How Acupuncture works?

Neuroscientific basis underlying Acupuncture Analgesia

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The mechanism of acupuncture analgesia and health care remains unclear,though it has been used for the treatment of pain and disease over 3,000 years in China. In the past half century,modern medical science findings,particularly fMRI findings have Opened a new access to get insight into the mystery mechanism of acupuncture in Treatment of pain and disorders. Summarily,modern research findings have shown that Acupuncture exerts its work through following approaches. 1Acupuncture sets up a roadblock on pain impulse pathway to block Pain signal passing through the gate in spinal cord.2.Acupuncture can release natural painkillers such as endorphin,enkephalin, endomorphin and dynorphine from bod to kill pain.3.Acupuncture analgesia works through altering brain's perception to pain stimulation.4.Acupuncture can help visceral pain and internal disorders by eliciting a somato- autonomic neural reflex. Based on a vast of scientific evidences from experimental and clinic studies ,we can conclude that acupuncture is effective for treatment of pain and disease and it works Through a neuroendocrine response induced by AP stimulation on acupoints.

Introduction

Acupuncture (AP) is a portion of traditional Chinese medicine and has been used for Health care in clinic over 3,000 years in China.

For acupuncture's magic effective for pain and disease,AP has spread to over 160 countries and regions in the world.The world health organization (WHO) has recommended AP as a therapeutic technics for 43 different kinds of diseases. In USA,NIH Proposed AP as a therapeutic intervention of complementary medicine in 1997. However, up to now there is not too many people who know about acupuncture Application due to absence of a convinced rationale.Acupuncture application often Be suspected as a scientific modality for health care because the Qi or channel Network of traditional Chinese medicine is invisible in human body.

In 1962, R..Molzack and P.wall developed the "gate control theory of Pain " and it has Been recognized as a mechanism of pain[1]. Furthermore,B.James in 1977 proposed the "gate control theory " as a mechanism of acupuncture analgesia {2}.

In the past decades, medical scientists have obtained a tremendous scientific Evidences regarding acupuncture application for health care.Specially,functionary MR image (fMRI) findings have provided an visible and convinced evidence to testify the neuroscientific basis of acupuncture [3]. The aim of this review is to collect new findings of medical research regarding AP application and provide a scientific interpretation of AP Application for our patients.We will focus on the updated new findings including Pain

signal pathway blockage endogenous pain killer release, fMRI findings, nerve Reflex theory,and so.

Traditional Acupuncture Theory

3,000 years ago,ancient Chinese medicine philosophers presume that there are two Natural forces: Yin and Yang in nature which interact to balance everything in the world.Yin and Yang also regulate the flow of " vital energy " known as Qi in Human body. They believed that Qi flows through a body circulation system,known as network of channels called Meridians to circulate in body from the internal Organs to body surface. When Qi pathway is open and Qi flow is smooth,the body Is in " good health ".However,when Qi pathway is blockage and Qi flow is Retarded, the body is in pain or disease.There are a number of acupuncture points (acupoint) on body surface. An acupuncturist can use a needle to unblock the blocked Qi pathway to cease pain or restore the body's health [4].

Pain signal pathway and mechanism of pain.

What is pain ? The pain is defined as an unpleasant feeling that is conveyed from body to the nociception center in the brain. The discomfort signals actual or potential injury to the body [5].

In human body, Three-order neurons connect each other to form a neural pathway,known As lateral spinothalamic tract to convey pain or temperature from body to the brain [6]. The larger δ A-type neural fibers transmit acute pain and smaller C-type fibers Transmit chronic pain.

The first-order pseudo-unipolar neuron embeds its body in dorsal root ganglia and extends its efferent branch to peripheral skin and stretches its afferent branch to dorsal Horn of the spinal cord.After 2^{nd}-order neuron's body made synaptic connection with 1^{st}-order neuron's synapse, 2^{nd}-order neuron's axon crosses obliquely to the opposite Side anterior gray horn and ascends in lateral spinothalamic tract and ends in the ventral Posterolateral nucleus of the contralateral thalamus.After 3^{rd}-order neuron made with Synaptic connection with 2^{nd}-order neuron, its axon now pass through the posterior limb of the internal capsule to reach nociception center on the postcentral gyrus of the cerebal cortex.(see Figure 1)

The pain impulse generated by noxious stimuli are transmitted through above pathway From body to spinal cord,and then to the brain [7].

Though the anatomic structure of pain pathway was found several decades in advance, but the mechanism of pain is not known until the " gate-control theory " developed by R.Melzack and P.D.Wall in 1962 [1] (See Figure 2).

According to " gate control theory ", the pain impulse generated by noxious stimulation are not directly transmitted from body to the brain and pain impulses can be blocked on Half pathway at gate in the Spinal cord by psychologic, physiologic,and pharmacologic Fators[1]The gate is located at substantia gelatinosa in posterior gray column of spinal cord.The gate is going to open or close dependence on the volume of afferent impulse. The activity of larger or A-type fiber (inhibitory fiber) tends to inhibit pain impulse transmission (close the gate) while Smaller or C-type fiber activity tends to

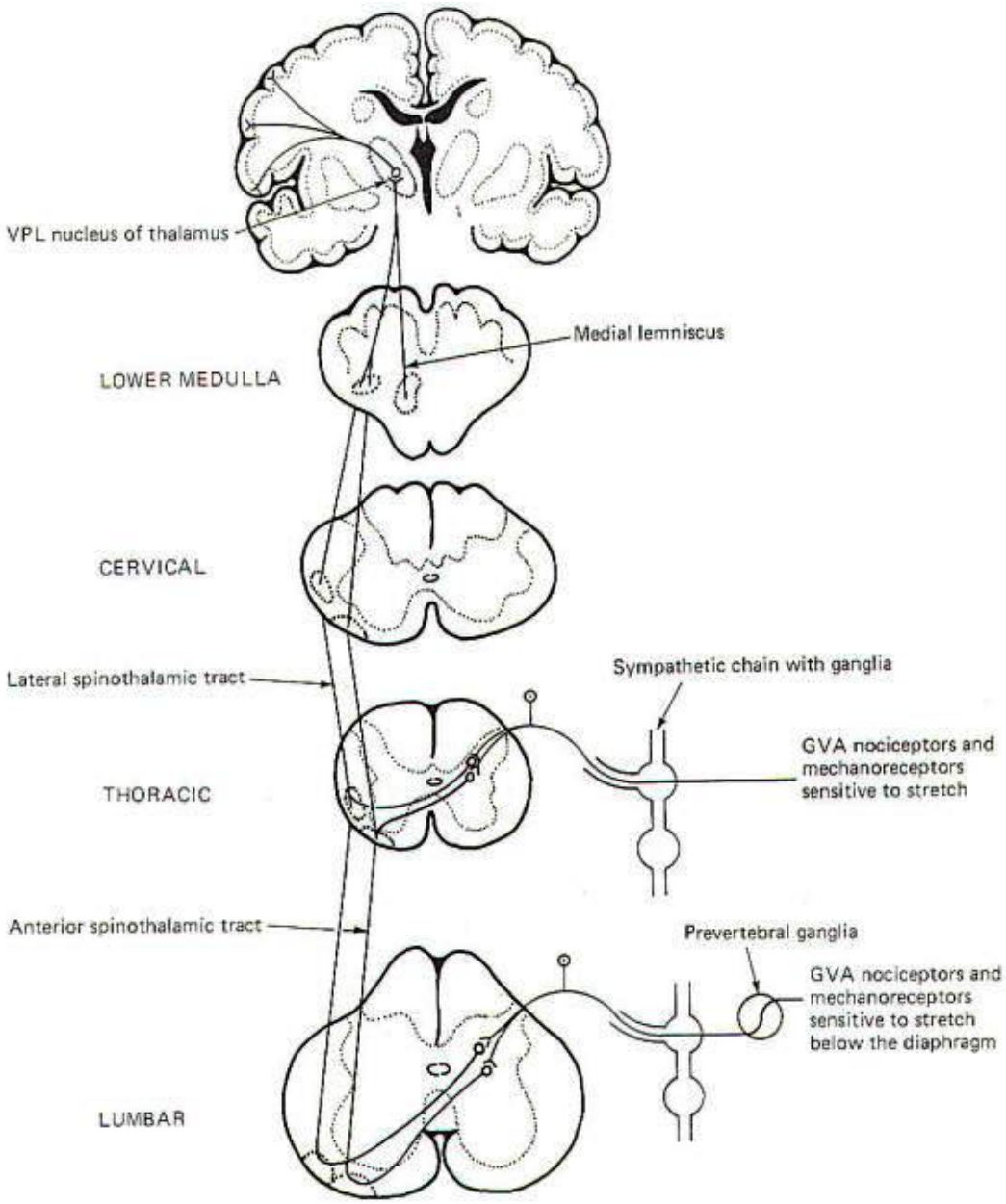

Figure 1. Pain and temperature pathways

facilitate pain impulse transmission (open the gate) [1].At the level of spinal cord,pain signal transmission via pain fibers can be blocked on pathway by surrounding inhibitory fibers resulting in no pain sensation onset in the brain [1,8, 9,].That is to mean when the central excitatory pain fiber activates to convey Pain impulse,its activity can be inhibited by stimulating surrounding cutaneous fibers.This phenomenon is same as we bump our head,pain can be relieved by rubbing the Surrounding skin [1].

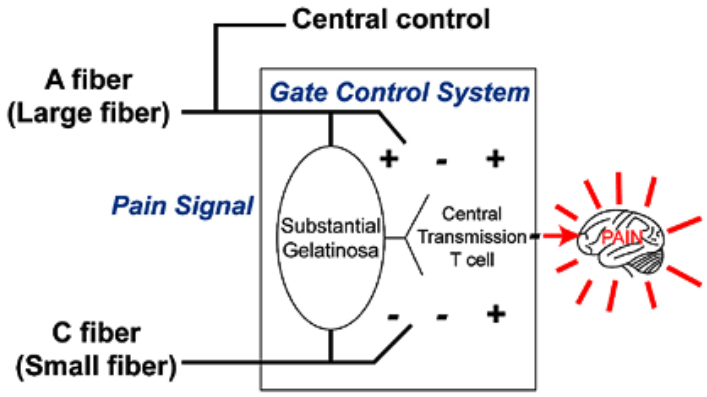

Figure 2 ." Gate control theory " , known as Mechanism of Pain

Peripheral mechanism of acupuncture analgesia

A new conception," neural acupuncture unit (NAU) " proposed by Dr.Zhang and His colleagues in 2011 [10] broke through the traditional acupuncture point (acupoint) Notion and opened door to uncover the mystery of acupuncture analgesia. NAU is defined as a the collection of activated neural and neuroactive components Distributed in the skin,muscle,connective tissue and nevous fibers surrounding the inserted needle [11].

According NAU conception,acupuncture neele insertion on acupoint is not a localized Stimulation but it elicits a neurovascular mediator release and neural reflex in entire body.The released mediators including histamine,serotonin(5-HT),substance P (SP), Nitric oxide (NO),cytokine, and prostaglandin elicits a Robust axon Reflex onset[12], And cutaneous vasodilatation and tissue congestion (Hyperemia) resulting in a Pink cycle (flare) occurrence around the inserted AP needle.

Robust axon reflex resulted from the sympathetic response generated by acupuncture Needle insertion on acupoint.

Apart from peripheral response, AP stimulation can release pain killers and central Nervous mediators including endorphin,enkephalin,morphine,acetylcholine(Ach), γ-aminobutyrate (GABA), Noradrenaline(NA) .These pain killers and inhibitory Mediator are not only implicated in peripheral response,but also involved in pain Pathway blockage to interfere pain impulse input in CNS [10].

Acupuncture-induced pain pathway blockage has been recognized as a mechanisms of acupuncture analgesia

In 1977, James B. Et al proposed " gate -control theory " as the mechanism of AP Analgesia [2].

In 1983,Lu,GW,et al first demonstrated that acupuncture impulses were conveyed By larger diameter A-type neural fibers [17] and then A-type fibers have been recognized As afferent neural fibers of acupuncture impulses [8,9,10,11,17,18]

As mentioned above,the activity of the larger neural fibers tends to inhibit activity of

smaller neural fiber which conveys pain impulse.At the level of spinal cord,Acupuncture-Induced impulse transmission in A-type fibers can block the signal transmission Of pain impulses in C-type fibers [1,8,10,11,17,18] (see figure 3).
Acupuncture-induced pain pathway blockage has been testified to accomplish with both ascending and descending inhibitory approaches.

Ascending(presynaptic) inhibition induced by acupuncture application

As mentioned above, AP impulses are transmitted in larger diameter A-type fibers and pain impulses are transmitted in smaller diameter C-type fibers[17,18].
" De Qi " is regarded as feeling generated by AP impulse transmission.The " De Qi " sensation is a kind of feeling described by both patients as soreness,numbness,distention warm and acupuncturists as needle caught by Something [17].The "De Qi" impulse induced by acupuncture needle stimulation on acupoints was proved to be transmitted by A-δ and A-θ fibers [17,23].
After AP impulse reached dorsal horn in spinal cord,the ascending fibers of AP impulse Will join ascending fibers of pain impulse transmission known as lateral spinothalamic tract to ascend to nucleus of the thalamus [6,22].

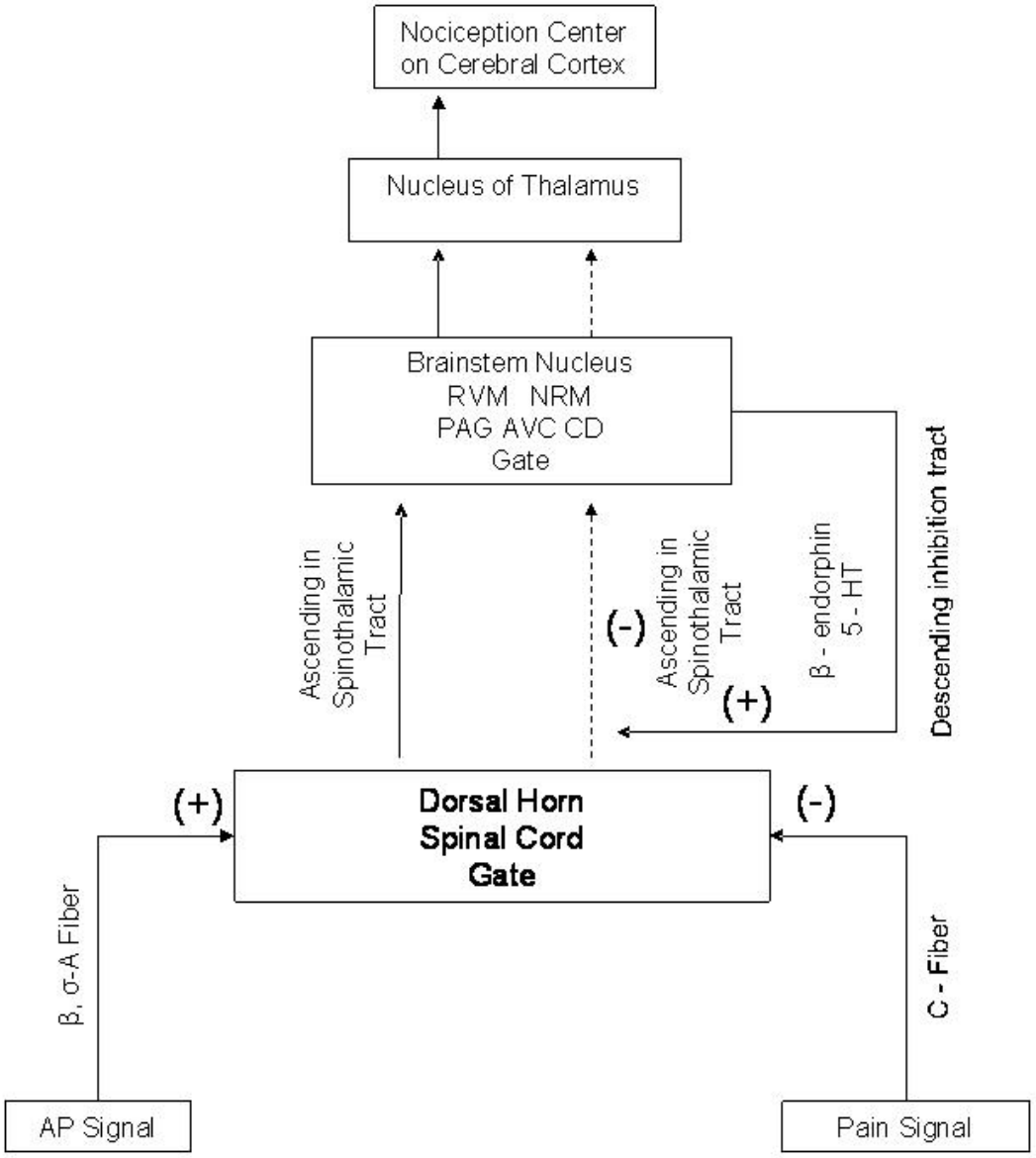

Figure 3, Ascending and Descending Inhibitory System on AP Pathway and Pain Pathway
RVM: NRM: Nucleus Raphe Magnus PAG: Periaqueductal gray AVC: Arcuate Nucleus
Cd: Caudate Nucleus

A number of studies have demonstrated that afferent fibers of AP impulses are inter-Woven with afferent fibers of pain impulses [19,20,21].

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ious stimulation will flow together With AP ımpulses at dorsal horn ın spınal cord.the confluence of pain impulses and AP impulses resulted in that the pain impulses transmitted by smaller fibers (C-type) Are flooded in AP impulses transmitted by larger fibers (A-type)
These pain impulses drowned in AP impulses at gate in the spinal cord resulted in absence of nociception in pain center on the cerebral cortex[10,20,21].

Descending (Postsynaptic) inhibition induced by acupuncture application

The electroacupuncture (AAP) stimulation on unilateral limb can produce bilateral analgesic effects in human volunteers and experimental animals [23,24,25].
In 1998,Ulett et al demonstrated that AP stimulation around periaqueductal gray(PAG) Region can produce analgesic effect [26]
In furthermore,Liu et al in 2004 have further demonstrated that an increased signal Activity area around (PAG) generated by AP stimulation on Hegu/LI-4 acupoint (on hand) is observed by fMRI [27].
These studies have proved that brainstem nucleus including caudale nucleus(CN), Arcuate nucleus(Arc),Parafascicularis (Pf), PAG,and Nucleus Raphe Magnus (NRM) Are implicated in descending inhibitory analgesia induced by acupuncture.
It was well demonstrated that AP-induced descending pain inhibitory effects is to happen At dorsal horn of the spinal cord[28].
In further studies,the descending axons act on pain impulse pathway to elicit analgesia By following approaches [34]: A.direct (postsynaptic) inhibition of spinal pain-relay Neurons [29,30,31],B.Indirect inhibition of spinal pain-relay neuron through activation Of inhibitory interneurons [32], the descending axons release neurotransmitter such as Endorphin,5-HT to inhibit 1st order afferent fibers (presynaptic) [33,34].
Recently,medical scientists have further verified that endogenous opiates and 5-HT Play an important role in the descending pain inhibitory system induced by acupuncture [35,36,37].
Han and his colleague have demonstrated that the descending pain inhibitory fibers Originating from upper brainstem exert their analgesic effect by release opoid peptide Such as β-endorphin ,Enkephalin [18,24,36].
Liu et al in 1986 [38] and kim et al in 2005 [37] have verified that the descending pain Inhibitory fibers originating from lower brainstem exert their AP-induced analgesic effects by releasing 5-HT, the latter can activate interneurons to release enkephalin which Can wipe the pain signals out[35,39].

Acupuncture analgesia works through release of endogenous pain killer--- opioid peptides

In 1973, Dr.Han and his colleagues first demonstrated in rabbit that the brain neurotransmitters involved in transcutaneous AP analgesia [51].
In 1977,Mayer and his colleagues further demonstrated in human that endogenous

 using naloxone,a opioid receptor Antagonist [40].
This finding was swiftly re-confirmed in healthy subjects and patients with chronic pain in 1978 [41].
It is well known that endogenous opioid peptides and their receptors widely exist throughout the central and peripheral nerve system[42].

Table 1. Endogenous opioid--Distribution & Biologic function

Opioid Peptide	Source	receptor	Biologic function
Endorphins	pituitary,hypothalamus Neurons of CNS&PNS	μ	1.na 2.preventing ob 3.Runners high
Enkephalins	Brain,spinal cord	d(δ)	1.regu 2.natural pain killer
Dynorphins	hypothalamus,Hippocampus Mid brain,pons,medulla Spinal cord	κ	1. 2.Appetite&w 3.rhythm,body temp 4.Homestasis maintain
Endomorphin	cerebral cortex,brain stem, Thalamus,hypothalamus Brainstem Nucleus	μ	2.sedative 3.Arousal

Biologic function
1.natural pain killer 2.preventing obesity 3.Runners high
1.regulating nociception 2.natural pain killer
1.pain modulateor, 2.Appetite&weight control 3.rhythm,body temperature 4.Homestasis maintain
1.pain killer 2.sedative 3.Arousal

In 1979,Cheng and Pomeranz demonstrated that an increased endogenous opiate concentration was found in plasma by transcutaneous electro-AP [43,44].
It was well demonstrated that β-endorphin level was elevated in cerebrospinal fluid (CSF) in rats [45],in rabbit [51],and in human [46] by transcutaneous AP stimulation.
In further studies,Chan and Han in 1992 further demonstrated that different frequency of Electro-AP can induce different-type opioid peptide release [47]..
Han and his colleagues have found that lower frequency (2Hz) AP analgesia is mediated by μ and δ receptors and high frequency (100 Hz) AP analgesia is mediated by κ-Opioid receptor so that they concluded that low frequency(2 Hz) stimulation can induce Release of β-endorphin , Enkephalin, and endomorphin [48,49]and high frequency (100 Hz) stimulation induced the release of Dynorphin [50].
It was also proved that AP stimulation can enhance opioid peptides to bind to their Receptors [52].
However, It is not completely understood how endogenous opioid peptides induced by AP stimulation can kill pain in acupuncture analgesia.
In 1984,Akil,et al and Frochlich,in 1997 have demonstrated that the endogenous opioid Peptides can suppress other neurotransmitters release from the primary afferent neural Terminals by hyperpolarizing the neurons where opioid peptides can decease Ca++ entry

 this hyperpolarization,the afferent Neuron's "firing rate" and neurotransmitter release are attenuated or wiped out so that The pain signal transmission is terminated [53,54].

Acupuncture analgesia works through altering the brain's processing of pain signal --------- fMRI evidences

Recently, fMRI (functionary magnetic resonance image)study on acupuncture analgesia has opened a new approach to understand the mechanism of acupuncture analgesia. In fMRI studies,medical scientists have found that the brain neuron cellular activity Signals induced by transcutaneous AP stimulation on acupoints such as Hegu/LI-4 (on hands) and Zusanli/St-36 (on legs) can be observed on fMR imagings [22,23,25,55,56]
In 1999,Dr.Wu et al demonstrated that an increased brain activity signals display in Brainstem nucleus of thalamus,hypothalamus,PAG, and NRM,and a decreased activity signal image appears on cerebral limbic regions including cingular cortex,hippocampal, And primary cortex by stimulating acupoints Hegu,and zusanli [25].
In additional,an increased or excited activity regions are found on pariental primary Somatosensory (pain and temperature) cortex and thalamus while an noxious stimulation (Prick) on non-acupoints [25].
In swiftly,Wu's study findings are reconfirmed by Hui et al and Zhang et al[22,23,56].
As mentioned above," Di Qi"is a sensation that patients are feeling a sour,numb,warm, And distension while they are experiencing AP stimulation on acupoints [22,23,25]
Wu and Hui respectively demonstrated that patients who experience "De Qi"sensation have shown a decreased or deactivated activity signal image on limbic regions (for Emotion control) and control subjects who experience a pain stimulation on non-Acupoints have shown an increased or activated signal image on brain limbic regions And somatosensory cortex [23,25,56].
In additional,when patients who experience both "De Qi" and pain stimulating sensation, The CNS responses are mixed [23,25,56].
These findings indicated that acupuncture impulses generated by AP stimulation on acupoints and pain impulses induced by noxious stimulation on non-acupoints trigger The different brain perceptive regions even though they share a common signal pathway At spinal level [22,56].
Furthermore,these findings also indicated that AP stimulation on acupoints can alter Brain response to the afferent pain signals [22,56].
In 2004,Liu et al demonstrated that an increased or activated image in PAG is found in patients who received AP stimulation on acupoints and a decreased or deactivated image in patients who received a pain stimulation on non-acupoints [27].
In additional,Wu et al [55],Yan et al[57] and Bai et al [58] also obtained same results in fMRI studies therefore they concluded that only stimulation on acupoint can induce a Specific brain cellular activity response in brain.
In 2005,Napadow et al compared the effect of electro-AP at 2 Hz or 100Hz ,Manual AP And tactile stimulation at acupoints or non-acupoints on human brain activity responses. They found that electro-AP produced more wide spread fMRI signal than manual-AP Did,low frequency (2 Hz) produce more signal Response than high frequency (100 Hz) did, and only AP stimulation on acupoint can induce a deactivated fMRI signal image in

ıded that the brain limbic system whıch control the mood related to paın stımulatıon plays an important role in acupuncture Analgesia [59].

Acupuncture application works for visceral pain and internal disorders through somato-Autonomic reflex

The transcutaneous acupuncture -induced efferent discharge of sympathetic nerve innervating internal organs is defined as somato-sympathetic reflex [60].These neuroendocrine-autonomic responses are predominantly mediated by hypothalamic-Pituitary-adrenal axis (HPA).The HPA axis plays an important role in maintaining Homeostatic constancy such as body temperature,blood pressure,feeding behavior, Weight control,mood control,growth and fluid balance [60].
It is well demonstrated that transcutaneous AP application is effective for chronic Visceral pain [61],and irritable bowel syndrome (IBS) [62].
A number of the experimental evidences have proved that AP-induced endogenous Endorphin release from hypothalamic β-endorphinergic system is regarded as The mechanism of acupuncture suppressing the pain of the internal organs [63, 64,65].

Cardiovascular disorder

Tam et al in 1975 and Rutkowski et al in 1980 have demonstrated that acupuncture Is effective for patients with hypertension by lowering sympathetic tone [66,67]. Li et al and Sae et al further demonstrated that acupuncture-induced attenuation Of sympathetic outflow is the mechanism of acupuncture intervening cardiovascular Disorders [68,69].

Gastroenteric disorders

A number of evidences have shown that acupuncture-induced inhibitory effect on GI motility can help patients with diarrhea , acid reflux,and IBS [61,62,70,71] and Acupuncture-induced facilitative effects on GI motility can help patients with Functionary dyspepsia,gastroparesis,and constipation [70,71,72].

Fertility and infertility

Recently, a number of the experimental and clinic studies have demonstrated that acupuncture can improve fertility ability and sterility through modulating endocrine System function or facilitating ovulation [73,74,75,76].
It is a worth mention that Dr.Xue Cui Xiang has obtained more than 100 successful Cases of female infertility by acupuncture application since she has co-operated with Mobile infirm hospital reproductive research center in 1993.

Immunologic disorders

:upuncture is effective for asthma, Allergic ,and auto-immmunologic disorders [77,78].

Anxiety and depression

A number of the experimental and clinic studies have demonstrated that AP application

Is effective in treatment of stress,anxiety, and depression through acupuncture-induced 5-HT release from the hypothalamus to modulate activity of the limbic system [23,79, 80,81,82].

Quit smoking and drug abuse

There are two theories ,endorphin and serotonin (5-HT) mechanism to explain how Acupuncture works for ceas-cigarette smoking and drug abuse [83,84]
The endorphin theory believes when the opioid receptor sites of a person who Abuses exogenous opioid such as morphine and heroin can be filled by endogenous Opioid peptides (endorphin, enkephalin) induced by AP stimulation,the person may Experience a feeling of wellbeing rather than a withdrawal symptoms or craving Feeling [45,84].
However,serotonin theory attributed the effects of AP-induced reduction of Withdrawal symptoms and craving feeling to the suppression of the brain limbic system (for Emotion control) resulted from acupuncture-induced increase of 5-HT and dopamine [37,39,85].
Same as detoxification, acupuncture application can help people to quit cigarette Smoking [86,87]. Tahiri M. Et al have demonstrated that both aural and body acupuncture are effective for smoking cessation in more than 1,000 testers [88, 89].
In Dr.Xue Cui Xiang's clinics, the clinic effect of acupuncture application on ceasing Cigarette smoking has shown that AP can reduce the craving feeling after 1st time AP treatment and patients can get a permanent cease-smoking no more than Four (4) treatments of body acupuncture with an aural needle wear. It is effective in 90 % of the patients who received AP treatments for quit smoking in Dr.Xiang's Clinic.

Weight loss and Obesity

Obesity is defined as a disease resulting from the over storage of fat in the body. Today medical scientists always attribute obesity to imbalance between energy intake and energy consumption.
In the treatment of obesity,acupuncture,particularly auricular AP is quite effective for weight loss in the procured obese patients [90,91]
It is well demonstrated that acupuncture can lower body weight down by means of both AP-induced appetite inhibition and AP-induced lipolytic activity increase in plasma [90, 92,93,94,95,96] (See Figure 4).
A number of experimental and clinic studies have shown that transcutaneous AP stimulation on body acupoints such as Hegu/LI-4,Tianshu/St-25, Zusanli/ST-36 and Ear acupoints such as Hungry,Shenmen can influence the satiety center on the

) and lateral hypothalamus (LH)
To lower people's appetite down [92,93,94,95].

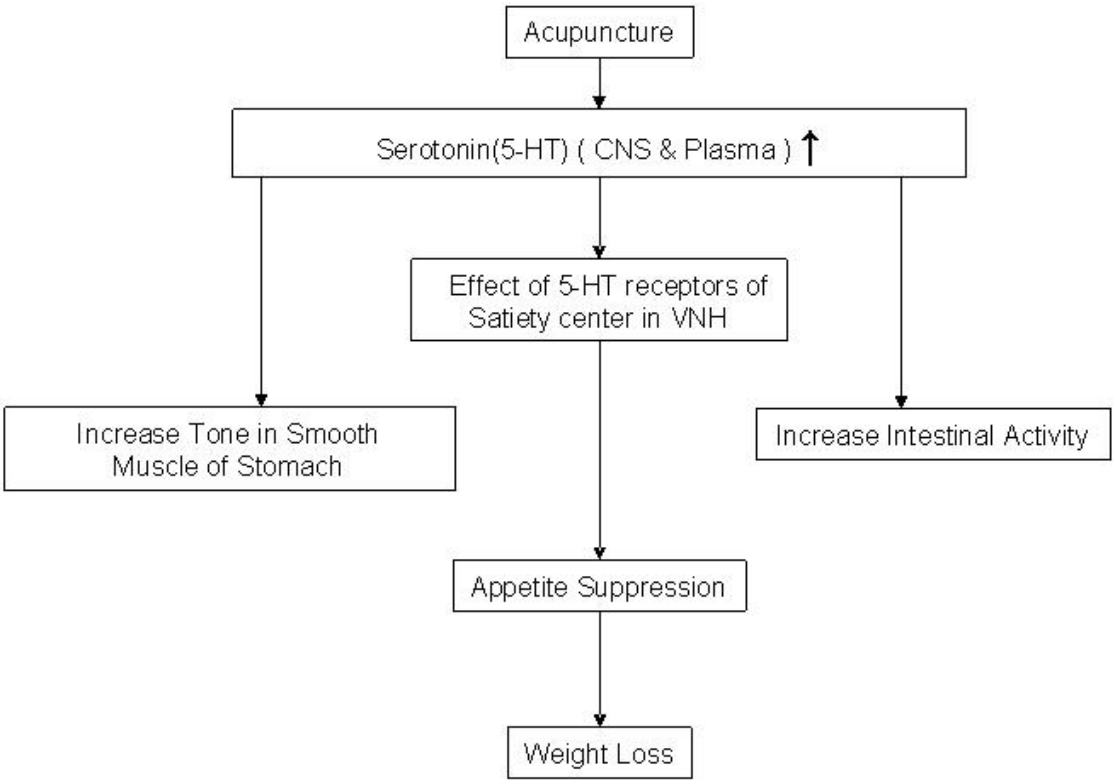

Figure 4. Acupuncture Application and Suppression of appetite

As mentioned above,transcutaneous AP stimulation on acupoints in relation to Satiety or hungry sensation can increase the level of serotonin (5-HT) in CNS [38, 39,97].The increased 5-HT will bind to the receptors of the satiety center in the Hypothalamus to induce the fullness feeling resulted in people's
Appetite suppressed [92,93,94,95,97]
Furthermore, the auricular AP stimulation on aural acupoints can activate the brach of The vagal nerve in the ears to inhibit people's appetite by increasing the tone of the stomach and motility of the intestine [92,93,94,98,99]
In addition,A number of studies have demonstrated that transcutaneous acupuncture can

Lower body weight down by increasing β-endorphin and Dynorphin level to elevate Lipolytic activity in the plasma [50,53,100].

Conclusions and consideration

In the past half century, medical investigator and acupuncturists have achieved a number Of amazing findings in exploring the mechanism of acupuncture analgesia and health care.A vast number of experimental and clinic studies have demonstrated that acupuncture application works through the neurophysiological mechanism as followings. A.Acupuncture can block pain signals on the pain impulse pathway .B.Acupuncture-Induced release of the endogenous pain killers such as β-endorphin,enkephalin, And endomorphin.C.Acupuncture -induced release of serotonin (5-HT) in CNS to Alter brain's perception to pain stimulation.D.Acupuncture can help the internal disorders

However, the mechanism of acupuncture application in treatment of pain and internal Disorders is complicate and still not be completely clarified today. The prospective studies Should further focus on insight into the mechanism of this ancient analgesic modality in the future.

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