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Acupuncture Mechanisms: Anesthesia, Analgesia and Protection on Organ Functions

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ABSTRACT

Acupuncture, as a healing art in traditional Chinese medicine, has been widely used to treat various diseases. In the history of acupuncture anesthesia, in the past decades, mechanisms of acupuncture analgesia has been widely investigated, and in recent years, acupuncture protection on organ functions has attracted great interest. This review summarized the research progress on mechanisms of acupuncture for analgesia and its protection against organ function injury in anesthesia, and its perspective of analgesia, immunomodulation, neuroendocrine regulation and multiple organ protection. The current evidence supports that acupuncture analgesia and its organ protection in anesthesia is associated with the integration of neuroendocrine-immune networks in the level of neurotransmitters, cytokines, hormones, neuronal ensembles, lymphocytes, and endocrine cells. Although the mechanisms of acupuncture analgesia and its organ protection are still not completely understood, basic as well as clinic researches on the mechanisms and applications of acupuncture and related techniques are being carried out.
Key words: Acupuncture, acupuncture analgesia, acupuncture anesthesia, organ function protection, immunomodulation

Acupuncture, as an important component of traditional Chinese medicine (TCM), has been used for more than two thousand years to treat diseases and relieve pain. Acupuncture is a procedure in which fine needles are inserted into an individual at discrete points (acupoints), and then manipulated, with specific sensations referred to as *deqi*[1, 2], including aching, numbness, tingling, and even warmth. Although Western medicine once treated acupuncture with considerable skepticism[3], a broader worldwide population has now granted it acceptance. For instance, the World Health Organization endorses acupuncture for at least two dozen conditions[4] and the US National Institutes of Health issued a consensus statement in 1997 proposing acupuncture as a therapeutic intervention for complementary medicine[5]. In addition to traditional manual acupuncture (MA), new acupuncture modalities, such as electroacupuncture (EA) and transcutaneous electrical acupoint stimulation (TEAS) are gaining in popularity.

Reviews conducted in the United States, United Kingdom, Europe and Canada suggest that acupuncture is effective for post-operative and chemotherapy nausea and vomiting, nausea of pregnancy, and post-operative dental pain[6]. For a number of other pain-related conditions, including but not being limited to, re-habilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, low back pain, carpal tunnel syndrome, and asthma, acupuncture may be also effective as an adjunct therapy[5]. In the last decades, there has been growing interest in acupuncture anesthesia. Although there is increasing evidence supporting the effectiveness of acupuncture and related techniques in anesthesia, there is still much skepticism about it and the mechanisms of acupuncture anesthesia is still not very clear. Therefore, this review aims to sumarrize some evidence and applicability of acupuncture and related techniques for the underlying mechanisms of acupuncture analgesia and anesthesia. In addition, mechanisms of acupuncture effects on immunoreguation, endocrine regulation and organ protection are also included because of their close relations with acupuncture anesthesia.

1. CLINICAL PRACTICE OF ACUPUNCTURE ANESTHESIA

Acupuncture as a functional modality employed in modern surgical technique was initiated in China more than 50 years ago. In 1958, the first report of surgery being performed with only acupuncture as an anesthetic in China indicated the official birth of acupuncture anesthesia[7]. Acupuncture anesthesia works for a wide range of conditions. The clinical application of acupuncture anesthesia started from small-scale surgical operations, such as tonsillectomy, appendectomy

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and thyroidectomy, and then expanded to major surgeries, like pneumonectomy, brain tumor resection, mitral commissurotomy, subtotal gastrectomy, subtotal splenectomy, caesarean section, subtotal hysterectomy, and kidney, bladder surgeries, et al[7, 8].

The initial goal was to develop acupuncture anesthesia as the substitution of chemical anesthetic drugs, considering its remarkable advantages as follows: Firstly, it was safe without drug-related adverse reactions; Secondly, the physiological functions of the body, such as the pulse rate and bold pressure, remained consistently stable during anesthesia; Thirdly, it kept the patient consciousness; Fourth, it was economic and simple. However, as anesthesiology developed safer and more reliable drugs, while manual acupuncture remained a complicated method to use in practice, clinicians transitioned to acupuncture-assisted anesthesia, using acupuncture itself as an adjuvant, and making it possible to achieve better outcomes with fewer anesthetic drugs[9]. Finally a new modality of "pre-operative induction – peri-operative anesthesia – post-operative analgesia" was built up, which was also the turning point of the development of acupuncture anesthesia[10].

2. MECHANISMS OF ACUPUNCTURE ANESTHESIA

Increasing experimental and clinical evidence supports that acupuncture and related techniques are effective in analgesia, neuroendocrine modulation, immunomodulation, and organ protection. In several decades, basic researchers have tried to explore acupuncture anesthesia from the anatomical and histological substrates of the traditional acupoints and meridians.

2.1. Acupuncture analgesia

Manual acupuncture or electro-acupuncture (EA) has convincing therapeutic effects in various painful conditions, and these effects could last for a long period of time even hours after acupuncture application being terminated[11–13]. The mechanisms of acupuncture analgesia have been widely explored since 1970s.

2.1.1. Peripheral mechanisms underlying acupuncture analgesia

2.1.1.1. Acupoints and meridians: trigger of acupuncture analgesia Based on the classical meridian theory, the meridians consist of channels "Jing" and their branches "Luo", with 361 acupoints being located. The meridians, as a network system, link acupoints via "Qi" (energy) streaming in the meridians. A disease-induced blockade of which causes pain perception. Given that no convincing evidence supports the existence of anatomical foundations of meridians and the meridian theory has been effectively used for treatment in traditional Chinese medicine, the meridians might be a functional constellation including the nervous, circulatory, endocrine and immune systems, in which fictive channels link various acupoints[14].

Traditional acupuncturists emphasize the functional specificity of acupoints according to the meridian theories. A general principle is to select the adjacent points or "Ashi" points. Fruitful clinical researches document the acupoint specificity based on clinical efficacy[15]. Increasing neuroimaging studies also provide the evidence for the specificity of acupuncture effects. A PET study in patients with migraine found traditional acupuncture treatment was more effective for pain reduction and showed different levels of cerebral glucose metabolism in pain-related brain regions, compared with the control acupuncture treatment[16]. An fMRI study in healthy subjects found that manual acupuncture at three acupoints (LI4, ST36, and LV3) showed common responses in the right subgenual BA25, medial subgenual cingulate and right BA31, and preferential differences in major sections of the medial prefrontal and medial temporal lobes among the three acupoints[17]. Besides, the analysis of the whole brain functional connectivity demonstrated that acupuncture at different acupoints elicit different correlations between brain regions, which indicated specific acupoints may exert heterogeneous modulatory effects on the post-stimulus resting brain[18].

2.1.1.2. Afferent nerve fibers activation by acupuncture Since the intensity, frequency, duration, modality, and interval between acupuncture stimuli directly influence the type of activated receptors, increasing evidence has revealed that the types of afferent nerve fibers activated by acupuncture are diverse. Accumulating studies suggest that gentle acupuncture stimulation induces the "De-qi" feeling, excites mainly Aδ-type fibers and activates the gate control system in the spinal cord to relieve pain. However, when the needles are twisted up and down repetitively, the deep tissues, particularly muscle, are locally injured, proinflammatory mediators are released and excite nociceptors directly or indirectly[19]. It is therefore, conceivable that C-type fibers are involved in manual acupuncture-induced analgesia, via activating the negative feedback regulatory mechanism or diffuse noxious inhibitory control in the brainstem[14].

The stimulating current at various parameters applied to acupoints through acupuncture needles can also produce bilateral analgesic effects in human subjects and experimental animals[20]. Since the 1970s, it has been controversial which kind of afferent fibers mediate EA analgesia. Numerous results support that the excitation of Aβ-type fibers and some Aδ-type fibers are involved in EA or transcutaneous electrical nerve stimulation (TENS) analgesia[20], whereas some studies seem to indicate the notion of C-type fiber involvement in EA analgesia[21]. The conflicting results may stem from the variety of stimulation parameters used, such as different frequencies, intensities and types of pulses.

2.1.2. Central mechanisms underlying acupuncture analgesia

Current researches mainly hold that acupuncture analgesia consists of psychological factors and physiological effects. There is considerable debate on whether acupuncture or EA

analgesia equals to the placebo analgesia. A PET study compared real acupuncture, placebo acupuncture and skin-prick[22]. Although real acupuncture and placebo (with the same expectation of effect as real acupuncture) caused greater activation than skin prick (no expectation of a therapeutic effect) in some brain regions, such as the right dorsolateral prefrontal cortex, anterior cingulate cortex and midbrain, the insula ipsilateral to the site of needling was activated to a greater extent during real acupuncture than during the placebo intervention. This result suggests that real acupuncture has a specific physiological effect. Another fMRI study also indicated that real acupuncture produced greater fMRI signal decrease in pain related brain regions during application of the heat pain stimuli, although real acupuncture with high expectation and sham acupuncture with high expectation induced subjective reports of analgesia of equal magnitude[23]. These findings provide convincing evidence for the existence of different mechanisms underlying acupuncture analgesia and expectancy evoked placebo analgesia.

A large body of researches shows that acupuncture analgesia manifested the integrative processes at different levels of the central nervous system (CNS) between the afferent impulses from the pain regions and impulses from acupoints[14]. The electrophysiological findings indicate that both pre- and post-synaptic inhibition probably get involved in EA or acupuncture-induced antinociceptive responses in spinal neurons. For example, researchers found that EA stimulation at "Huantiao" and "Yanglingquan" or "Zusanli" induced significant enhancement of depolarization in pre-synaptic primary C-afferent terminals and thus resulted in inhibition of release of neurotransmitters, such as substance P and glutamate, from terminals[24, 25]. Our previous studies have reported that electro-acupuncture at low frequency of 2 Hz had greater and more prolonged analgesic effects on mechanical allodynia and thermal hyperalgesia than EA at high frequency of 100 Hz in rats with neuropathic pain, and induced long term depression (LTD) of the C-fiber-evoked potential in dorsol horn in spinal nerve ligation (SNL) rats[26, 27], which suggests involvement of post-synaptic inhibition in EA analgesia.

The ascending (lateral system and medial system) and the descending pathways of pain are well-documented[28, 29]. Our previous behavioral studies in animal models showed that the periaqueductal gray (PAG) – rostral ventromedial medulla (RVM) system plays a key role in acupuncture or EA analgesia. In addition, anterior cingulate cortex is also crucial for contra- but not ipsi-lateral EA in the formalin-induced inflammatory pain model of rats[30]. Our and other clinical observations and experimental studies suggest that the pathways of acupuncture signals are interwoven with pain pathways[31–33], acupuncture or EA elicits widespread changes in cerebrocerebellar brain regions, such as RVM, PAG, hypothalamus, thalamus, prefrontal cortex, somatosensory cortex, and limbic system.

By activating or deactivating these brain structures, acupuncture stimulus, on one side, inhibits the activities of nociceptive-sensitive neurons through the cortical-subcortical systems, on the other side, blocks the nociceptive afferents through PAG – RVM – spinal dorsal cord descending inhibition pathway[14]. Both impulses originating from pain sites and from acupoints get converged in the spinal dorsal horn and medial thalamus[14]. Some fMRI studies found long-period TEAS could elicit more secure and spatially extended connectivity of both the default mode network (DMN) and sensorimotor network (SMN)[34], and alter the nodal efficiencies in short-range connections of brain functional networks and the limbic system[35]. In addition, fMRI studies found that electrical acupoint stimulation (EAS) with low and high frequencies seemed to be mediated by different, though overlapped, brain networks[33]. Another study showed different functional connectivity of different networks recruited in different acupuncture modalities[36].

Acupuncture could also directly affect electroencephalogram (EEG) activities on healthy volunteers as well as on animals[37–39]. Under the tonic pathological pain conditions, our work found that EA treatment decreased the power at high frequency bands and reversed the enhancement of cross-frequency coupling strength between high and low-frequency bands induced by the postincisional pain[40].

2.1.3. Roles of neurotransmitters and neuromodulators in acupuncture analgesia

Numerous findings in human and animal studies have demonstrated that acupuncture analgesia is a complex physiological process mediated by various neurotransmitters and neuromodulators, such as opioid peptides, 5-hydroxytryptamin (5-HT), noradrenalin (NA), glutamate and its receptors, γ-amino-butyric acid (GABA), substance P, angiotensin II, somatostatin, arginine vasopressin, neurotensin, dopamine (DA), and so on[14].

Han and his colleagues have made important contributions to this field[20]. Their work showed that under the physiological pain conditions, 2 and 100 Hz EA-induced analgesic effects were mediated by accelerating the release of β-endorphin and enkephalins in the CNS, respectively, and EA effects were differentially reduced by blockade of μ-/δ- and κ-opioid receptors. Further studies showed that low and high frequency EA induced different brain network activation[14], and lesions of the arcuate nuclei abolished high-frequency EA-induced analgesia, whereas selective lesions of the parabrachial nuclei attenuated high-frequency EA-induced analgesia[41], which indicated that low- and high-frequency EA analgesia were probably mediated by different brain nuclei.

Evidence has shown the involvement of cholecyctokinin octapeptide (CCK-8) in EA analgesia. In the behavioral test, intrathecal administration of CCK-8 or CCK receptor antagonists significantly depressed or potentiated EA-induced antinociception, respectively[42]. Besides, the blockade of NMDA and AMPA/KA receptors can reinforce acupuncture analgesia. In the rat neuropathic pain model of spinal nerve ligation (SNL), ketamine, an NMDA receptor antagonist, potentiated the anti-allodynic effects induced by 2 Hz EA[43]. Immunochemical studies further revealed that low-frequency EA reduced the enhanced expression of

NMDA receptor subtype NR1 immunoreactivity in the spinal superficial laminae in the rat SNL model[44]. Also, in the CFA-induced inflammatory pain model of rats, EA decreased the expression of NR1 and NR2 GluR1 in the spinal cord and the number of DRG neurons with IB4 and NR1 double-labeling[45, 46]. The early work from Han and his colleagues found that EA increased the central content of 5-HT and its metabolic products, particularly in the nucleus raphes magnus (NRM) and the spinal cord[47, 48]. Further studies found that intrathecal injection or intracerebroventricular administration of antagonists of 5-HT_{1A} and 5-HT_3 receptors, but not 5-HT_{2A} antagonists, significantly blocked the EA-induced analgesia[49, 50]. About the role of GABA receptors in acupuncture analgesia, current studies show that EA analgesia induces an increase of GABA concentration, and $GABA_B$ receptors in the supraspinal structures contribute to mediating acupuncture analgesia, whereas both $GABA_A$ and $GABA_B$ receptors in the spinal cord are associated with acupuncture analgesia[14].

The endocannabinoid system has also been verified to get involved in EA analgesia. In an animal model of inflammatory pain, EA potentiates the local release of endogenous anandamide and reduces proinflammatory cytokines from inflammatory skin tissues th activation of cannabinoid CB2 receptors CB2Rs[51, 52]. Further study found EA increased endogenous opioid expression in keratinocytes and infiltrating immune cells at the inflammatory site through CB2R activation[53].

In addition, increasing evidence has revealed that analgesic effects of EA might be associated with its counter-regulation to spinal glia activation. Connexin 43 (Cx43) is a gap junction protein, which is extensively expressed in the CNS and serves in signal transmission between glia and neurons. In Cx43 gene knock-out mice, EA analgesia was partially reduced in comparison with the wild-type mice[54]. Some studies have indicated the inhibition of extracellular signal-regulated protein kinase (ERK) phosphorylation, increased expression of the *c-fos* gene and nuclear factor-kappa B (NF-κB) in the spinal dorsal horn[14], and increased release of adenosine around the site of acupoints[55] might also be involved in EA or acupuncture analgesia.

As mentioned above, there are individual differences and EA frequency-dependency in acupuncture analgesia. Our previous work also revealed the effect of genotype on sensitivity to EA analgesia using 10 common inbred mouse strain, suggesting the different allelic forms of the gene show variation in their analgesic responses to EA[11]. The further study was conducted to identify and characterize the genes that differ between high-responders and low-responders to acupuncture stimulation in human volunteers, and found 353 and 22 genes were up- and down- regulated, respectively[56]. These findings hint inherited genetic factors as a possible explanation of individual differences in acupuncture analgesia.

It is, therefore, conceivable that acupuncture analgesia has physiological, anatomical and neurochemical basis, despite the involvement of psychological factors in acupuncture treatment of patients and stress in animal behavioral tests. Acupuncture analgesia is essentially a manifestation of integrative processes involving various molecules, proteins and neuronal ensemble networks at different levels of the CNS.

2.2. Immunomodulation of acupuncture

A large number of clinical evidences confirm that acupuncture or EA can reduce nausea and vomiting, improve postoperative analgesia, and reduce opioid consumption in surgery[57]. The immune fuction is disturbed by the surgical trauma and anesthesia during the perioperative period. It is believed that acupuncture or acupuncture assisted anesthesia (AAA) plays its immunomodulatory role through local immunity and neuro-immunitiy mediated by endogenous opioid peptides, cytokines, NK cells and T lymphocytes and other mechanisms, which is of far reaching significance in the peri-operative application[58].

NK cells, as the third lymphocyte population, play a vital role in innate immune responses. Fruitful findings suggest that the EA or acupuncture stimulation can enhance the NK cell activity, which is probably mediated by increased levels of interferon-γ (IFN-γ) and β-endorphin secretion caused by EA or acupuncture[59]. Another study noticed that the enforcement of NK cell cytotoxicity induced by EA was abolished by lesion in the lateral hypothalamic area[60]. Studies[59] at the transcriptional level showed that EA treatment increased NK cell activity through decreasing mRNA expression of protein tyrosine phosphatases-q (SHP-1) and up-regulating expression of protein tyrosine kinase (PTK), and anchored cell to the target cells by increasing gene expression of vascular cell adhesion molecule-1 (VCAM-1) through the increased level of IFN-γ.

Acupuncture-induced modulation of Th1/Th2 balance is considered as another key mechanism in the treatment of various immune disorders. Generally, Th1 cells produce interleukin-2 (IL-2), IFN-γ and tumor necrosis factor-β (TNF-β) that are mainly involved in cell mediated immunity or delayed-type hypersensitivity (DTH), whereas Th2 cells produce humoral immunity-related IL-4, IL-5, IL-10 and IL-13. The Th1- and Th2-specific cytokines augment the development of the same subset and inhibit the proliferation and activity of the other subset[59]. A previous study[61] found that sequential EA stimulation at acupoints ST36 greatly decreased the elevated serum levels of IgE by suppressing the increase of Th2 cytokines, especially IL-4. Interestingly, for the Th1 dominant disorders, the positive effect of acupuncture seems to be mediated by down-regulating serum levels of TNF-α and IFN-γ, which are linked to the induction of Th1 responses.

In addition, macrophages and neutrophil seem to be involved in the immunomodulation induced by acupuncture. A study[62] found that EA suppressed the production of the TNF-α by the macrophages induced by lipopolysaccharide (LPS), which could be antagonized by naloxone. Another study found that the acupuncture treatment reversed the neutrophil impairment, and enhanced their migration toward the peritoneal cavity in rats with sepsis[63].

It is well-documented that the acupuncture- or EA-induced release of opioids in the CNS could facilitate either sympathetic or parasympathetic nervous systems. The hypothalamus, as a primary core for neuroendocrine-immune modulation, has been widely reported to be activated, and the amount of β-endorphin, which is mainly released from the hypothalamus, was also largely increased by EA treatment, coincided with the increase of IFN-γ levels and NK cell activity, and naloxone pre-treatment reduced such an effect on IFN-γ and NK cells[63]. In addition, there has been evidence, however, suggesting non-opioid mechanisms, such as catecholamine and serotonin systems, are also involved in the modulatory effects of acupuncture on the immune system. For example, pre-administration of phentolamine (an α-adrenoceptor antagonist) completely blocked the inhibitory effect of EA on antigen-specific IgE in serum and IL-4 production[64]. Gene expression of serotonin receptor 3a in the hypothalamus markedly increased after EA with enhanced NK cell activity[65]. In addition, a recent study[66] reported that sciatic nerve activation with EA controlled systemic inflammation and rescued mice from polymicrobial peritonitis by inducing vagal activation of aromatic L-amino acid decarboxylase, leading to the production of dopamine in the adrenal medulla.

2.3. Neuroendocrine regulation of acupuncture

The endocrine regulation of acupuncture or EA is mainly mediated by the CNS, including the hypothalamo-pituitary-adrenal (HPA) axis and hypothalamus-pituitary-thyroid (HPT) axis. As mentioned before, hypothalamus, as an integrative hug of "neuroendocrine converter", plays a critical role in interactions and couplings between neurotransmitters and hypothalamic hypophysiotropic hormones. Increasing evidence have suggested that EA stimulation exerted an anti-depressive effect through weakening the metabolism of 5-HT in the cortex, enhancing the activities of 5-HTergic neurons and regulation of NE/5-HT balance. A series of researches verified that EA markedly reversed the decreased concentration of thyroxine 3 (T3) and T4 in the serum in hypothyroidism, and decreased the level of T3 and T4 in hyperthyroidism. In addition, EA or acupuncture stimulation is effective to the regulation of the estrogen, androgen, insulin, and growth hormones[67–69].

2.4. Organ protection of acupuncture

Increasing evidence has shown that acupuncture or EA exerts protective effect on multi-organ systems, including the brain, the heart, the gastrointestinal system and others.

In the aspect of brain protection, acupuncture significantly improved memory impairment induced by cerebral multi-infarction via regulating the expression of apoptosis related anti-apoptotic gene Bcl-2 and pro-apoptotic Bax gene in the hippocampus[70]. Compelling evidence suggests that δ-opioid receptor activation attenuates oxidative injury in the ischemic rat brain, EA with specific intensity and frequency can increase cerebral blood flow and effectively protects the brain from ischemic injury, which might be mediated by EA-induced maintenance of blood-brain barrier (BBB) integrity, inhibition of apoptosis, activation of endocannabinoid system, and attenuation of glutamate excitotoxicity[71–73].

Table 1. Summary of mechanisms underlying acupuncture effects

Effects		Mechanisms
Analgesia	Peripheral mechanisms	Trigger: acupoints and meridians Afferent nerve fibers activation
	Central mechanisms	Spinal neurons: pre- and post-synaptic inhibition Cerebrocerebellar brain structures activation or deactivation: rostro-ventral medulla (RVM), periaqueductal grey (PAG), hypothalamus, thalamus, prefrontal cortex, somatosensory cortex, and limbic system. Network regulation: DMN, SMN, neural oscillations modulation.
	Neurotransmitters and neuromodulators	Opioid peptides, cholecystokinin octapeptide (CCK-8), 5-hydroxytryptamin (5-HT), noradrenalin (NA), glutamate and its receptors, γ-amino-butyric acid (GABA), substance P, angiotensin II, somatostatin, arginine vasopressin, neurotensin, dopamine (DA), endocannabinoid.
	Others	Gial activation, expression of the c-*fos* gene and nuclear factor-kappa B (NF-κB), local release of adenosine, genetic sensitivity.
Immunomodulation	Immunocyte	NK cell activation, modulation of Th1/Th2 balance, macrophages and neutrophil.
	Cytokines and neurotransmitters	IFN-γ, antigen-specific IgE, IL-4, IL-5, IL-10 and IL-13, endogenous opioid peptides, dopamine.
Neuroendocrine regulation	Hypothalamo-pituitary-adrenal (HPA) axis and hypothalamus-pituitary-thyroid (HPT) axis	Hypothalamus, thyroxines (T3, T4), estrogen, androgen, insulin, and growth hormones; regulation of NE/5-HT balance.
Organ protection	Brain	Maintenance of blood-brain barrier (BBB) integrity; Inhibition of apoptosis; Activation of endocannabinoid system; Attenuation of glutamate excitotoxicity; Up-regulation the level of BDNF.
	Cardioprotection	Inhibition of cardiac β-adrenoceptors signaling pathway as well as opioid peptides and PKC-dependent pathways
	Gastrointestinal system	Regulation of gastrointestinal motor activity, the secretion of opioid peptides and the gastric acid, and other neural pathways

Studies on the effectiveness of EA in the treatment of Parkinson's disease (PD) found that long-term high-frequency EA is effective in halting the degeneration of dopaminergic neurons in the substantia nigra (SN) and up-regulating the levels of brain-derived neurotrophic factor (BDNF) in the subfields of the ventral midbrain[74].

Studies on the cardioprotection of acupuncture have shown that in rat model with ischemia and reperfusion, EA or acupuncture treatment significantly attenuated the elevated ST segment of electrocardiogram (ECG), cardiac arrhythmia score, and the ratio of the infarct size/risk zone, which was mediated via inhibition of cardiac β-adrenoceptors signaling pathway as well as opioid peptides and protein kinase C (PKC)-dependent pathways[75–78]. A recent study also showed that acupuncture alleviated the pathological changes of cardiac tissue of rats with myocardial ischemia and regulated the protein expression of cystic fibrosis transmembrane conductance regulator (CFTR) and CL^- channels CLC02[79]. In addition, direct electrical or peripheral neural stimulation might evoke the release of cardioprotective substances into the bloodstream with comparable effects to that of remote ischemic pre-conditioning by limb ischemia (rIPC)[80].

In gastroenterology, acupuncture has also been used successfully to treat different gastrointestinal disorders, since its efficacy in the regulation of gastrointestinal motor activity, the secretion of opioid peptides and the gastric acid, and other neural pathways[67].

3. CONCLUSION

Current available data compellingly support that acupuncture has it considerable overwhelming advantages in analgesia, preventing postoperative nausea and vomiting, neuroendocrine-immunomodulation, and multi-organ protection, as shown in Table 1. The mechanisms of acupuncture are not completely understood. Nevertheless, it has been understood that interaction and integration of neurotransmitters, neuronal activities, and neuronal ensemble networks coordinate the acupuncture effects. It has been paid more attention to the modulation of acupuncture or EA on neuroendocrine-immune network and organ protections. Because of these effects, the use of acupuncture and application of acupuncture anesthesia will manifest it greater prospect in the future, with the gradual illumination of the underlying mechanism of acupuncture effects.

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