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Acupuncture: Emerging evidence for its use as an analgesic (Review)

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Abstract. Acupuncture is an ancient Chinese technique, developed over >3,000 years, in which 'acupoints' are stimulated with the aim of treating various diseases. A number of previous studies have indicated that acupuncture may play a role in inducing analgesia. Acupuncture-induced analgesia has been hypothesized to act on various parts of the central nervous system, including the spinal cord, brain stem, cerebral ganglia and cerebral cortex. The mechanisms underlying the effects of acupuncture have been purported to include neurohumors and neurotransmitters, such as opioids and γ-aminobutyric acid, signaling pathways and the immune response, which are all involved in the induction of analgesia.

Contents

1. Introduction

Acupuncture is an ancient Chinese technique that has been developed over a period of >3,000 years, in which 'acupoints' are stimulated to treat a variety of diseases. Acupuncture has numerous functions (1-3), including use as an auxiliary method of treatment for acute or chronic pain (4,5). Certain studies have proposed that acupuncture-induced analgesia is a complex physiological adjustment process that involves the entire nervous system, including the central nervous system (CNS) and the peripheral nervous system (6-8). Mechanisms underlying acupuncture are intimately associated with neurohumoral and neurotransmitter pathways. A number of studies have hypothesized that acupuncture may play a role in inducing analgesia (8-11).

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2. Acupuncture-induced analgesia may act on different levels of the nervous system

Acupuncture-induced analgesia is widely acknowledged to be associated with the functions of the entire nervous system, including the spinal cord, brain stem, limbic system and the cerebral cortex. Acupuncture-induced effects interact with and coordinate different levels of the CNS. The effect of acupuncture-induced analgesia is considered to be a complicated process (12-30).

Acupuncture and the spinal cord. The spinal cord is the first station of nociceptive information processing and interpretation, in addition to functioning as a pain reflex center. Peripheral nociception involves transmission into the spinal cord via the dorsal root, followed by sorting and analyzing by the spinal cord. The spinal cord is hypothesized to be the primary level of acupuncture analgesia, and the underlying mechanism may be associated with the release of certain neurotransmitters, such as 5-hydroxytryptamine (5-HT), somatostatin and substance P (SP) (12-14). Furthermore, opioid peptides may be involved in acupuncture analgesia in the spinal cord to varying degrees (15). Pharmacological inhibition of ascending nociceptive control at the spinal cord, nucleus accumbens or supraspinal may prevent acupuncture-induced analgesia (16).

Acupuncture and the brain stem. The brain stem is the relay station for sorting, discriminating and synthesizing information associated with pain. A proposed mechanism underlying acupuncture-induced analgesia in the brain stem involves the activation of the reticular formation of the brain stem descending pain-inhibitory system. The majority of this system is located in the periaqueductal gray and medulla oblongata nucleus raphe magnus, and is associated with a variety of neurotransmitters involved in analgesia, such as 5-HT and opioid peptides (17,18). A previous study demonstrated that damage to the locus coeruleus may improve the analgesic efficacy of acupuncture (19).

Acupuncture and the cerebral ganglia. The cerebral ganglia is involved in analyzing and adjusting various types of information, and is modulated by a number of neurohumoral substances. These substances may be central for improving the efficacy of acupuncture-induced analgesia. Habenula nuclei serve key functions in monitoring pain, and activation of these structures may result in the inhibition of the raphe nuclei, which may in turn excite the locus coeruleus (20,21). Norepinephrine and acetylcholine are generated from the locus coeruleus or habenula nuclei; they can improve the activities of these nuclei by interacting with each other and are also involved in acupuncture analgesia (18,22-24). The arcuate nucleus, paraventricular nucleus and preoptic area are located within the hypothalamus, and are associated with the modulation of antinociception to nociception (25-27). There are a number of possible mechanisms to explain this modulation, including the activation of the periaqueductal gray-nucleus raphe magnus pathway, excitation of the dorsal raphe nucleus and inhibition of the locus coeruleus (27). In addition, the preoptic area contains numerous neurotransmitters, among which opioid peptides and noradrenaline serve particularly crucial roles for analgesia (28).

Acupuncture and the cerebral cortex. The cerebral cortex is the center of higher nervous activity, including consciousness, intelligence, analysis and synthesis, reasoning and judgment. In the cerebral cortex, the effect of acupuncture-induced analgesia is not a simple excitatory or inhibition process, but a complex adjustment process (25,29,30). The cumulative effect of repeated acupuncture stimulation was consistent with the characteristic habituation effects associated with functional magnetic resonance imaging examination (8).

3. Proposed mechanisms of acupuncture-induced analgesia

Acupuncture and opioids. Previous studies have suggested that acupuncture-induced analgesia is mediated by the release of endogenous opioids (31). Locally administered exogenous opioid receptor agonists bind to opioid receptors to produce analgesia. Acupuncture has been hypothesized to generate an increased release of endogenous opioids, and increase receptor affinity and/or number (32). Opioid peptides bind to their receptors on central neurons and subsequently induce antinociception (33).

The expression of all four subsets of opioid peptides, including endomorphin (μ-opioid agonist), dynorphin (κ-opioid agonist), enkephalin and β-endorphin (μ- and δ-opioid agonists), may be upregulated following acupuncture treatment (34); however, β-endorphin appears to be the most abundant opioid in acupuncture patients (35). Furthermore, the peripheral release of opioids may be involved in acupuncture-induced analgesia (36). There are multiple lines of evidence that suggest the possibility of acupuncture-induced peripheral opioid release. Firstly, acupuncture has been observed to modulate immunological activities (37), and immune cells are key components of the peripheral opioid system. Secondly, central opioid mechanisms present no evident mechanism through which needling an acupuncture point adjacent to a painful area may be able to reduce pain; however, central sensitization includes the malfunction of descending pain inhibitory pathways, which may result in dysfunctional endogenous analgesia (38). Thirdly, in clinical practice, acupuncture is generally more effective in relieving local pain compared with needling distal areas, a phenomenon that is comparable with the presence of a localized analgesic mechanism (39-41). Due to the lack of endogenous analgesia, increased temporal summation of secondary pain may contribute to the development or maintenance of central sensitization in patients with chronic pain (42). However, endogenous opioids released by acupuncture may induce analgesia and prevent the development of chronic pain (42).

Acupuncture and γ-aminobutyric acid (GABA). Certain studies have hypothesized that pain sensation may be suppressed by acupuncture, and the regulation of the glutamatergic and the GABAergic systems has been proposed as a possible mechanism (43. Inhibition of the excitatory glutamatergic system and stimulation of the inhibitory system contribute to antinociception. Stimulation of the GABA-A and GABA-B receptors has been demonstrated to result in pain suppression (44,45).

Peripheral C-fiber stimulation activates inhibitory spinal mechanisms that are dependent on μ-opioid and GABA receptors, which suppress ongoing ascending activity and induce analgesia via an opioidergic connection to the nucleus accumbens (46). GABA transporter 1 (GAT1) has been demonstrated to be involved in pain sensation in transgenic mice with knockout or overexpression of GAT1 (47). Activation of the δ-opioid receptor may reduce the rate of GABA uptake and GAT1-mediated current. In a previous study, μ-opioid receptor activation did not affect the number of transporters, the rate of GABA uptake or GAT1-mediated current (48). However, inhibition of GAT1-mediated current via the activation of the δ-opioid receptor has been demonstrated in whole-cell patch-clamp experiments with rat brain slices of the periaqueductal gray. Therefore, the inhibition of GAT1 function may enhance the inhibitory effects of the GABAergic system and contribute to acupuncture-induced analgesia (49).

Acupuncture and signaling pathways. During nerve injury, phospho-P38 mitogen-activated protein kinase (p-P38 MAPK) levels have been observed to sequentially increase in the neurons, microglia and astrocytes of the spinal dorsal horn (49,50). In addition, nerve injury-induced upregulation of p-P38 MAPK may occur rapidly and persist for an extended period. Previous studies have demonstrated a significant increase in the levels of p-P38 MAPK during spinal dorsal horn-induced inflammation (51,52). Furthermore, studies have indicated that p-P38 MAPK levels are increased in the spinal cord following application of complete Freund's adjuvant (CFA), and the administration of the P38 inhibitor prevents inflammation (53,54). It has been indicated that the numbers of p-P38 MAPK-immunoreactive cells in the spinal dorsal horn increase rapidly and peak in a short time following CFA injection, and are maintained over an extended period (54).

Acupuncture may provoke extracellular signal-regulated kinase (ERK) activation in fibroblasts and keratinocytes of the dermal layer, and this analgesic effect has been demonstrated to be blocked when the ERK cascade is interrupted following administration of the MEK/MAPK inhibitor, U0126 (55).

The ERK signaling pathway has been regarded as a marker for central sensitization (56). Cheng *et al* suggested that the protein levels of p-ERK1/2 were slightly increased and attenuated nociception in acupuncture-treated rats (57). A number of time-dependent effects have been observed as a result of MAPK-ERK1/2 pathway activation in the peripheral and CNS following acupuncture-induced analgesia (58).

Acupuncture and the immune system. Cytokines exert a central analgesic effect, the underlying mechanism of which may be associated with neuropeptide receptors (59). The immune system is able to participate in the occurrence of pain and signal transmission. A 'neuropeptide-cytokine network' has been hypothesized as a possible mechanism underlying acupuncture-induced analgesia and immune regulation (60). In this network of associations between neuropeptides and cytokines, neuropeptides may affect the differentiation and development of immune cells, which may in turn cause the synthesis and secretion of neuropeptides (61,62). Thus, cytokines are not only key immunoregulatory factors, but also participate in pain signal conduction. In addition, cytokines are able to modulate the extent of neuropeptide secretion (63). Acupuncture has been hypothesized to stimulate receptors on complex structures, such as nerves, blood vessels and lymph vessels, in the acupuncture-point area (64,65). Acupuncture has an effect on all levels of the 'nervous immune network'. It initiates neuropeptide production, cytokine processing and integration, and causes nerve impulses to pass through the peripheral and autonomic nerve system, thus generating a complete and precise regulation of the 'neuropeptide cytokine network.' Therefore, certain studies have suggested that acupuncture may exert an effect on pain and immune regulation (66-68).

5-HT serves a crucial function in specific physical and emotional responses. For example, low levels of 5-HT have been associated with anxiety, depression and stress (69). 5-HT is a neuroactive substance that participates in analgesic activity in the descending pain-inhibitory system of the brain stem, and it has been proposed that acupuncture affects 5-HT activity in the central neurons. A previous study suggested that the levels of 5-HT were correlated with acupuncture analgesia (70). 5-HT and its receptors in the CNS are known to be associated with the modulation of nociceptors (71). It was hypothesized that the lower pain scoring and increased friendliness observed in acupuncture-treated dogs may be due to increased acupuncture-induced secretion of 5-HT (70,71).

Cholecystokinin octapeptide (CCK-8) and/or CCK receptors have been reported to be involved in acupuncture-induced analgesia. CCK-8 has been demonstrated to possess notable anti-opioid activity at the spinal level. Thus, inhibition of the spinal cholecystokinin effect may be expected to potentiate opiate analgesia (72). Opioid activity *in vivo* is able to increase the expression of CCK-8, resulting in negative feedback regulation (73). Exogenous and endogenous opioid substances are able to promote the central release of CCK-8. A previous study demonstrated that systemic morphine produces a marked increase in CCK-8 immunoreactivity in the perfusate of the rat spinal cord, an effect that is reversed by naloxone (74). Opioid agonists of the κ- and μ-opioid receptors are known to increase CCK-8 release, while the effects of α-agonists are invalid (75). Furthermore, nociception may result in the development of serious pain due to the release of mediators, such as SP (76). Immunohistochemical studies have suggested that acupuncture depresses the pain response and increases SP-immunoreactivity, possibly due to the inhibition of SP release (77). Therefore, the inhibition of SP may reduce early pain perception.

4. Conclusion

Acupuncture is an ancient medical technology and comes from developed practises. Although preliminary, the neurobiological findings of previous studies have suggested a number of potential underlying mechanisms for an association between acupuncture and analgesia (78,79). Therefore, the application of acupuncture for analgesia is a useful method in clinical practice.

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