural sensitization in the reinstatement of drug-seeking behavior is still disputed, this sensitization is thought to play an important role in a priming-induced reinstatement of cocaine-seeking in rats extinguished from cocaine self-administration (Anderson and Pierce, 2005; Steketee and Kalivas, 2011). Accordingly, it seems reasonable to propose that acupuncture may help to attenuate relapse to cocaine-seeking behavior.

3.2. A role for VTA GABA neurons in acupuncture

3.2.1. Mesolimbic dopamine transmission

The enhanced glutamate transmission in the VTA by repeated exposure to psychostimulants and stressors seems to mediate a sensitized behavioral response and relapse to drug-seeking behavior through an NMDA receptor-dependent AMPA receptor-induced long-term potentiation (LTP) of dopamine neurons in the VTA (Self, 2004; Steketee and Kalivas, 2011). Interestingly, repeated administration of cocaine causes LTP of VTA dopamine neurons via suppression of γ-aminobutyric acid (GABA)-ergic inhibition (Pan et al., 2008). As VTA GABA neurons are the significant source of inhibitory afferents to VTA dopamine neurons, inhibition of VTA GABA neurons by acutely administrating abused drugs would lead to activation of VTA dopamine neurons and would increase dopamine release in the NAc (Bocklisch et al., 2013; Johnson and North, 1992). Thus, it can be suggested that the increased GABAergic inhibition in the VTA produces a strong inhibitory effect on cocaine-seeking behavior (Backes and Hemby, 2008; Mathon et al., 2005). Collectively, these findings reviewed above provide insight into the role of VTA GABA neurons in acupuncture modulation of cocaine effects.

As expected, a recent study demonstrated that HT7 acupuncture

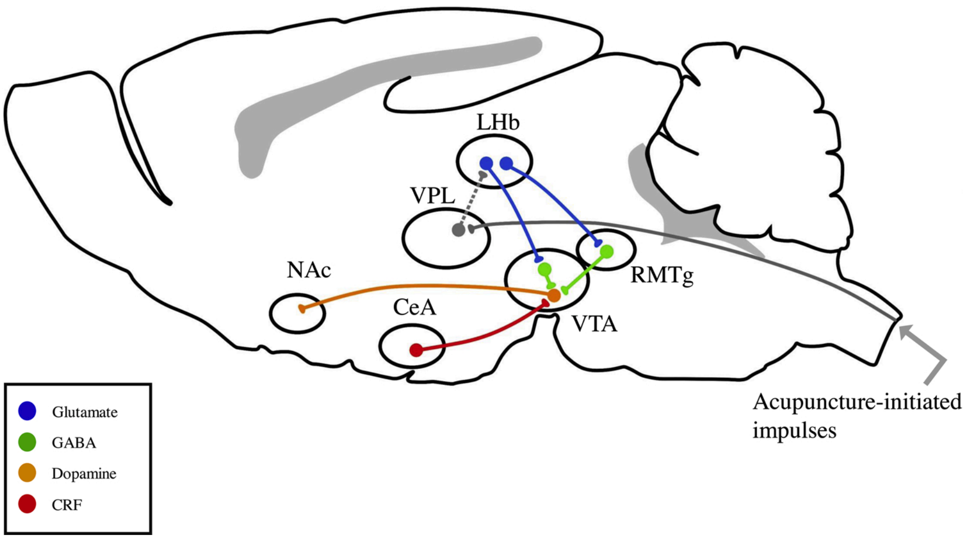

Fig. 1. The role of acupuncture in the neurocircuitry involved in drug sensitization.
In animals sensitized to cocaine that promote cocaine-seeking via drug sensitization mechanisms, acupuncture at Shenmen (HT7) points may activate GABA interneurons in the VTA or GABA neurons in the RMTg through the glutamatergic projection from the LHb and thus, eventually enhances GABAergic inhibition of VTA dopamine neurons. As a result, acupuncture can suppress behavioral sensitization and relapse to cocaine-seeking via modulation of mesolimbic dopamine release. Additionally, acupuncture can play a role in inhibiting the central amygdala CRF neurons-mediated increase of mesolimbic dopamine release and reducing stress-induced cocaine-seeking behavior through activation of VTA GABA neurons. Solid and dashed lines indicate established and putative projections, respectively. Gray dashed lines indicate unidentified projections. Abbreviations: VTA, ventral tegmental area; NAc, nucleus accumbens; RMTg, rostromedial tegmental nucleus; LHb, lateral habenula; VPL, ventral posterolateral nucleus; CeA, central nucleus of the amygdala; CRF, corticotropin-releasing factor; GABA, γ-aminobutyric acid.

inhibited cocaine-induced decreases in GABA release and GABA neuron firing rates in the VTA in rats (Jin et al., 2018). Additionally, acupuncture blunted acute cocaine-induced dopamine release in the NAc, which were blocked by the selective $GABA_B$ receptor antagonist 2-hydroxysaclofen (Jin et al., 2018). This study implies that acupuncture effectively decreases dopamine neuron activity through activation of GABA neurons in the VTA. These results are supported by earlier studies showing that HT7 acupuncture inhibited acute ethanol-induced dopamine release in the NAc through the $GABA_B$ receptor (Yoon et al., 2004).

3.2.2. Reinstatement of drug seeking

As with animals receiving passive injections of drugs, animals self-administering drugs showed that activation of VTA GABA neurons may mediate acupuncture's role in modulating mesolimbic dopamine release and the reinforcing effects of drugs. One study of intravenous cocaine self-administration has shown that HT7 acupuncture reduced stress-induced reinstatement of cocaine seeking and neuronal activation in the NAc in extinguished rats (Yoon et al., 2012). Stress induces the reinstatement of cocaine-seeking and facilitates the induction of LTP at excitatory synapses in dopamine neurons in the VTA (Saal et al., 2003). In contrast, stress inhibits LTP at GABAergic synapses on VTA dopamine neurons (Graziane et al., 2013). It was postulated that CRF released in response to stress triggers glutamate release in the VTA, which induces drug-seeking via activation of dopamine neurons in the VTA (Wise and Morales, 2010). Thus, the suppression of stress-induced cocaine-seeking behavior produced by acupuncture may be due to the increased GABAergic inhibition of dopamine neuron activity in the VTA. There is some direct support for this hypothesis in studies using rat model of cocaine-primed reinstatement. HT7 stimulation has been demonstrated to attenuate relapse to cocaine-seeking behavior, which was reversed by the selective $GABA_B$ receptor antagonist 2-hydroxysaclofen (Jin et al., 2018). Given that acupuncture attenuates acute cocaine-induced dopamine release in the NAc through activation of VTA GABA neurons (Jin et al., 2018), these results suggest that acupuncture may reduce relapse to cocaine-seeking behavior by enhancing GABAergic inhibition in the VTA. These findings are in line with considerable evidence. Acupuncture at Yanggu (SI5) significantly reduced the expected increases in breakpoint under a progressive ratio schedule and the reinstatement of morphine-seeking behavior in rats trained to self-administer morphine, which was blocked by intraperitoneal injection of GABA receptor antagonists (Lee et al., 2012, 2015). This suggests that acupuncture may suppress motivation for morphine reward presumably through the GABA pathway. Furthermore, HT7 acupuncture has been further shown to attenuate morphine self-administration rates through the GABA pathway (Lee et al., 2014; Yoon et al., 2010). Interestingly, results obtained in a study of operant oral ethanol self-administration and single-cell electrophysiology for ethanol support the view that opioid synaptic input to VTA GABA neurons is particularly important for acupuncture's role in modulating the reinforcing actions of ethanol. This study showed that acupuncture suppresses ethanol-reinforced behavior and the inhibitory effect of ethanol on VTA GABA neuron activity through accumbal GABA input to VTA GABA neurons via DORs (Yang et al., 2010).

3.2.3. Extinction of drug seeking

Significant evidence suggests that acupuncture can be effective in enhancing extinction learning. EA at ST36 and Sanyinjiao (SP6) promoted the extinction response of cue-induced heroin seeking and decreased FosB expression in the NAc core in rats after the extinction of heroin self-administration in rats (Hu et al., 2013). Furthermore, EA inhibited cue-induced reinstatement of heroin-seeking behavior and c-Fos expression in the NAc core in heroin-experienced rats (Liu et al., 2012). Based on the finding that extinction promotes active learning to suppress the motivation for drugs of abuse induced by drug-related cues (Havermans and Jansen, 2003) and the FosB expression in the NAc is associated with drug-seeking behavior (Kelz et al., 1999), it has been claimed that EA can attenuate cue-induced heroin seeking by facilitating the extinction of heroin cues (Hu et al., 2013). Drug-associated contextual cue affects synaptic plasticity which endures after long withdrawal from chronic drug administration and consequently triggers drug craving and seeking behavior (Crombag et al., 2008). However, the reinstatement of drug seeking can be inhibited by extinction training (Leite-Morris et al., 2014). GABA has been hypothesized to have a role in the extinction of opiate CPP (Heinrichs et al., 2010). The mesolimbic dopamine pathway has been linked to cue-induced reinstatement of drug-seeking (Namba et al., 2018). Extinction training can blunt dopamine release in the NAc core induced by exposure to the cue (Sunsay and Rebec, 2014). Thus, given acupuncture-mediated activation of GABAergic input to dopamine neurons in the VTA, it can be speculated that acupuncture may alter VTA dopamine activity and cue-induced reinstatement, presumably by enhancing GABAergic inhibition during extinction. In summary, the results of the studies reviewed above suggest an important role of VTA GABA neurons in acupuncture inhibition of the reinstatement of drug seeking (Fig. 1).

3.3. A role for endogenous κ-opioid systems in acupuncture

A systematic series of studies exploring acupuncture's role in suppressing the motivational effects of morphine using the CPP paradigm in rats have suggested a functional role for endogenous κ-opioid systems. High-frequency EA stimulation at ST36 and SP6 reduced morphine-induced CPP, which was blocked by intracerebroventricular administration of the selective κ-opioid receptor antagonist norbinaltorphimine (Shi et al., 2003). This EA inhibition of morphine motivational effects has been replicated using the CPP reinstatement model. It has been demonstrated that repeated high-frequency EA has inhibited the acquisition and reinstatement of morphine-induced CPP, but increased preprodynorphin mRNA levels in the NAc (Shi et al., 2004). These results indicate that dynorphin in the NAc might be involved in EA effects on morphine reinforcement. High-frequency EA has been shown to increase dynorphin release (Han, 2004), which could activate κ-opioid receptors on VTA dopamine neurons. Indeed, κ-opioid receptor agonists including dynorphin decrease dopamine release in the NAc (Spanagel et al., 1990, 1992). As activation of κ-opioid receptors located presynaptically on dopamine terminals reduces dopamine release in the NAc (Ebner et al., 2010; Svingos et al., 2001), this study implicates presynaptic modulation of dopamine release in the NAc by high-frequency EA. Drug-associated context increases dopamine levels in the NAc that in tum are associated with morphine-induced CPP in rats (Ma et al., 2009). However, high-frequency EA has been demonstrated to produce simultaneous decreases of dopamine levels in the NAc and morphine - induced CPP and (Ma et al., 2008). Based on a previous study indicating that a morphine CPP paradigm may reflect the incubation of craving (Sun et al., 2018), it is highly likely that κ-opioid receptor-mediated opioid modulation of VTA dopamine neurons mediates EA's role in suppressing relapse to morphine-seeking behavior.

4. Acupuncture as a therapeutic intervention for the negative reinforcement of drug addiction

4.1. Acupuncture and opponent motivational processes

Both deficits in brain reward neurotransmission and activation of brain stress systems in the opponent motivational processes produced by the negative emotional state contribute to compulsive drug seeking and use (Koob and Le Moal, 2008b; Koob and Volkow, 2016). The therapeutic strategy to prevent the high rate of drug craving and relapse in drug addiction should, therefore, be able to reduce deficits in reward function and negative emotional state. Several studies have validated the neurochemical and behavioral evidence for the effectiveness of acupuncture in an animal model of drug addiction by regulating selectively target neurotransmitters or receptors in the brain reward and stress systems (Chang et al., 2019a; Yoshimoto et al., 2001; Zhao et al., 2013).

4.2. Acupuncture and dopaminergic neurotransmission

The role of acupuncture in regulating the dopamine system of the NAc during ethanol withdrawal was obtained from previous studies where rats were chronically treated with an intoxicating dose of ethanol by intraperitoneal injection. These studies have reported that HT7 acupuncture prevented ethanol-induced dopamine depletion in the NAc and behavioral withdrawal signs during ethanol withdrawal (Zhao et al., 2006; Lee et al., 2008). These results agree with more recent report that HT7 acupuncture suppressed the hypodopaminergic activity in the mesolimbic dopamine pathway and anxiety-like behavior in ethanol-withdrawn rats, which was abolished by intra-NAc infusions of selective dopamine receptor antagonists (Zhao et al., 2015). As withdrawal from chronic ethanol elicits the reduction in dopamine release in the NAc, which may represent the mechanism underlying physical withdrawal signs and negative emotional state (Diana et al., 1993; Rossetti et al., 1999) and provoke ethanol-seeking behavior (Weiss et al., 1996), it can be hypothesized that acupuncture may reduce negative emotional state and ethanol-seeking behavior during withdrawal by restoring the release of dopamine in the NAc.

Inhibition of the reinforcing effects of drugs by acupuncture-mediated normalization of hypodopaminergic neurotransmission was replicated in other studies. When 100 Hz EA at ST36 and SP6 was applied to rats dependent on morphine and subjected to more prolonged withdrawal from chronic morphine, EA prevented decreases in dopamine neuron size in the VTA presumably via activation of endogenous brain-derived neurotrophic factor (Chu et al., 2007). This EA-mediated reversal of hypodopaminergic state was extended by the observation that EA abolished the chronic morphine-induced inhibition of VTA dopamine neuron activity, the response of VTA dopamine neurons to subsequent morphine challenge, and the sensitivity of morphine-induced CPP, suggesting an inhibitory role for EA in the tolerance to the reinforcing effects of morphine (Hu et al., 2009).

4.3. Acupuncture and endogenous opioid systems

It has been recently demonstrated that low frequency (45–80 Hz) EA-like stimulation applied to cervical vertebrae in rats decreased VTA GABA neuron firing rate while increasing dopamine release in the NAc. Inactivation of the NAc by intra - NAc infusions of lidocaine or intraperitoneal injection of the selective DOR antagonist naltrindole also blocked EA-like stimulation inhibition of VTA GABA neuron activity, suggesting the involvement of DORs on accumbal GABA input to VTA GABA neurons. In keeping with this finding, this study has shown that EA-like stimulation produced the parallel increase of c-Fos expression and induction of translocation DORs to neuronal membranes in the NAc (Bills et al., 2020). As VTA GABA neurons modulate VTA dopamine neuron activity and dopamine release in the NAc (Steffensen et al., 2009), increased response of dopamine neurons produced by EA-like stimulation is most likely mediated via activation of opioidergic inputs to NAc GABA neurons via DORs, perhaps from the acupuncture-sensitive arcuate nucleus of the hypothalamus (ARC) (Chang et al., 2019a; Wang et al., 1990a, b). These results support the view that acupuncture may serve to compensate for profound deficits in mesolimbic dopaminergic activity during drug withdrawal through the endogenous opioid system.

There is some evidence for a role of opioids in acupuncture inhibition of drug-taking and -seeking behaviors. In two-bottle choice studies during ethanol withdrawal, EA at ST36 and SP6 decreased ethanol intake in ethanol-preferring rats dependent on ethanol, which was blocked by naltrexone, implying that EA effects on ethanol intake might result from activation of the endogenous opioid system (Overstreet et al., 2008). Similarly, 2 Hz EA produced increases in met-enkephalin release and preproenkephalin mRNA level in the NAc of morphine-induced CPP rats. Moreover, the MOR antagonist or DOR antagonist, when injected into the cerebroventricular system, blocks EA inhibition of morphine-induced CPP expression (Liang et al., 2010). Taken together, these findings suggest that electrical stimulation of acupuncture points activates enkephalinergic inputs to the NAc, thereby inhibiting morphine-reinforced responding and the craving by normalizing dopamine release in the NAc via the mediation of MORs or DORs in the NAc.

4.4. Acupuncture and interaction of opioid-dopaminergic interactions

Research involving rats chronically maintained on a liquid diet containing ethanol showed that symptoms of ethanol-withdrawal including ethanol-seeking behavior were inhibited by acupuncture. Specifically, HT7 acupuncture reduced tremor, anxiety-like behavior, and ethanol self-administration without affecting general

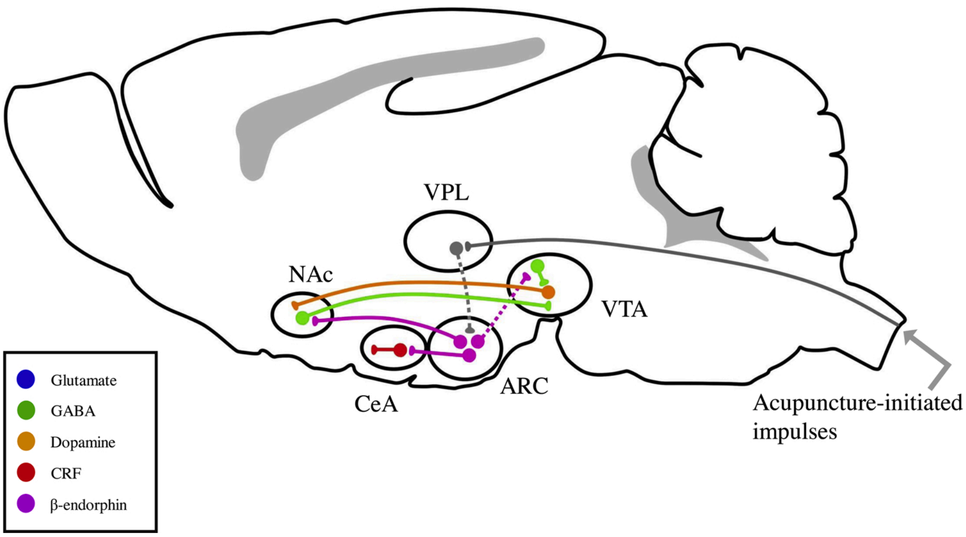

Fig. 2. The role of acupuncture in the neurocircuitry involved in the negative reinforcement of drug addiction.
In ethanol-dependent animals that drive ethanol-seeking via negative reinforcement mechanisms, acupuncture at Shenmen (HT7) points may activate β-endorphinergic neurons in the ARC projecting to GABA neurons in the NAc or VTA. β-Endorphin released from β-endorphinergic fibers can in tum activate opioid receptors on GABA neurons in the NAc, resulting in disinhibiting dopamine neurons in the VTA. Consequently, acupuncture can reduce the negative emotional state during withdrawal by normalization of hypodopaminergic state and thus inhibit ethanol craving and relapse. In addition, acupuncture can suppress anxiety-like behavior and ethanol-seeking behavior by modulating the role of CRF neurons in the CeA through endogenous opioid systems. Solid and dashed lines indicate established and putative projections, respectively. Gray dashed lines indicate unidentified projections. Abbreviations: VTA, ventral tegmental area; NAc, nucleus accumbens; ARC, arcuate nucleus of the hypothalamus; VPL, ventral posterolateral nucleus; CeA, central nucleus of the amygdala; CRF, corticotropin-releasing factor; GABA, γ-aminobutyric acid.

consummatory behavior in dependent rats, which were mimicked by microinfusion of β-endorphin into the NAc. In addition, acupuncture reversed the decrease in β-endorphin levels in the NAc in dependent rats through activation of the putative β-endorphinergic neurons that originate in the ARC of the hypothalamus and projects to the NAc. Local injection of β-endorphin into the NAc caused the reversal of the hypodopaminergic state during withdrawal (Chang et al., 2019a). Given these findings and interaction between the endogenous opioid system and dopaminergic neurotransmission in the NAc (Sher, 2003; Spanagel et al., 1991), it is suggested that acupuncture may reduce anxiety-like behavior by normalizing dopamine release in the NAc through activation of β-endorphinregic neurons and consequently reduce ethanol-seeking behavior in ethanol withdrawal state (Fig. 2).

This role for the endogenous opioid system in acupuncture effects was supported by the previous observation that EA at ST36 reduced the expected increase in ethanol drinking behavior and enhanced dopamine levels in the striatum in rats challenged with immobilization stress (Yoshimoto et al., 2001). Given that EA at ST36 can trigger the release of endogenous opioids to activate MORs (Chen and Han, 1992), one possible mechanism where electrical stimulation could diminish ethanol drinking behavior seen during immobilization stress is by increasing striatal dopamine levels presumably via activation of the endogenous opioid system. Subsequently, the activated striatal dopaminergic neurons can compensate for the reduction in striatal dopamine levels in rats subjected to stress, resulting in EA suppression of motivation for the consumption of ethanol (Yoshimoto et al., 2001).

4.5. Modulation of the brain stress system by acupuncture

Studies of drug addiction have implicated brain stress systems responsible for the negative emotional state that reinforces the desire to seek drugs through negative reinforcement (Koob, 2020). The critical substrate for the negative emotional state in drug addiction is thought to involve the CRF and norepinephrine systems of the extended amygdala including the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis, as an interface of stress and addiction (Koob, 2009).

4.5.1. Acupuncture and endogenous CRF systems

To explore the possibility that acupuncture at HT7 would alter the function of the amygdala concerning ethanol withdrawal, the activity of CRF neurons in the CeA and anxiety-like behavior in ethanol-dependent rats were measured using the reverse transcription-polymerase chain reaction analysis and the elevated plus-maze test (Zhao et al., 2013). This study showed that acupuncture effectively reduced increases in anxiety-like behavior, CRF mRNA levels in the CeA, and plasma corticosterone levels during withdrawal from chronic ethanol administration (Zhao et al., 2013). Additional evidence to support the role of acupuncture in alcohol dependence was provided by the findings from an earlier study that HT7 acupuncture reduced the expected increases in CRF mRNA levels in the amygdala and anxiety-like behavior in response to nicotine withdrawal in rats (Chae et al., 2008). As this elevation in CRF mRNA levels in the CeA and plasma corticosterone levels in nicotine-withdrawn rats may be responsible for negative emotional states associated with drug withdrawal, these results suggest a possible role of CeA CRF neurons in acupuncture inhibition of an anxiety-like response. These data, combined with observations of acupuncture inhibition of ethanol self-administration in ethanol-withdrawn rats (Chang et al., 2019a), suggest that acupuncture may play a role in suppressing motivation for ethanol-seeking during ethanol withdrawal through modulation of CRF neurons in the CeA.

The involvement of endogenous brain CRF neurons in acupuncture effects is supported by some animal studies investigating the effect of acupuncture on the stress response. These stress-related studies have provided evidence that acupuncture can reduce the activity of CRF neurons in the hypothalamic paraventricular nucleus and CeA in animals exposed to restraint stress (He et al., 2018) and suppress increases in depression- and anxiety-like behaviors as well as blood ACTH and corticosterone levels in animals exposed to cold stress (Eshkevari et al., 2015, 2013).

4.5.2. Acupuncture and endogenous opioid system

Importantly, the endogenous opioid system has been implicated in acupuncture inhibition of anxiety-like behavior during ethanol withdrawal (Chang et al., 2019a; Zhao et al., 2015). Several studies have revealed that β-endorphin mediates an adaptive response to stress and regulating the hypothalamic-pituitary-adrenal (HPA) axis. Neuronal transplantation of β-endorphin into the hypothalamic paraventricular nucleus reduced plasma corticosterone increases and anxiety-like behavior increases in prenatal alcohol-exposed rats challenged with stress (Logan et al., 2015). Female β-endorphin knockout mice display increases in the basal negative emotional state, plasma corticosterone levels, and CRF mRNA expression in the extended amygdala, which were normalized by binge-like ethanol intake (Nentwig et al., 2019). CRF release in the HPA axis appears to be regulated by β-endorphin in the ARC of the hypothalamus (Buckingham, 1986; Plotsky, 1986; Suda et al., 1992). Thus, given β-endorphinergic input to the CeA from the ARC (Gray et al., 1984) and the role of opioids in the CeA in modulating negative affective state associated with stress (Neugebauer et al., 2020), these findings support the hypothesis that the endogenous opioid system may mediate acupuncture's role in modulating CRF neuron activity in the CeA and suppressing negative emotional state during ethanol withdrawal (Fig. 2).

4.5.3. Acupuncture and endogenous noradrenergic system

A recent study revealed that HT7 acupuncture effectively reduced plasma corticosterone increase in rats challenged with a single intraperitoneal injection of yohimbine, an angiogenic compound (Chang et al., 2019a). Animal studies also reported that yohimbine might increase stress response via noradrenergic control of the HPA axis (Johnston et al., 1988) and induce the potentiated norepinephrine response in the locus coeruleus to stressors observed during naloxone precipitated-withdrawal from chronic morphine (Nakai et al., 2002). Thus, acupuncture is thought to suppress the activity of noradrenergic neurons in the locus coeruleus involved with the negative affective state associated with drug withdrawal. Norepinephrine neurons in the locus coeruleus appear to stimulate CRF neurons in the CeA through the direct synaptic interaction and thus contribute to the mediation of anxiety-related behaviors (Kravets et al., 2015). There is evidence for acupuncture's role in modulating noradrenergic response in the CeA. Evidence showed that chronic ethanol administration led a rise in norepinephrine levels in the CeA and anxiety-like behavior during ethanol withdrawal, which was suppressed by HT7 acupuncture, suggesting that acupuncture inhibition of anxiety-like behavior in ethanol-withdrawn rats might result from an inhibition of CRF-norepinephrine interaction in the CeA (Zhao et al., 2011).

5. Afferent mechanisms underlying acupuncture for drug addictive behaviors

5.1. Somatic afferents in acupuncture

Despite a lot of interest in understanding how acupuncture sends messages to the brain to influence addictive behaviors, few experiments have investigated the mechanisms that underlie the actions of acupuncture. Some animal and clinical studies provided evidence that peripheral electrical stimulation as somatosensory stimuli may achieve their therapeutic effects on drug seeking and craving (Cui et al., 2008; Zhong et al., 2006). Interestingly, a combined fMRI and microdialysis study in rodents has demonstrated that EA-like stimulation applied to the median nerve attenuated the expected increases in dopamine release and neural activity in the striatum induced by amphetamine (Chen et al., 2008). Conversely, the same EA-like stimulation was able to restore deficient dopamine levels in the striatum induced by local injection of 6-hydroxydopamine into the striatum (Chen et al., 2012). These findings can lead to suggestions that additional research using animal models of drug addiction is of primary importance to understand how acupuncture-initiated impulses stimulate afferent fibers in the skin and muscle and sensory stimulation can modulate the brain's reward pathway. Theoretically, manually twisting acupuncture needles inserted to acupuncture points produce mechanical stimulation, and acupuncture stimulation causes subsequent activation of peripheral mechanoreceptors involved in afferent nerve discharge (Andersson and Lundeberg, 1995). Activation of mechanoreceptors is essential to obtain effective treatments of manual acupuncture and EA as the common sensory mechanism (Yamamoto et al., 2011). Manual acupuncture and EA seem to recruit the identical peripheral afferent pathway for producing acupuncture analgesia, although there are some differences between the two (Zhao, 2008).

The exact peripheral mechanisms mediating acupuncture inhibition of neurobehavioral responses to drugs of abuse are unknown but some evidence exists to suggest the sensory mechanisms of acupuncture to modulate cocaine response. Acupuncture at HT7 decreased both neural activation in the NAc and locomotor activity in cocaine-treated rats, showing that peripheral afferents in deep tissue are more effective in the mediation of acupuncture effects than those in superficial tissue (Jin et al., 2018). These results agree with reports that stimulation at muscle is greater than that at superficial tissue in the analgesic effects of acupuncture (Ceccheerelli et al., 2001; Itoh et al., 2011). Moreover, HT7 inhibition of neural activation in the NAc and locomotor activity induced by a systemic cocaine challenge was blocked by injecting local anesthesia into the acupoints. Together, these findings support the view that muscular afferents may be more important for transmitting acupuncture signals to the brain to cause the needling sensation *Deqi* compared with skin afferents, although acupuncture triggers mechanoreceptors in the skin and muscle (Li et al., 2004). As Aβ afferent fibers innervate most somatic mechanoreceptors, the activation of mechanoreceptors and their Aβ afferent fibers in the deep muscular tissue appears to play a dominant role in the peripheral afferent mechanisms of acupuncture (Zhang et al., 2012). Thus, it can be expected that acupuncture may exert modulatory effects on the mesolimbic dopamine system by conveying somatosensory information to the brain via the sensory mechanisms including mechanoreceptors and Aβ afferent fibers in the skin and muscle.

Using a mechanical acupuncture instrument in rats injected with acute cocaine, systematic studies were conducted to identify afferent mechanisms underlying acupuncture inhibition of cocaine response. This form of acupuncture was developed to produce predictable and reproducible stimulation as an alternative to manual acupuncture. A study showed that acupuncture stimulation applied to HT7 acupuncture points lying adjacent to the ulnar nerve (Peuker and Cummings, 2003) inhibits cocaine-induced locomotor activity, which was blocked by injecting local anesthesia into HT7 points and severing the ulnar nerve. When rats received HT7 stimulation with the vibrational stimulus at frequencies of 50 or 200 Hz, they showed a decrease in cocaine-induced locomotor activity (Kim et al., 2013). Pacinian corpuscles mainly located in the deep subcutaneous tissue are responsive to stimuli at a high frequency of 200 Hz and Meissner corpuscles found in the superficial layer of the dermis are sensitive to the low frequency of 10−50 Hz (Purves et al., 2001). Thus, the effects of acupuncture might result from activation of mechanoreceptors in the subcutaneous tissue. Also, other approaches involving single-cell electrophysiology provide significant evidence for mechanical stimulation modulation of VTA GABA and dopamine neurons in rats (Bills et al., 2020). Together, these results imply that mechanoreceptors may have a functional role in the brain beyond simply carrying somatosensory information to the brain. Additionally, results showed that acupuncture inhibition of cocaine-induced locomotion was not affected by a specific C/A-fiber blocker resiniferatoxin or stimulation of C/Aδ-fiber with capsaicin, while acupuncture stimulation activates A-fiber and C/Aδ-fiber in the ulnar nerve (Kim et al., 2013). These findings indicate that acupuncture-mediated suppression of the locomotor response to cocaine takes place by A-fiber activation of ulnar nerve projecting from mechanoreceptors in superficial and deep tissue. Indeed, it has been shown that mechanical stimulation of the ulnar nerve inhibits cocaine-induced locomotion (Chang et al., 2017). Further support for the implication of A-fiber in peripheral afferent mechanisms of acupuncture was obtained from the observation that acupuncture at HT7 activates retrograde tracer-labeled A-fiber induced by local injection of retrograde tracer into HT7 points (Kim et al., 2013).

5.2. Dorsal column pathway in acupuncture

Studies regarding the specific sensory afferent mechanisms involved in acupuncture inhibition of psychomotor response to cocaine have

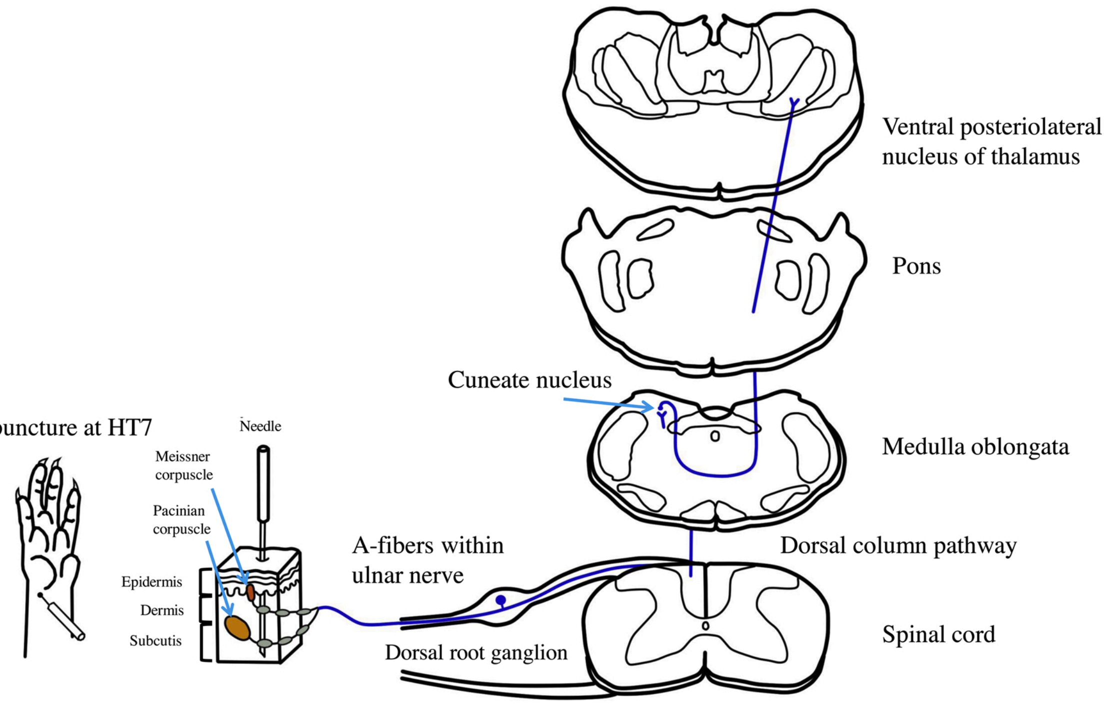

Fig. 3. Transmission of acupuncture afferent signals.
Acupuncture stimulation activates peripheral mechanoreceptors in skin and muscle, causing them to send impulses to large A-fibers within the ulnar nerve. Subsequently, sensory signals are transmitted to the ventral posterolateral nucleus of the thalamus via the dorsal column pathway, and can in tum activate the lateral habenula, thereby leading to the activation of excitatory inputs to ventral tegmental area GABA neurons.

revealed that the dorsal column pathway might be particularly important for transmitting acupuncture signals from the periphery to the mesolimbic dopamine system. Surgical lesions of the dorsal column pathway including the cuneate nucleus (CN), but not those of the spinothalamic tract, prevented the suppression of the locomotor response to cocaine by acupuncture-like stimulation of the ulnar nerve. Mechanical stimulation of the ulnar nerve activated the CN and lateral habenula (LHb) neurons projecting to the rostromedial tegmental nucleus (RMTg), as evidenced by increases in neuron firing rate in the LHb and c-Fos expression in the CN and LHb neurons retrogradely labeled from the RMTg regions. However, lesions of the LHb eliminated the inhibition of cocaine-induced locomotion produced by peripheral sensory stimulation. In addition, blockade of cocaine-induced neuronal activation in the NAc was displayed using electrolytic lesions of the dorsal column pathway and the LHb (Chang et al., 2017). This suggests that acupuncture may activate the LHb neurons projecting to the RMTg via the dorsal column pathway and reduce VTA dopamine neuron activity. As the LHb appears to particularly send inhibitory reward signals to the VTA dopamine neurons via GABA neurons in the RMTg or GABA neurons in the VTA that receive glutamate input from the LHb (Velasquez et al., 2014), the reduction in dopamine neuron activity may be responsible for acupuncture inhibition of cocaine response. As acupuncture activates the LHb via the ulnar nerve and the dorsal column pathway, sensory stimulation of acupuncture appear to activate GABA neurons in the RMTg via afferent neurons from the LHb, and GABAergic fibers projecting from the RMTg can, in turn, reduce the expected increases in VTA dopamine neuron activity and locomotor activity in response to cocaine. A role for the spinal dorsal column pathway in acupuncture inhibition of addictive behaviors was extended by the recent observation that acupuncture reduced intravenous morphine and oral ethanol self-administration, which was blocked by surgical lesion of the CN. Also, HT7 stimulation produced an enhancement of neuronal firing rate in the CN (Chang et al., 2019b).

While results show that HT7 stimulation is capable of activating the LHb-RMTg pathway, it is unclear how peripheral input activated by acupuncture enters the LHb. A previous study revealed that lesions of the ventral posterolateral nucleus (VPL) of the thalamus abolish activation of LHb neurons induced by acupuncture-like stimulation of the ulnar nerve, indicating a putative VPL-LHb circuit (Chang et al., 2017). However, little is known about how the VPL is connected to the LHb via a neural circuit that allows the transmission of signals. It has been shown that the VPL projects to the insular cortex (Zhang and Oppenheimer, 2000) and the insular projection neurons send afferents to the prefrontal cortex (Hoover and Vertes, 2007), which projects to the LHb (Kim and Lee, 2012). Interestingly, evidence from a neuroimaging study in healthy subjects showed that HT7 acupuncture activated the prefrontal cortex and insular cortex (Yang et al., 2017). Thus, it can be speculated that the prefrontal cortex may be a relay site where peripheral sensory signals induced by HT7 acupuncture are transmitted from the VPL to the LHb. Despite the uncertainty on the connection between the VPL and the LHb, results indicate that a putative circuit linking the VPL-LHb-RMTg may provide neural mechanisms for acupuncture inhibition of cocaine-induced psychomotor responses (Fig. 3).

6. Human functional neuroimaging of acupuncture for drug craving

6.1. Neural correlates of drug cue reactivity

Functional neuroimaging methods provide the fundamental basis for neural communication in the brain with the indirect measurement of neural activity. Functional magnetic resonance imaging (fMRI), as a non-invasive and high spatial resolution neuroimaging, has become a valuable tool for investigating the human brain function. An important aspect of this method is that increased neural activity in brain regions is related to a particular behavioral function (Buckner et al., 2009; Hsieh et al., 2011).

According to the incentive sensitization theory of addiction, repeated drug administration induces sensitization in the mesolimbic dopamine pathway that attributes incentive salience to drugs and drug-associated cues, resulting in wanting or craving for drugs (Robinson and Berridge, 2008). Cue-elicited craving for drugs has long been considered a driving force for compulsive drug seeking and relapse in addicts (Brody et al., 2002; Grusser et al., 2004). Such increased incentive salience of drug-related cues has been demonstrated in human studies using functional neuroimaging, as elicited by enhanced brain activation in the mesocorticolimbic pathway, including the VTA, NAc, amygdala, anterior cingulate cortex, prefrontal cortex, insular, and hippocampus (Jasinska et al., 2014). Neuroimaging methods have been commonly used to identify brain regions related to cue-elicited craving during the presentation of visual cue-exposure including photographs or movies associated with the drug, drug use, or episodes of drug use. A few fMRI studies were undertaken to investigate the neural substrates involved in reactivity from cues, craving for drugs, in drug addicts. An fMRI study of cue-induced heroin craving in heroin addicts has shown a significant positive correlation between VTA activation and cue-elicited craving during exposure to heroin-related visual cues, suggesting the prominent involvement of VTA in cue-induced heroin craving. Addicts also displayed significant activation in the prefrontal cortex and limbic areas such as the amygdala and hippocampus (Zijlstra et al., 2009). Given VTA afferents to the prefrontal cortex and limbic areas, this study suggests that heroin-related stimuli might induce craving through activation of the mesocorticolimbic dopaminergic system. Similar results have been achieved using fMRI for alcoholics. The alcoholics exhibited a significant increase in cue-elicited craving and brain activation in the prefrontal cortex, limbic areas, and VTA, showing a positive correlation between craving and neural activation in these areas induced by alcohol cues (Myrick et al., 2004). Other studies have assessed brain activity after exposure to smoking-related cue in smoking-deprived smokers. The fMRI finding revealed that exposure to smoking-related cue produced significant activation in mesolimbic dopamine reward circuits including the right posterior amygdala, posterior hippocampal region, and VTA (Due et al., 2002; Smolka et al., 2006). In summary, these results demonstrate the consistent neural response to drug-related cues, implying a common set of brain regions engaged in response to cue-induced drug craving across all cue-induced craving studies. These regions include the mesocorticolimbic circuitry implicated in the reward, motivation, and goal-directed behavior in response to drug-related stimuli (Jasinska et al., 2014; Kuhn and Gallinat, 2011).

6.2. *Brain circuits related to acupuncture*

6.2.1. *The mesolimbic pathway in acupuncture*

The neural underpinnings of acupuncture revealed by fMRI studies in humans ultimately may help us to accept acupuncture therapy into the practice of modern medicine. Considerable evidence has demonstrated that fMRI has allowed brain responses to acupuncture to be possibly studied. Brain responses to acupuncture stimulation involve a broad neuronal network of regions including not only emotion, motivation, and reward processing but also somatosensory processing (He et al., 2015). One study attempted to determine changes in the neural activity of discrete brain regions in 13 normal subjects exposed to acupuncture at Hegu (LI4) using fMRI. This study showed that acupuncture produced significant decreases in the activity of the limbic system, including the mesolimbic pathway, in 11 subjects who experienced a clinical *Deqi* sensation of acupuncture, an essential prerequisite for a clinical acupuncture effect, while the two subjects who experienced pain during acupuncture stimulation displayed signal increases in the limbic system. On the contrary, superficial tactile stimulation as control stimulation activated mainly the somatosensory cortex (Hui et al., 2000). These results provide evidence for the involvement of the limbic system including the mesolimbic dopamine pathway in the central effects of acupuncture. Based on the ability of psychostimulants including cocaine and nicotine to increase activity in limbic areas including the NAc (Breiter et al., 1997) and the known therapeutic effects of acupuncture on cocaine addiction (Margolin et al., 1993), it was suggested that these brain areas might be involved in a role for acupuncture in reducing drug craving (Hui et al., 2000). How might be the *Deqi* sensation modeled in animals studies? Although there have been no reports regarding the *Deqi* sensation in rats, it would be interesting to assess the effect of acupuncture on the *Deqi* sensation in rats. While it is not possible for rats to report themselves, they are known to have the ability to communicate by ultrasonic vocalization (USV). Indeed, it has been demonstrated that rats emit 22 kHz USV in response to painful stimuli (Barroso et al., 2019) and 50 kHz USV in appetitive situation (Brudzynski, 2009). Thus, it opens the possibility that difference in acupuncture sensation (*Deqi* vs. pain) can be indirectly measured in rats using an USV test.

These acupuncture effects on the activities of the limbic system related to *Deqi* sensations have been confirmed in a successive fMRI study (Hui et al., 2005). Thus, given the ability of dopamine as a neuromodulator in the limbic system (Avery and Krichmar, 2017), dopamine may be important for the actions of acupuncture in the limbic system. In addition, the significant deactivation of abundant dopamine neurons in the limbic system of human brains by acupuncture (Hui et al., 2000), combined with observations of EA inhibition of the neural activity linked to dopamine release in the striatum induced by amphetamine as measured in rats by combined fMRI and microdialysis (Chen et al., 2008), support the possible role of EA in modulating dopaminergic neuron activity in the limbic system and drug-seeking and craving. In support of this finding, an fMRI study in healthy adults has shown that acupuncture at Taichong (LR3), Xingjian (LR2), and Neiting (ST44) produced deactivation of the limbic-paralimbic-neocortical network, suggesting that acupuncture may reduce anxiety through the modulation of intrinsic neural circuits including the amygdala, the structure implicated in emotion and motivation (Fang et al., 2009). As the amygdala has long been implicated in motivational significance for anxiety-like effects of drug withdrawal (Koob, 2020), these findings show the possibility that acupuncture may work in the brain motivational systems to reduce drug-seeking motivation.

Another fMRI study in heroin addicts suggests the role of the hypothalamus in the typical acupuncture sensation and the central effects of acupuncture. This study has reported that heroin addicts exhibit greater neural activation in the hypothalamus as well as the magnitude of the *Deqi* sensation than healthy subjects during acupuncture stimulation. Furthermore, a significant positive correlation was found between the hypothalamus activation and the magnitude of *Deqi* sensation (Liu et al., 2007). Based on the previous finding that acupuncture activates the hypothalamus containing abundant endorphinergic neurons projecting to the mesolimbic dopamine system (Chang et al., 2019a), the hypothalamus can be recruited for another candidate possibly involved in acupuncture's role in suppressing drug-seeking and craving in the negative reinforcement of drug addiction.

6.2.2. *Cue-elicited drug craving in acupuncture*

Although introduced relatively less, studies using fMRI in humans have provided some evidence for a neural substrate in acupuncture modulation of brain activation and addictive behaviors, in particular cue-elicited craving. An interesting study was undertaken to identify the effects of acupuncture on cue-induced craving by stimulating HT7 acupuncture points in male smokers during smoking abstinence. This was compared with the effects of sham acupuncture by poking the skin over HT7 points with von Frey monofilament. Acupuncture produced significant decreases in smoking craving and brain activation in the medial prefrontal cortex, the amygdala, and the hippocampus induced by smoking-related visual cues. This study implicates acupuncture inhibition of smoking craving by modulating brain responses to smoking-related cues (Kang et al., 2013). The reduction in the activity of the amygdala by acupuncture appears to support a role for acupuncture in suppressing anxiety-like behavior in nicotine-withdrawn rat through modulation CRF in the amygdala associated with nicotine dependence (Chae et al., 2008). As brain stress systems contribute to the negative emotional state responsible for drug-seeking through the negative

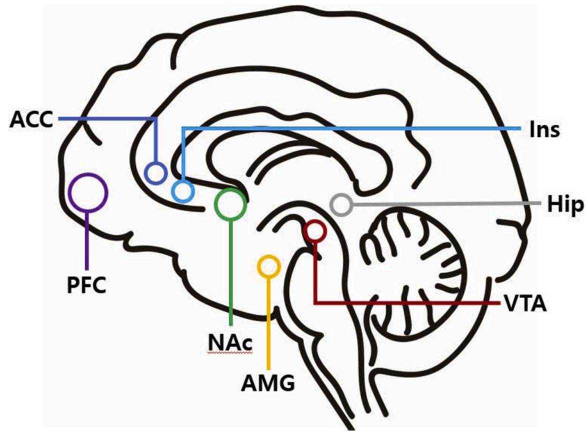

Fig. 4. Diagram depicting the major brain areas implicated in acupuncture inhibition of cue-elicited drug craving in humans. Studies using functional magnetic resonance imaging in an individual with drug use disorder provide some evidence for neural substrates including the mesocorticolimbic dopamine pathway in acupuncture-mediated inhibition of cue-elicited craving. Abbreviations: PFC, prefrontal cortex; ACC, anterior cingulate cortex; Ins, insular cortex; NAc, nucleus accumbens; AMG, amygdala; VTA, ventral tegmental area; Hip, hippocampus.

reinforcement (Koob, 2020), acupuncture may reduce smoking seeking and craving by ameliorating negative effects. On the other hand, the processing of contextual cues and memories associated with drug-seeking behavior may involve the amygdala and hippocampus. Additionally, sensitization of the mesocorticolimbic dopamine pathway that originates in the VTA and projects to the amygdala, prefrontal cortex, and nucleus accumbens, may result in enhanced responding to contextual cues, which facilitates drug-seeking and craving (Zijlstra et al., 2009). Although signal changes on fMRI in response to smoking-related cues were not observed in the VTA, this raises an interesting possibility that the inhibitory action of acupuncture on smoking cue-induced craving may result from decreased dopaminergic transmission in the mesocorticolimbic network.

Similar results have been obtained from the other fMRI study where heroin addicts were given acupuncture at ST36 after exposure to the heroin-related cue. This study showed that acupuncture significantly attenuates the expected increases in the activity of craving-related brain areas including the cingulate cortex and the insula (Cai et al., 2012). In support of acupuncture for craving-related brain areas, 2 Hz transcutaneous electrical nerve stimulation has been shown to decrease cue-induced heroin craving in heroin addicts (Zhong et al., 2006). Although difficult to explain based on this finding that cue reactivity was observed mainly in cortical territories but not subcortical limbic areas (Cai et al., 2012), it can be speculated that acupuncture may play a role in suppressing drug relapse and alleviating craving in addicts in response to heroin-related stimuli perhaps by modulating the cingulate cortex and the insula, structures engaged in craving response to drug-related stimuli (Jasinska et al., 2014; Ray and Roche, 2018). Through the fMRI results, the cingulate cortex and insula also proved to be the sensitive site for acupuncture to reduce self-developed cravings for smoking (Wang et al., 2019). The other fMRI study, carried out on social drinkers without a history of psychiatric diseases, has suggested that acupuncture at HT7 points, but not at LI5 points increased activity in brain regions related with emotional self-control including the prefrontal cortex, the inferior parietal lobule, and the insular cortex and significantly enhanced alcohol abstinence self-efficacy in female (Yang et al., 2017). Based on neuroimaging studies showing brain functional and structural anomalies that reflect emotion-regulation deficits in individuals with drug use disorders (Ersche et al., 2013; Kober et al., 2014), this suggests the possibility that acupuncture may ameliorate deficient emotional self-control to drugs of abuse.

Taken together, notwithstanding the insufficiency of fMRI data, the evidence reviewed here might lead to a suggestion that acupuncture may alleviate cue-elicited drug craving possibly through regulation of brain activation involved in cue-elicited drug craving (Fig. 4). Indeed, a systematic review identified that there was a trend for acupuncture to reduce craving and anxiety during drug withdrawal (Grant et al., 2016). However, it is difficult to reach a strong conclusion that acupuncture is effective in treating drug craving due to the generally poor methodological quality and lack of useful evidence in clinical studies (Grant et al., 2016).

7. Discussion

Acupuncture plays a pivotal role in restoring the harmonic balance between Yin and Yang when the innate potentialities for maintaining homeostasis in the body are overwhelmed by the cause of illness (Leung, 2012). Acupuncture is essentially a therapeutic intervention for correcting reversible physiological malfunction of the body by the stimulation of specific acupuncture points located along the meridian through the insertion of metallic needles (Stux et al., 2003). Consequently, the view of how acupuncture inhibits drug relapse reviewed here suggests that acupuncture can achieve recovery of homeostasis by providing the biochemical balance in the central nervous system through the regulation of neurotransmitters that control addictive behaviors.

There are two different theories in the role of brain reward pathways in mediating drug-seeking behavior: the incentive sensitization theory (Robinson and Berridge, 2003) and the opponent process as a motivational theory for the negative reinforcement (Koob and Le Moal, 2008b) Although it is commonly accepted that the same neural systems are responsible for drug reward and drug-associated learning, these theories have seemingly opposite views on the role of the mesolimbic dopamine pathway in mediating drug-seeking behavior. The incentive-sensitization theory proposes that drug seeking is triggered by specific drug effects and drug-associated stimuli that activate a sensitized reward pathway. In contrast, opponent process theory proposes that drug-opposite or opponent process contributes to drug seeking by causing a hypo-functional state of reward pathway which leads to negative emotional state that accompanies drug withdrawal. This suggests that drug craving can arise from states involving either hyper- or hypofunction of brain reward system including the mesolimbic dopamine pathway. From this suggestion, it seems reasonable to propose that a therapeutic intervention to correct both dysfunctions may be an effective solution to drug addiction. This review provides evidence that acupuncture normalizes hyper-reactive or hypoactive states of the mesolimbic dopamine system in these opposed process in drug addiction. The Yin and Yang theory may likely account for these two different theories of opposite views on the role of the brain reward pathway in drug pursuit. Thus, it is hypothesized that acupuncture may contribute to the homeostasis and balance between negative and positive impact on drug addiction.

Indeed, there is some direct support for this hypothesis in an in vivo microdialysis study during ethanol withdrawal and after the ethanol challenge in chronic ethanol-treated rats (Zhao et al., 2006). Acupuncture at HT7 significantly inhibited both a decrease of dopamine release during ethanol withdrawal and an increase in dopamine release after the ethanol challenge in ethanol dependent rats. This dual paradoxical effect of acupuncture on accumbal dopamine release implies that acupuncture enables the function of the brain reward pathway to return to its normal operating level. This result shows, for the first time, neurochemical evidence for bidirectional role of acupuncture in animal model of drug addiction. In support of this finding, growing evidence suggests that acupuncture can contribute to recovery of homeostasis by activating the adaptive control of the central nervous system (Pan, 2019). It would be interesting to determine the possible mechanism underlying the bidirectional regulation role of acupuncture in regulating accumbal dopamine release in ethanol-dependent rats.

Acupuncture activates β-endorphinergic neurons in the ARC of the hypothalamus (Wang et al., 1990a, b) and endorphinergic fibers projecting from the ARC can, in turn, activate opioid receptors on GABA neurons in the VTA and NAc (Mansour et al., 1988). A previous study showed that acupuncture reverses ethanol's inhibitory effects on VTA GABA neurons (Yang et al., 2010). As ethanol and acupuncture both inhibit GABA neurons via MORs on VTA GABA neurons, this counter-intuitive result suggests that acupuncture effects may result from desensitization of MORs on GABA neurons, thereby causing an increase in GABA neuron activity. Subsequently, enhancing GABAergic inhibition in the VTA inhibits dopamine release in NAc induced by a systemic ethanol challenge. In contrast, recent results demonstrated that acupuncture increases β-endorphin release in the NAc during ethanol withdrawal and accumbal β-endorphin in turn activates VTA dopamine neurons (Chang et al., 2019a). Given that β-endorphin activates MORs expressed on accumbal GABA input to VTA dopamine neurons (Watabe-Uchida et al., 2012), this finding suggests that β-endorphin may disinhibit VTA GABA neuron activity and subsequently cause an increase on dopamine release in the NAc. Accordingly, it can be hypothesized that the central endorphin system may mediate acupuncture's role in bidirectional regulation of hyper- or hypofunction of the mesolimbic dopamine system. This interesting subject merits additional studies to identify how acupuncture works in the brain to correct dysfunctions of the mesolimbic dopamine system.

The review provides evidence that acupuncture modulates the mesolimbic dopamine system and drug-seeking behavior by directly activating the brain pathway via somatosensory stimulation. This implicates the specific role for peripheral sensory afferents in the treatment of drug addiction. Yet, to date, there has been little known about the extra-somatosensory effects of peripheral sensory nerve. However, the evidence reviewed above suggests that peripheral sensory afferents including mechanoreceptors in the superficial and deep tissue are doing more than simply relaying sensory information. From this standpoint, this review demonstrates the need to broadly explore the extra-somatosensory effects of somatosensory stimulation.

Innovative therapeutic intervention directly targeting the mesolimbic dopamine system may also be efficacious for various functional disorders including depression, ADHD, and anxiety. Now more than ever, new treatment approaches to these mental disorders are urgently needed. Thus, it would be interesting to determine whether somatosensory stimulation as a therapeutic intervention plays a role in the development of alternative treatment for mental disorders. Given the evidence reviewed here, there seems to be an answer to the question that somatosensory stimulation may be effective for treating mental illness. Furthermore, translational findings in other brain regions will expand our understanding of the role of somatosensory stimulation, while evidence indicates that somatosensory stimulation's effects are specific to the mesolimbic dopamine pathway.

Table 1
Anatomical location of acupoints commonly used in experimental studies on acupuncture for drug addiction.

Acupoint	Location
HT7	At the palmar wrist crease, on the anteromedial aspect of the wrist, radial to the tendon of the flexor carpi ulnaris
LI4	On the dorsal aspect of the hand, in the middle of the 2nd metacarpal bone on the radial side
LI5	On the posterolateral side of the wrist, at the radial side of the dorsal wrist crease, in the depression between the tendons m. extensor pollicis longus and brevis and between the radial styloid process and scaphoid bone
LR2	On the dorsal aspect of the foot, between the first and second toes, proximal to the margin of the web, at the junction between the red and white flesh
LR3	On the dorsal aspect of the foot, in the depression distal to the junctions of the 1 st and 2nd metatarsal bones
KI9	On the posteromedial side of the leg, between the soleus muscle and the calcaneal tendon, 5 B-cun above the prominence of the medial malleolus on the line connecting KI3 and KI10
SI5	On the ulnar side of the wrist, in the depression between the triquetrum bone and the ulnar styloid process
SP6	On the tibial side of the leg, posterior to the medial border of the tibia, 3 B-cun directly above the prominence of the medial malleolus
ST36	With the leg straight, on the anterior border of the tibia, on the line connecting ST35 with ST41, 3 B-cun below ST35.
ST44	On the dorsal aspect of the foot, between the 2nd and 3rd metatarsal bones, proximal to the web margin, at the border between the red and white flesh.

While animal studies revealed consistent results that acupuncture suppresses relapse to drug-seeking behavior (Motlagh et al., 2016), some clinical studies have provided inconsistent evidence for the inhibitory effect of acupuncture on substance use disorders (Grant et al., 2016). Such inconsistency may be at least in part related to many vagaries, including the location of stimulated acupoints, and the period, frequency, and intensity of acupuncture stimulation, thereby resulting in low reproducibility and high individual variations among acupuncturists in clinical trials. More well-designed and rigorous clinical studies are of primary importance for determining the effectiveness of acupuncture in the treatment of drug relapse. Importantly, a systematic review and meta-analysis have shown that there is a significant difference in withdrawal symptoms including craving and anxiety, but not in relapse between acupuncture and comparators at post-intervention. These results were limited by inadequate quality bodies of evidence, however (Grant et al., 2016). These data, combined with observations of brain response as measured by fMRI and the craving intensity, suggest that acupuncture may be a solution to provide effective therapeutic intervention in drug addiction. The neurobiological data reviewed above imparts evidence that acupuncture therapy reduces drug relapse by regulating neurotransmitters in the brain through stimulation of specific sensory receptors on the skin and muscle around acupuncture points (Table 1, Fig. 5). However, there are still many unanswered basic mechanisms underlying acupuncture's effectiveness in the treatment of drug addiction. More research using animal models is needed to elucidate the mechanism of acupuncture-mediated inhibition of chronic drug relapse and to assess acupuncture's therapeutic value in the treatment of drug addiction. Understanding the specific neurobiological mechanisms of acupuncture may ultimately help guide us in utilizing acupuncture to treat drug addiction.

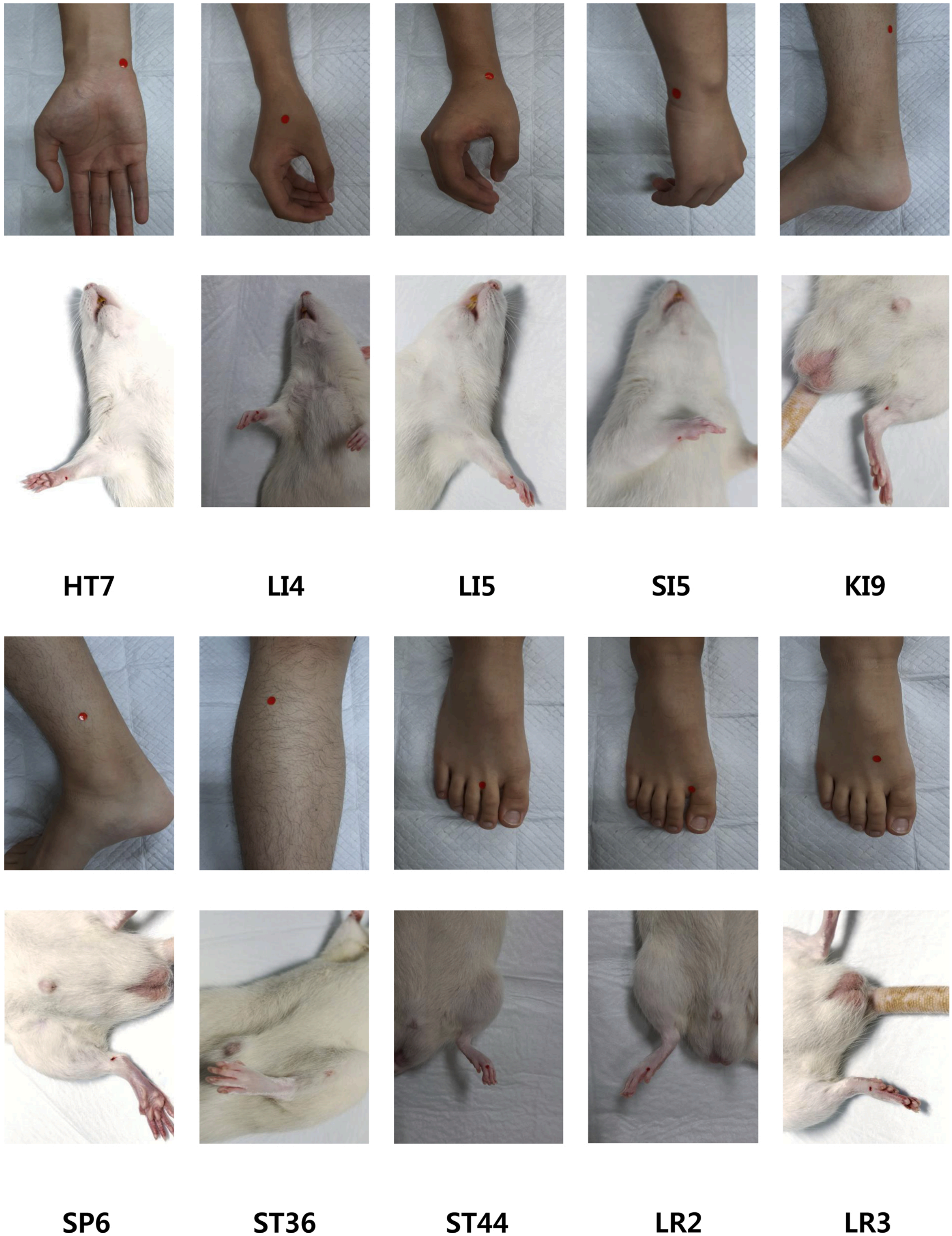

Fig. 5. Locations of acupoints commonly used in experimental studies on acupuncture for drug addiction. Anatomical location of stimulated acupoints in animals were those corresponding to acupoints in human as described in WHO standard acupuncture point locations in the western pacific region (WHO Regional Office for the Western Pacific, 2008).

Author contributions

MYL and CHY devised and drafted the contents of the manuscript. BHL and HYK carried out bibliographical research. All authors reviewed the content and contributed to approving the final version for publication.

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