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Review article

The endocannabinoid system, a novel and key participant in acupuncture's multiple beneficial effects

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ABSTRACT

Acupuncture and its modified forms have been used to treat multiple medical conditions, but whether the diverse effects of acupuncture are intrinsically linked at the cellular and molecular level and how they might be connected have yet to be determined. Recently, an emerging role for the endocannabinoid system (ECS) in the regulation of a variety of physiological/pathological conditions has been identified. Overlap between the biological and therapeutic effects induced by ECS activation and acupuncture has facilitated investigations into the participation of ECS in the acupuncture-induced beneficial effects, which have shed light on the idea that the ECS may be a primary mediator and regulatory factor of acupuncture's beneficial effects. This review seeks to provide a comprehensive summary of the existing literature concerning the role of endocannabinoid signaling in the various effects of acupuncture, and suggests a novel notion that acupuncture may restore homeostasis under different pathological conditions by regulating similar networks of signaling pathways, resulting in the activation of different reaction cascades in specific tissues in response to pathological insults.

1. Introduction

Acupuncture is an important component of traditional Chinese medicine (TCM). It has been established as an effective treatment and used therapeutically in China and other Asian countries for centuries. As a modified form of traditional acupuncture, electroacupuncture (EA) uses electrical currents with standard parameters, and EA is believed to be more accurate, reliable and without harmful side-effects. EA is now widely used in clinical practice as a complementary therapy to treat a variety of conditions, such as pain and cerebral/cardiac ischemia-reperfusion injury. In 1997, the National Institutes of Health acknowledged the efficacy and potential therapeutic effects of acupuncture for treating multiple pathological conditions, such as chronic pain and stroke. Although basic research findings have begun to clarify the mechanisms underlying the action of acupuncture, these mechanisms have yet to be firmly established (NIH, 1997). Acupuncture signals that originate at acupoints activate peripheral nerves, and the input signals are transmitted to the spinal cord and brain via various neuronal pathways. This induces a series of neurological effects at peripheral, spinal and supraspinal levels, which in turn, leads to various physiological and functional effects, such as neuroprotection and analgesia. To date, the most well-studied endogenous system known to be involved in regulating these pathways both centrally and peripherally is the endogenous opioid system (Zhao, 2008). To better understand the underlying mechanisms and scientific basis of acupuncture as well as to explore the roles and contributions of other endogenous systems in its biological effectiveness, a growing number of researchers have begun to focus their efforts on acupuncture research (Cheng, 2014; Li et al., 2012).

In 2009, Wang and colleagues firstly found that EA conferred neuroprotection against cerebral ischemia by stimulating the mobilization of endocannabinoids in the brain and activating CB1 receptors (Wang et al., 2009). Furthermore, Tjen-A-Looi and colleagues demonstrated that EA attenuated sympathoexcitatory reflex responses by causing the release of endocannabinoids and the activation of presynaptic CB1 receptors in the ventrolateral periaqueductal gray (vlPAG) (Tjen et al., 2009). Chen and colleagues also showed that EA increased levels of the endocannabinoid anandamide (N-arachidonoylethanolamine, AEA) in inflamed skin tissues and induced analgesia by activating CB2 receptors (Chen et al., 2009). These interesting findings indicated a potential link between EA and the endocannabinoid system (ECS), both centrally and peripherally, and suggested that this endogenous system might play a key role in the therapeutic effects of EA.

Because acupuncture and ECS activation are associated with many

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of the same biological effects, such as neuronal and cardiovascular protection, analgesic and antiemetic effects, and the maintenance of energy balance (Centonze et al., 2007; Chang, 2013; Pacher and Kunos, 2013), it is not surprising that recent studies have repeatedly described the involvement of ECS activation in EA-induced analgesic, neuroprotective and cardiovascular regulatory effects under various pathological conditions (Chen et al., 2009; Tjen et al., 2009; Wang et al., 2009). These interesting findings strongly suggest that ECS might be one of the primary mediators as well as a regulatory factor of all of the beneficial effects of acupuncture. Thus, to highlight the existence and importance of this newly discovered role, we have specifically reviewed the analgesic, neuroprotective and cardiovascular regulatory effects of both EA and the ECS in the following sections. We also focus on the evidence that supports the role of the ECS as a novel and key regulator of the multiple biological and therapeutic effects of EA.

2. Acupuncture induces biological effects related to ECS activation

2.1. Overview of acupuncture

Acupuncture is an important therapeutic technique that has been used for thousands of years in ancient China. It involves the insertion and manipulation of fine needles into specific acupoints. The TCM concepts of “meridian” and the vital energy “Qi” are part of the theoretical basis of acupuncture (Yang et al., 2011). Currently, a variety of acupuncture-related techniques, such as manual acupuncture (MA), EA, transcutaneous electrical acupoint stimulation (TEAS), and transcutaneous electrical nerve stimulation (TENS) are being used in clinical practice treating various disorders (Han, 2011; Kasat et al., 2014; Liu et al., 2016). EA is the most frequently used strategy. EA is similar to regular acupuncture in that it incorporates the physiological effects of traditional acupuncture needling and integrates them with the benefits of electrotherapy. It is performed by inserting acupuncture needles that are connected to an electrical stimulator into acupoints. The stimulation frequency, current intensity, pulse width, and pulse interval are adjusted for optimal effect (Yu et al., 2014). Compared to traditional acupuncture, there are several advantages to using EA. For example, the electrical stimulation can be easily regulated and repeated, and the frequency and intensity of the stimulation can be precisely adjusted. Different sets of parameters may produce different physiological effects. For instance, EA at different frequencies (e.g., 2, 15, and 200 Hz) may lead to the release of different opioid peptides (Han, 2003). Alternatives to EA, such as TENS, use electrodes that are applied to the skin instead of needle insertion. TENS is applied under specific conditions, such as in patients contraindicated for needle insertion (Kasat et al., 2014). Several transmitters and modulators have been hypothesized to be responsible for the effects of acupuncture, such as opioid peptides (Han, 2003), cholecystokinin octapeptide (CCK-8) (Han et al., 1986) and 5-hydroxytryptamine (5-HT) (Kim et al., 2005). Nonetheless, our understanding of how acupuncture works remains incomplete.

2.2. Acupuncture-induced analgesia

Acupuncture has been used in China and other Asian regions for nearly 3000 years to alleviate pain. Its increasing popularity among patients and physicians in the Western world, where it is incorporated as part of TCM, in recent years is remarkable, and it is especially valued for its effectiveness and persistence of the effects in treating chronic pain (Eshkevari and Heath, 2005; Han and Ho, 2011; MacPherson et al., 2016). Since the first study of acupuncture’s analgesic effects was published in the early 1970s (Andersson et al., 1973), acupuncture and related therapies have been shown to serve as effective treatments for various types of pain (Wang et al., 2008) by triggering a series of biological effects in the nervous system (Zhang et al., 2017; Zhao, 2008). For example, the opioid system has been shown to be involved in acupuncture-induced analgesia, both centrally and peripherally, due to the release of opioids and the activation of μ-, δ-and κ-opioid receptors (Han, 2003; Zhang et al., 2005a). Moreover, other endogenous substances in the central nervous system (CNS), including CCK-8 (Han et al., 1986), 5-HT (Kim et al., 2005) and adenosine (Goldman et al., 2010), also contribute to acupuncture-induced analgesia.

Because it is a safe, cost-effective and user-friendly therapy (White et al., 2001; Zhu et al., 2013a), acupuncture has become a common pain treatment option in the clinic, especially for chronic pain (Eshkevari and Heath, 2005). Consistent with laboratory findings, increasing evidence from randomized controlled trials (RCTs) and meta-analyses shows that acupuncture is clinically effective in treating painful conditions, such as chronic back pain (Manheimer et al., 2005), chronic neck pain (Blossfeldt, 2004; Vas et al., 2006), osteoarthritis of the knee (Witt et al., 2005), headache (Schiapparelli et al., 2011) and post-operative pain (Lu et al., 2015b). For example, an RCT reported by Dang and Yang investigated the efficacy of acupuncture in alleviating stomach carcinoma pain and showed that patients undergoing acupuncture for two months experienced less pain than patients who underwent sham acupuncture or those in the control group (Dang and Yang, 1998). Similarly, a systematic review of RCTs also suggested that acupuncture and related techniques were effective in reducing post-operative pain scores and opioid consumption (Sun et al., 2008). Furthermore, results from other clinical studies support the idea that acupuncture is superior to typical care in treating chronic back pain (Trigkilidas, 2010). Such clinical investigations have enabled the identification of optimal acupuncture parameters for different pain conditions and shed light on the mechanisms that underlie acupuncture-induced analgesia in humans.

2.3. Acupuncture-induced neuroprotection against stroke

Studies have demonstrated the neuroprotective effects of acupuncture against CNS disorders, especially cerebral ischemic stroke. For example, in 2003, Xiong and colleagues reported that pretreatment of rats with repeated EA stimulation at the Baihui acupoint (GV20) before cerebral ischemia significantly reduced the volume of infarcts caused by transient middle cerebral artery occlusion (MCAO) and improved subsequent neurological outcomes (Xiong et al., 2003). A single 30-min session of EA stimulation at the Baihui acupoint induced biphasic tolerance against focal cerebral ischemia; the acute phase was observed 2 h after EA pretreatment, while the delayed ischemic tolerance was observed 24 h after the stimulus (Wang et al., 2005; Ma et al., 2011). In addition to the protection provided against ischemic cerebral injury, EA pretreatment also protected rats that were exposed to high-sustained positive acceleration (+Gz) by reducing pathological injury to hippocampal neurons and the number of apoptotic neurons in area CA1 as well as by improving learning and memory caused by +Gz exposure (Feng et al., 2010).

Acupuncture-induced neuroprotection against stroke has also been consistently reported in clinical trials. Hu and colleagues investigated the feasibility of the use of acupuncture in combination with conventional supportive treatments for acute stroke patients in an RCT and found that acupuncture more effectively improved neurological outcomes than the standard rehabilitation procedure (Hu et al., 1993). This finding was later verified by Magnusson and colleagues, who found that in stroke patients, electrostimulation resulted in better functional recovery than the control treatments (Magnusson et al., 1994). Similarly, in a meta-analysis of 8 RCTs, Wang and colleagues found that compared to conventional western medicines, scalp acupuncture was associated with greater improvement in neurological deficit scores and higher clinical efficacy rates in patients after acute ischemic stroke (Wang et al., 2012). Wu and colleagues comprehensively assessed the efficacy of acupuncture in post-stroke rehabilitation and found that acupuncture was associated with significantly better outcomes than sham treatment or no acupuncture in the treatment of post-stroke rehabilitation (Wu et al., 2010). Consistently, acupuncture is also