

Arousal effect and potential mechanism of dopamine-mediated acupuncture on traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is a brain injury caused by direct external forces, and its prognosis depends on the extent of the damage and the changes in level of consciousness. Timely awakening from a coma is the first thorny problem to be solved in TBI treatment. Therefore, there is a need for the development of safe and effective methods for timely awakening after TBI coma. Dopamine (DA) and its receptors in the nervous system are involved in the regulation of wakefulness. The amount and activity of dopaminergic neurons can affect cellular function and neuroinflammatory response, and are also significant for the awakening process after TBI. The current common awakening therapy for TBI may also be related to the activation of dopaminergic neurons. Acupuncture plays a beneficial role in timely awakening, recovery of conscious level, and functional rehabilitation after TBI. The mechanism may be related to the targeted regulation of DA and its receptors via acupuncture. Among acupuncture first aid therapies, acupuncture at hand 12 Jing-Well points, with its advantages of simple operation and ultra-early intervention, has shown great promise in timely awakening following TBI and triggering a series of subsequent nerve repair effects in the treatment of TBI. We here present a review that provides a new perspective for the timely awakening from TBI-induced coma, with a focus on the role of DA in the regulation of wakefulness and the efficacy and potential mechanism of DA systems in the treatment of TBI by acupuncture.

Keywords: Acupuncture, Coma, Dopamine, Traumatic brain injury, Wakefulness

1 Introduction

Traumatic brain injury (TBI) is a global public health problem and one of the major causes of death and disability^[1]. It is estimated that there are 50 million cases of TBI worldwide each year, of which traffic accidents and falls are the main causes^[2–3]. In addition, TBI costs the global economy about \$400 billion annually, that is, 0.5% of the global gross domestic product^[4–5]. Patients with severe TBI usually experience coma and serious disturbance of consciousness, movement, language, cognition, and activities of daily life. About 10% to

15% of patients with TBI remain in a coma or vegetative state (VS) for a long time, which brings heavy economic burden on their family and society^[6]. Therefore, the prompt recovery of consciousness of coma patients following TBI is an important goal in the field of neurological rehabilitation.

The maintenance of normal consciousness depends on the brainstem ascending reticular activation system (ARAS) and its projection to the bilateral thalamus and telencephalon. Dopaminergic neurons in the ventral periaqueductal gray (vPAG) are located at the crosstalk of two arousal routes of the ARAS and can project to the hypothalamus via the dopamine (DA) receptor system^[7]. DA is an essential endogenous catecholamine that plays a wide range of roles in neuronal and non-neuronal tissues as a neurotransmitter or in an autocrine or paracrine signaling manner^[8]. Various physiological functions of DA are mediated by at least five different G protein-coupled receptor subtypes (GPCRs) (ie, D1, D2, D3, D4, and D5)^[9]. In the central nervous system (CNS), dopaminergic neurons play a key role in the regulation of consciousness, movement, learning, memory, motivation, cognition, and emotion^[10]. DA affects various regions of the brain, mainly the hippocampus, substantia nigra (SN), striatum, ventral tegmental area (VTA), and frontal cortex^[11]. Damage to these regions and destruction of dopaminergic neural circuits lead to reduced DA synthesis, loss of dopaminergic neurons, and destruction of the dopaminergic system, which are closely related to the degree of coma and disturbance of consciousness after TBI^[12]. There is evidence that TBI-induced coma is closely related to the content and activity of DA, and the activity of the dopaminergic system^[13]. At present, the treatment methods of TBI for wakefulness and recovery from consciousness disturbance include neurotransmitter

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drugs, surgery, and nerve stimulation^[4]. However, there is limited high-quality medical evidence for the therapeutic effects of these awakening therapies. Moreover, these therapies must be carried out in patients with stable vital signs, which limits their use and makes it difficult to achieve ultra-early intervention. Therefore, the development of safe and effective methods for timely awakening after TBI coma is still a challenging area in neuroscience research.

Acupuncture originated in China and has been used for nearly 5,000 years, with the meridian and selective acupoints are stimulated to maintain health or treat disease via various techniques such as manual acupuncture, electroacupuncture, and moxibustion^[14]. A meta-analysis and systematic review of acupuncture intervention in the treatment of TBI in the acute and rehabilitation phases concluded that acupuncture can achieve TBI awakening, improvement of consciousness disorders, and recovery of neurological function, and the mechanism may be related to acupuncture enhancing the excitability of the ARAS circuit and the dopaminergic system^[15–16]. At present, acupoints such as Shuigou (GV26), Yingxiang (LI20), Sishencong (EX-HN1), Baihui (GV20), 12 Jing-Well points and Shixuan (EX-UE11) acupoints are internationally recognized acupoints with arousal ability to a certain extent^[17–18]. Among the above acupoints with effectiveness as first aid, hand 12 Jing-Well points (HTWP) were first found in *Inner Canon of Huangdi (Huang Di Nei Jing)*, and have the advantage that they can be used in early intervention in a timely manner after coma. Basic research also suggests that HTWP can effectively improve acute central nervous injury (ACNI)-caused clinical symptoms such as coma, disturbance of consciousness, and nerve function defect; their action mechanism is associated with brain protection and neuroprotection^[19]. Our recently published study found that HTWP-treated TBI coma and disturbance of consciousness are also associated with the brainstem neural network and the dopaminergic system^[20]. By searching the China National Knowledge Infrastructure (CNKI) and PubMed, we collected the relevant literatures in the past 20 years on acupuncture intervention in TBI, systematically evaluated the efficacy of acupuncture intervention in TBI and explored the potential mechanism of DA system in the process of acupuncture promoting awakening. This review provides a new perspective for the timely awakening from TBI-induced coma by reviewing the role of DA in the regulation of wakefulness, and the efficacy and potential mechanism of DA systems in the treatment of TBI by acupuncture.

2 The dopaminergic system is involved in the regulation of wakefulness

2.1 Pivotal wakefulness circuits in the human body

Arousal is an important part of consciousness and a prerequisite for the brain to perform other functions. ARAS is characterized by a variety of neurons and multiple synapses, which can maintain the awake state of the cerebral cortex by broadly upward projection of arousal neurons to other brain regions^[7,21]. The ARAS nucleus arises from the bulbar brainstem and extends to the diencephalon, where it divides into two arousal pathways, both of which eventually project to the cerebral cortex^[7]. These two arousal pathways of ARAS present a

wide range of cell populations that extend to the limbic system and the entire cerebral cortex, including the following projections: (1) noradrenergic fibers from the locus ceruleus; (2) serotonergic fibers from the median raphe nucleus; (3) acetylcholinergic fibers from the tegmental nucleus; and (4) dopaminergic fibers emitted by vPAG. These neural circuits are closely related to the maintenance of awakening, and the damage to any pathway will affect the state of consciousness awakening. Thus, the normal activity and disorder of ARAS is the anatomical basis of consciousness awakening and coma, respectively.

2.2 Dopamine and other neurotransmitters are involved in the regulation of wakefulness

Studies prior to 2,000 found that the firing activity of acetylcholinergic, noradrenergic, and serotonergic neurons varied widely during the sleep-wake cycle, while the firing frequency of dopaminergic neurons varied only slightly^[22]. Therefore, changes in acetylcholine (ACh), serotonin (5-HT), or norepinephrine (NE) are considered to be more critical in the regulation of arousal-related cortical electroencephalography (EEG), while dopaminergic neuron activity is more involved in the regulation of movement or behavior, and its role in the regulation of arousal is controversial. However, in a study published in 2001, Wisor et al.^[23] found that the loss of dopamine transporter (DAT) reduces the duration of non-REM sleep and is involved in the regulation of arousal independently of motor and behavioral functions, suggesting that DAT also plays an important role in the regulation of arousal. Since then, the ability of the dopaminergic system to mediate wakefulness has been gradually discovered. It has been shown that the brainstem reticulum can be subdivided into different functional regions, in which the damage to the brain region where dopaminergic neurons are widely distributed will disrupt the wakefulness system and lead to coma^[24]. Specifically, during wakefulness, dopaminergic neurons in striatum inhibit the globus pallidus, thereby preventing it from inhibiting the thalamus; then, the thalamus activates the cerebral cortex and receives positive feedback, and excitatory inputs from the cortex and thalamus activate striatum to maintain normal neural circuits. In addition, the excitation of neurons can induce the release of various neurotransmitters, leading to the excitation or inhibition of effector cells, among which DA serves as an excitatory neurotransmitter to maintain circadian rhythm and wakefulness^[25]. Therefore, the detection of changes in the content of neurotransmitters can indirectly reflect the structural integrity and functional status of relevant neural nuclei. As Ach and DA are important neurotransmitters in the brain, their balance and coordination not only affect changes in muscle tension, but also play an important role in the regulation of the sleep-wake cycle and the maintenance of consciousness.

3 Dopaminergic system is involved in awakening after TBI coma

3.1 Dopaminergic system and TBI-induced coma

TBI refers to the brain dysfunction caused by external forces or damage to the brain structure^[26]. The induced coma is closely related to the dysfunction of ARAS and the

dopaminergic system. DA receptors are known to be highly expressed in brain regions that are damaged following TBI, such as the frontal cortex and striatum^[27]. Severe TBI may damage the thalamocortical projections and affect the SN-striatum circuit^[28]. Therefore, it is very important to clarify the changes in DA after TBI, in order to treat the TBI and recover consciousness. DA level in the cerebrospinal fluid (CSF) is positively correlated with the level of consciousness one hour after TBI (ie, acute phase), and the disturbance of consciousness in TBI patients with frontal lobe damage is also associated with abnormal dopaminergic neuron projection^[29–30]. It has been reported that, from the occurrence of TBI to the stable illness condition, DA level in brain regions associated with TBI were slightly elevated, followed by a low DA state. After 28 d of cortical injury, the number of dopaminergic neurons in SN and CSF decreased, the blood-brain barrier was destroyed, and microglia were activated, subsequently causing neuroinflammation^[31–32]. DAT expression was also decreased after TBI, which may be due to the loss or reduction of dopaminergic neurons leading to compensatory down-regulation of DAT and reduced DA activity^[33–34]. Human imaging studies have shown changes in DAT and D2 receptor levels and binding affinity in striatum after TBI coma^[35]: reduced DA after TBI may lead to increased D2 receptor binding due to reduced competitive binding of endogenous DA and/or compensatory upregulation of D2 receptor following impairment of the dopaminergic system. In the subregion with increased D2 receptor binding (ventral striatum), DAT levels did not decrease, indicating that there may be regional differences in the compensatory downregulation of DAT, which may cause changes in DA levels throughout striatum in order to maintain DA levels. Donnemiller et al.^[36] used single-photon emission computed tomography (SPECT) to demonstrate, for the first time, significant deficits in presynaptic and postsynaptic dopaminergic neurotransmitters in TBI survivors, suggesting that TBI is associated with the destruction of dopaminergic neural networks, which include the SN-striatum pathway, and that the increased severity of the damage may lead to more severe loss of dopaminergic neurons. In addition, elevated levels of tyrosine hydroxylase (TH) after TBI further suggest a potential pathologic compensatory mechanism, since TH is a monooxidase, a rate-limiting enzyme that catalyzes the synthesis of the first step of the L-DA, that is, the precursor of DA, series reactions by the organism itself^[37].

vPAG plays an important role in REM sleep gating^[38]. vPAG is not only one of the key projection sites of the arousal system, but also the relay station of the ventral and dorsal arousal pathways in the ARAS^[7]. Among them, the vPAG nucleus and its dopaminergic neurons are involved in maintaining arousal, an important part of arousal conduction. In the transmission pathway of ARAS, the dopaminergic neurons of vPAG play a vital role in the transmitters of the two wakefulness pathways, and its activity and quantity affect the waking state of the body^[39]. If the dopaminergic neurons of vPAG are damaged, sleep can be increased. The dopaminergic neurons of vPAG are projected to the histaminergic hypothalamic tuberomammillary nucleus and orexinergic hypothalamic region through their receptors. Therefore, we speculate that vPAG and its DA neurons may be critical for inducing coma and awakening.

3.2 Dopaminergic system and TBI wakefulness therapies

Since DA has come to be regarded as a key regulator of arousal, DA-related medication or alternative therapies have been used for the treatment of coma after TBI^[40]. At present, the commonly used therapies for awakening TBI coma include drug therapy, sensory stimulation, neuro-stimulation, hyperbaric oxygen therapy, and stem cell transplantation. Most of these methods have been demonstrated to promote arousal by regulating the ARAS and dopaminergic neurons.

3.2.1 Medication

The commonly used drugs for wakening are catechol-aminergic agents that act on different locations of the synapse, mainly amantadine^[41], bromocriptine^[42], levodopa, and apomorphine^[43–44]. By acting on different parts of the synapse, these drugs regulate the dopaminergic system, increase the production of dopaminergic neurons and the activity of DA receptors, and prevent DA reabsorption, thereby activating ARAS^[45]. Amantadine is an agonist of the dopaminergic system that alters the glutaminergic neurotransmitter and restores the balance between the dopaminergic and glutaminergic neurotransmitter systems. It is by far the best drug recommended by the United States Practice Guidelines for Disorders of Consciousness for TBI^[46]. Several clinical randomized controlled trials (RCTs) have shown that amantadine can significantly improve Glasgow Coma Scale (GCS) scores in patients with TBI coma^[47–48]. One RCT found that in 184 patients in a VS or minimally conscious state (MCS) caused by TBI, who received amantadine intervention for 6 weeks, function was recovered earlier than in the control group, with no increase in the risk of adverse reactions such as epilepsy. However, it is unclear whether prolonged application of amantadine would lead to resistance and side effects^[41].

Apomorphine is a subcutaneous dopaminergic agonist. A prospective clinical trial with a sample size of 8 was conducted in patients in a VS or MCS after TBI, with patients waking up within 24 h to 4 weeks of initiation of treatment, and 7 patients fully recovered from their disturbance of consciousness^[49]. However, there is no large RCT of apomorphine's effect on wakening, so the evidence for its effectiveness remains insufficient. Bromocriptine, a postsynaptic D2 receptor agonist, improved arousal and consciousness in 5 patients with TBI^[28]. In addition, in a clinical study involving 36 patients with mild TBI, bromocriptine promoted recovery and improved neurological sequelae and prognosis in patients with TBI^[50]. However, these DA drugs are more focused on the recovery from chronic disorders of consciousness after TBI, rather than timely awakening from the acute phase of TBI. Some reviews systematically evaluated the effects of DA agonist on different symptoms of TBI patients^[51], such as cognition, behavior, and safety, but there is significant clinical heterogeneity in the outcome assessments used in different studies, a lack of high-quality related RCTs, and no systematic screening of potential side effects. Therefore, it is difficult to draw definitive conclusions about the safety and efficacy of dopaminergic drugs in patients with TBI.

3.2.2 Stimulation therapy

Median nerve stimulation (MNS)^[52–53], spinal cord stimulation (SCS)^[54], sensory stimulation (SS)^[55], deep

brain stimulation (DBS)^[56], transcranial magnetic stimulation (TMS)^[57–58], and vagus nerve stimulation (VNS)^[59] are the most widely used wake-promoting therapies worldwide, and have been used in neurosurgery for more than 20 years^[60]. Right median nerve stimulation (RMNS) is a method of placing electrodes on the volar surface of the wrist to provide electrical stimulation, which can activate central nuclei and increase local cerebral blood flow (CBF) and nerve firing activity. RMNS has shown effects on improving consciousness disturbance, coma duration, and associated complications^[53]. RMNS can activate ARAS, which connects the brainstem reticular structure with the cerebral cortex through the excitatory transmission of the thalamic core layer, which may be one of the ways nerves are stimulated to promote awakening^[61]. Electrical nerve stimulation is also found to affect the secretion of neurotransmitters. The contents of neurotransmitters in CSF were measured before and after electrical nerve stimulation and it was found that the levels of ACh, 5-HT, DA, and NE in CSF increased to different degrees in a short period. The increase of DA and NE in the brain can enhance the energy metabolism of the cerebral cortex, reduce the oxidative stress response and reperfusion injury, and eventually delay and reduce the formation and development of brain edema, as well as promote the functional recovery of the cerebral ischemic penumbra, thus promoting the recovery of brain function^[62–64]. Although MNS and SCS therapy have been proven to improve TBI coma to a certain extent, they are both invasive stimuli with many complications and relatively expensive operating costs; thus, it is difficult to achieve intervention in the acute phase. Therefore, the application of these two methods in patients with early TBI coma is limited. For other stimulation therapies, such as SCS, DBS, TMS, and VNS, the relevant studies are still in the clinical research stage, and the awakening effect needs to be further confirmed by large RCTs.

In brief, the clinical efficacy of current arousal therapy, especially for patients in the acute phase of TBI, remains unsatisfactory. Therefore, an important direction of future research should be developing therapies that target the ARAS and dopaminergic system as early as possible, while ensuring patient safety.

4 Dopaminergic system is involved in acupuncture treatment of TBI-induced coma

4.1 Clinical effect of acupuncture on TBI

The brain governs human vital activities, both consciousness and sensorimotor. When TBI occurs, blood vessels in the brain are damaged and blood spills out of the vessels, resulting in abnormal brain function. Therefore, the main principle of traditional Chinese medicine (TCM) treatment for TBI is to promote blood circulation, remove extravasated blood, dredge meridians and collaterals, and restore the normal function of the brain^[65]. Acupuncture, an indispensable part of TCM and a unique medical method, has been proven to be effective in timely awakening and recovery from consciousness disorders. In clinical studies, the duration of coma, GCS, or Glasgow Outcome Scale was used to assess the degree of coma and level of consciousness in patients with TBI, and the Barthel Index, Functional Independence Measure, and Fugl-Meyer Assessment were used to assess motor and language function. Using the above therapeutic evaluation tools, it was found that

acupuncture exerts a awakening effect on patients with TBI, reduces the mortality rate after TBI, and is conducive to the rehabilitation of various functional disorders after TBI^[66–68]. A meta-analysis showed a significant reduction in coma status [relative risk (RR): 1.95, 95% confidence interval (CI): 1.64–2.31, $P < 0.01$], arousal rate (RR, 1.48, 95% CI: 1.19–1.83, $P < 0.01$), and GCS (RR, 1.78, 95% CI: 1.10–2.45, $P < 0.01$) after treatment in the acupuncture group compared to the control group^[69].

Acupuncture interventions for TBI-induced coma include various acupoint selection methods, such as acupoints in the scalp, body, ear, tongue, or a combination of these. Acupuncture at the scalp acupoints represented by GV20, EX-HN1, Shenting (GV24), GV26, Fengchi (GB20), Fengfu (GV16), and Yamen (GV15) is a common method to promote wakefulness. It mainly affects the function of the cerebral cortex and improves the blood flow velocity of the vertebrobasilar artery through the reticular structure of the brain, and changes its excitability, so as to make the process of nerve excitation and inhibition gradually return to normal^[69]. One study showed that conventional treatment combined with acupuncture of GV20, EX-HN1, GV24, anterior oblique parietotemporal line, and GV26 can improve the awakening rate of patients compared to that of the control group, and the average awakening time was significantly shorter than that of the control group^[70]. Huang et al.^[71] found that medication combined with scalp acupuncture could improve cognitive impairment after TBI, and with prolongation of the treatment time, the patients who received the acupuncture treatment showed a better therapeutic effect. In terms of body acupuncture, Xu et al.^[72] compared acupuncture at Suliao (DU25), Yongquan (KI1), Hegu (LI4), Taichong (LR3), and the control group (“Xingnao Kaiqiao” acupuncture) for the clinical efficacy of patients with coma after severe TBI. They found the average awakening time, awakening rate, and GCS score were improved in the two groups, but that respiratory function was improved and arousal effect better in the treatment group than in the control group. Furthermore, it has been found that DU25 can stimulate the respiratory center, and the more the sneezing reflex appears following acupuncture at DU25, the closer the patient is to the state of awakening. TBI can cause damage to the brainstem network structure such as neuron loss, myelin sheath degeneration, nerve cell necrosis, and other pathological changes such as focal glial hyperplasia, dural hematoma, cerebral edema, and intracranial hypertension, and the lesion damages the respiratory center, so that patients in TBI-induced coma often require tracheotomy and sputum suction nursing^[73]. Specific acupoints have specific effects on awakening after TBI. For example, Huiyin (CV1) can regulate the balance of *yin* and *yang* in the brain, smooth *qi* and blood, so as to achieve the arousal effect^[74]. Moreover, Mei et al.^[75] compared the awakening effects of acupuncture on the scalp and ear acupoints combined with “Xingnao Kaiqiao” acupuncture and single “Xingnao Kaiqiao” acupuncture on patients with coma caused by TBI. The cerebral cortex and brainstem network of the patient have an excitatory effect, and this effect shortens the time of coma, improving language function and restoring limb function. However, due to the limitations of the part damaged by TBI and the complexity of acupoint positioning and acupuncture techniques, the above methods may be difficult to implement as ultra-early intervention after TBI injury.

Acupuncture at HTWP uses triangular needles or other sharp objects to pierce acupoints and release a small amount of blood to treat diseases. In modern clinical application, the preliminary research of our laboratory and a cooperation project with Tianjin Medical University General Hospital and Tianjin Huanhu Hospital objectively evaluated the effect of acupuncture HTWP as first aid after coma. The arousal effect of acupuncture on HTWP has been confirmed in large samples, multicenter RCTs of ACNI-induced coma, such as following acute stroke ($n = 362^{[76]}$, $n = 175^{[77]}$), acute carbon monoxide poisoning^[78], and severe TBI^[79–80]. On the foundation of conventional treatment, acupuncture combined with strong stimulation or bloodletting of HTWP can significantly shorten the duration of coma and the course of disease, and improve the awakening and consciousness recovery of patients with TBI-induced coma^[81]. With ultra-early acupuncture intervention on top of clinical conventional treatment after TBI, after 3 weeks of treatment, the GCS score, awakening rate, and coma duration of patients were significantly improved, and accompanied by CBF improved and the level of inflammatory factor reduced, indicating that acupuncture may also reduce the neuroinflammatory reaction^[82]. In addition, the arousal effect of acupuncture intervention combined with conventional treatment has also been confirmed by measuring brain electrophysiological activities (EEG and brainstem auditory evoked potential)^[83]. These clinical studies provide evidence that the ultra-early intervention of acupuncture in the acute phase of TBI can increase the patient's awakening rate, shorten the coma duration, and have obvious positive effects in improving their prognosis. Acupuncture on HTWP is a simple and rapidly implemented first aid method, with clear positioning and minimally limited by injury site and acupuncture tools. Therefore, its use to treat TBI is a promising direction for future development and clinical application.

Although most studies show that acupuncture has a positive effect on TBI-induced coma and restores normal consciousness, the results of these RCTs are somewhat controversial due to research design issues. Therefore, more high-quality studies are needed in the future to investigate the awakening effect of acupuncture on TBI patients, and the mechanism of its arousal effect. For example, the use of widely recognized and standardized measurement indicators to ensure the reliability, comparability, and validity of the results, monitoring of the acupuncture process and the reporting of adverse events, and, using more objective measures (such as EEG and functional magnetic resonance imaging), evaluating the short-term and long-term efficacy and quality of acupuncture in patients with TBI. In addition, more evidence is needed to prove whether it has a significant advantage over sham acupuncture.

4.2 Dopamine may be the target of acupuncture in treating TBI-induced coma

The acute primary injury of TBI usually consists of focal contusion and more diffuse structural damage with a series of secondary reactions, including but not limited to excitatory toxicity, ischemia, oxidative stress, and other lesions^[84]. Previous studies have found that acupuncture can regulate the neuroendocrine system^[85], increase the excitability of neurons and the supply of blood flow and

oxygen in the brain damaged area, improve the supply state of cerebral ischemia and hypoxia after TBI^[86–87], promote nerve regeneration in the injured tissue, and achieve the purpose of awakening and recovery from consciousness disturbance^[88].

Our previous study and others from domestic and foreign scientific groups have confirmed that acupuncture on HTWP has a definite awakening effect on ACNI-induced coma, and can improve cerebrovascular circulation disorder leading to the symptoms of consciousness obstacle, nerve defect, and brain edema^[19]. Acupuncture also reverses the hypocoagulability state after acute TBI by regulating multiple markers of TBI hypercoagulability, causing the level of procoagulant factor synthesis, reducing vasogenic and cytotoxic edema, and finally achieving the arousal effect after TBI-induced coma and improving the neurological function deficit^[89].

TBI-induced coma is induced by the injury of the brainstem ARAS or the inhibition of its functional conduction^[90]. Our previous study has demonstrated that dopaminergic neurons expressed P2RX7/P2RX3/TRPV1, and the excitability of DA and P2RX7 was significantly increased in the study of the conduction pathway behind awakening. Acupuncture on HTWP can enhance the activity of dopaminergic neurons of vPAG and up-regulate the gene content of D3 receptor in the brainstem^[20]. Since vPAG is further projected to the hypothalamus and basal forebrain in the ARAS^[7], we hypothesize that acupuncture of HTWP may promote the expression of ATP receptor P2RX7 on the membrane of dopaminergic neurons, and increase intracellular Ca^{2+} content through ion channels, thereby exciting the cell and causing it to produce more DA. The dopaminergic neurons project to lower neurons in the form of neurotransmitters, including target nuclei such as hypothalamus and basal forebrain, and combine with DA receptors including D3 receptors on their membranes, so as to increase the excitability of neurons expressing DA receptors and enhance the release of excitatory neurotransmitters to stimulate awakening. D1-D3 receptors are mainly distributed in the hypothalamus, nucleus accumbens (NAc) and other nuclei associated with arousal^[9]. NAc-D1 receptor neurons project to the midbrain and lateral hypothalamus, activating inhibitory projection neurons from NAc to the midbrain and promoting arousal by inhibiting γ -aminobutyric acid (GABA) neurons. This feedback regulation mechanism can increase the amount of DA released by NAc. Activation of NAc neurons expressing D1 receptor induces behavioral arousal, suggesting that NAc controls arousal through neuron subsets expressing D1 receptor^[38]. D2 and D3 receptors are inhibitory GPCRs whose activation inhibits neuronal activity by inducing hyperpolarization. But D2 and D3 receptors may inhibit GABA-mediated neurons, resulting in the activation of projection neurons^[91]. Our experimental results offer preliminary evidence that acupuncture can up-regulate D3 receptors and exert arousal effect, but whether acupuncture can exert awakening effect on other receptor types of DA and its active sites still needs further verification. A follow-up experiment is planned to verify the neuroprojection-related receptors screened out from the brainstem in the damaged cortex, further screen the effect pathway and potential target of acupuncture on HTWP in the damaged cortex after TBI, and map the brain circuit of acupuncture on HTWP to realize the arousal effect^[92].

In addition, TH as a marker of dopaminergic neurons has increased activity, which indirectly reflects the increase in the number of dopaminergic neurons, and thus can relatively increase the secretion content and activity of DA. Studies have shown that acupuncture can increase the mRNA level of TH in the SN and hypothalamus region, which may further increase the number of dopaminergic neurons, promote their synthesis and reuptake, and inhibit their apoptosis and a series of reactions^[93]. Therefore, the regulation of the dopaminergic system may be a potential therapeutic strategy for TBI-induced coma. However, the potential mechanism of acupuncture in promoting awakening and rehabilitation of TBI has not been fully studied, and further exploration is needed. Researching on the dopaminergic system may be the key direction for clarifying the wakefulness mechanism of acupuncture.

4.3 Acupuncture regulates the dopamine system for a variety of TBI-targeted therapeutic effects

In addition to coma, TBI often leaves patients with other serious complications, including impairment of cognitive, motor, and sensory function, language dysfunction, emotional stress response, visual impairment and other serious neurological impairment, which may also be related to disruption of the dopaminergic system. There are four dopaminergic neural circuits with different functions^[94]: (1) the SN-striatum circuit is mainly involved in regulating body movement; (2) the VTA-cerebral cortical circuits are involved in regulating cognitive ability; (3) the VTA-limbic circuits are involved in the regulation of reward, emotion, and memory; and (4) the tuberoinfundibular circuit can regulate the secretion of pituitary hormones. Based on these neural circuits, the dopaminergic system in the brain mediates a variety of CNS disorders^[95–96]. Therefore, regulating dopaminergic neurotransmission, increasing the neuroactivity of DA, and inducing the related adaptive response of DA receptors in specific brain regions are important targets for the treatment of CNS disease^[97]. Numerous research data show that acupuncture can change the activity and quantity of neurotransmitters, including amino acids, monoamines, peptides, and other central neurotransmitters, which have varying degrees of regulation effect^[98–99]. Acupuncture, similar to neuroprotective drugs, has anti-inflammatory, anti-oxidative stress, anti-apoptosis, neurotrophic, and neuroprotective effects to increase the availability of DA, and improve the post-synaptic functional changes caused by DA deficiency by changing the expression of some genes and proteins^[100]. Notably, SPECT scans have shown that acupuncture can increase neurotransmission^[101]. Analysis of synaptic changes has shown that acupuncture enhanced the activity of brain neurons in DA via regulating D1 receptor and DAT^[102]. Therefore, by regulating the dopaminergic system, acupuncture can not only prompt awakening, but also achieve multiple neuroprotective effects and improve neurological function defects.

Specifically, in the treatment of stroke, both DA and its metabolites can cause neurotoxic effects after ischemic stroke, yet acupuncture can effectively reduce the release of DA caused by ischemia^[103]. First, acupuncture can reduce calcium influx and inhibit depolarization around the infarction area by releasing endogenous neuroprotective agents in the ischemic area^[104]. Acupuncture therapy can significantly increase the excessively de-

creased cAMP content in plasma of patients with cerebral ischemia, and significantly decrease the abnormally elevated cGMP content, and the ratio of cAMP/cGMP is also recovered from the pathological decrease after infarction, thus effectively inhibiting the calcium overload in ischemic focal areas^[105]. Second, acupuncture can improve the adenosine triphosphate (ATP) metabolism in ischemic brain areas and microvascular walls, increase the content and activity of ATP, protect the transmembrane transport function of sodium and potassium ions, and finally reduce the release of DA after cerebral ischemia^[19]. In addition, in the aspect of brain protection, acupuncture can increase the activity of superoxide dismutase, dilate blood vessels, improve circulation disorders, and inhibit the excessive formation of free radicals and NO under the condition of cerebral ischemic injury, thus improving antioxidant capacity and reducing neurotoxicity, so that brain cell damage after stroke is reduced^[106]. The study also found that acupuncture Yanglingquan (GB34) and Quchi (LI11) can significantly increase the cerebral apoplexy rat cerebral cortex D1 and D2 receptor mRNA expression and improve the spasticity state, suggesting that acupuncture may by adjusting the content and function of DA and its receptor in the brain be able to alleviate nerve damage after cerebral ischemia^[107].

Acupuncture also has great advantages in regulating mood, improving sleep, and enhancing immunity. Sun et al.^[108] found that acupuncture can improve the behavior of post-stroke depression model rats and repair the damage to hippocampal neurons, which may be related to the up-regulation of the levels of monoamine neurotransmitters (NE, 5-HT, DA) in the hippocampus by acupuncture. Electroacupuncture can increase the content of DA in the hypothalamus and decrease the content of DA in the amygdala of chronic emotional stress model rats, suggesting that the antianxiety effect of electroacupuncture may be related to the decrease of central catecholamine neurotransmitters such as DA^[109]. The main effects of acupuncture on monoamine neurotransmitters in rats with insomnia are to reduce the contents of DA, NE, and adrenaline, and to increase the content of 5-HT to improve the sleep-wake period and play a sedative role^[110]. Other studies have shown that acupuncture at Zhongwan (RN12), Zusanli (ST36), Zhaohai (KI6), and Shenmai (BL62) can reduce the content of DA in striatum of rats with gastric mucosa injury, thus promoting the healing of gastric ulcer and prolonging sleep time^[111].

Moreover, acupuncture can reactivate dysfunctional neural circuits related to motor and non-motor functions, thereby alleviating the symptoms of most CNS diseases^[112]. Acupuncture transmits signals to multiple brain regions through different signal transduction pathways, affecting the release and degradation of DA and the expression of DA receptors. Acupuncture may also affect the level of neurotransmitters such as 5-HT and DA in the limbic system. The limbic system is composed of central structures including the hippocampus, amygdala, and hypothalamus, which are related to behaviors such as emotion, drive, and appetite. While DA exerts its own functions, it is closely related to other neurotransmitters and plays a common regulatory role^[113].

The present data demonstrate that acupuncture can modulate the amount, activity, and related synaptic pathways of DA by altering neuronal plasticity^[114]. Therefore, we speculate that the regulation of acupuncture on the dopaminergic system may be a potential bridge for

the treatment of TBI and various complications. We further hypothesize that the mechanism by which acupuncture mediates a variety of neuro-consciousness disorders, including stroke, coma, and psychiatric and sleep disorders, by regulating the dopaminergic system may also be the mechanism of acupuncture in the treatment of TBI. In the future, this may be a useful direction for exploring the mechanism of acupuncture in the treatment of TBI.

5 Conclusions

Acupuncture therapy, specifically HTWP acupuncture, can help effect wakefulness and there is scientific evidence for this. Although the specific mechanism of acupuncture on TBI-induced coma is not completely clear, there are neurobiological models that can preliminarily explain how acupuncture achieves arousal effect. Furthermore, the use of acupuncture on the dopaminergic system has a potential awakening effect, which provides an important target for the clinical promotion and application of acupuncture in the treatment of TBI, and may become a novel and effective strategy for treatment especially in the timely awakening from the acute stage of TBI. In the future, with further clinical studies and the in-depth investigation of the related mechanism, stronger evidence can be expected for the awakening and neuroprotective effects of acupuncture on TBI by regulating the dopaminergic system.

Conflict of interest statement

Yi Guo and Luis Ulloa are the editorial board members of this journal and other authors declare no conflicts of interest.

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Author contributions

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