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Review

The role of electroacupuncture in stroke treatment: A systematic review of the literature

Panagiotis Zogopoulos*, Georgios Vretakos and Dimitrios Rologis

Department of Neurosurgery, Metropolitan Hospital, Athens, Greece.

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Stroke is a major cause of serious neurological disability, and the second leading cause of death worldwide with more than 6 million deaths each year. Although pharmaceutical treatment of stroke has advanced over the last decades, clinical treatment or prevention of motor impairment (which is the most frequent complication) is still inadequate. Therefore, it is imperative to develop new techniques and strategies aimed at reducing this complication. Acupuncture has been widely used for treating stroke in China for a long time and stroke is one of the most common diseases for which acupuncture treatment is recommended, according to the World Health Organization. The study presents the available experimental and clinical data to date regarding the role of electroacupuncture (a combination of traditional acupuncture and electrical stimulation) in the treatment of stroke.

Key words: Acupuncture, electroacupuncture, stroke, rehabilitation, motor recovery, ischemia.

INTRODUCTION

Stroke is the leading cause of serious, long-term disability and the second leading cause of death, affecting approximately 800,000 people of whom more than 140,000 die each year in the United States (Donnan et al., 2008; Roger et al., 2011). The total societal and healthcare costs related to stroke in the USA have risen from $53.6 billion in 2004 to $68.9 billion in 2009 (American Heart Association, 2004, 2009). Despite recent advances in pharmaceutical therapy of stroke, clinical treatment of this debilitating disorder is still inadequate. Motor impairment is a frequent complication after stroke, and the ability to live independently depends largely on the reduction of motor impairment and the recovery of motor function (Stinear, 2010). Thus, there is a huge unmet need for developing new techniques and strategies aimed at reducing impairment after stroke. Acupuncture has been widely used for treating stroke in China for a long time, and stroke is one of the most common diseases for which acupuncture treatment is recommended, according to the World Health Organization (Zhang et al., 2005).

Ischemic strokes, due to thrombosis, embolism or systemic hypoperfusion, are more prevalent than hemorrhagic, and numerous studies have shown that pretreatment with electroacupuncture (EA) (a combination of traditional acupuncture and electrical stimulation) induces significant tolerance to focal cerebral ischemia (Wang et al., 2005, 2009). This review study presents the available experimental and clinical data, to date, regarding the role of electroacupuncture in the

*Corresponding author. E-mail: p.zogopoulos@yahoo.com; Tel: +306976053555.

treatment of stroke.

METHODOLOGY

The source of data for this review was the PubMed/MEDLINE database. Search criteria were keywords: acupuncture, electroacupuncture, stroke, rehabilitation, motor recovery, ischemia. This study included both animal and human studies, studies comparing acupuncture versus EA and studies comparing classical stroke treatment versus EA. Exclusion criteria were studies with unclear methodology and studies with very small number of subjects.

Electroacupuncture and stroke

EA, an alternative more potent form of traditional acupuncture combined with modern electrotherapy is currently under investigation regarding its potential neuroprotective effects especially in stroke patients (Si et al., 1998; Hopwood and Lewith, 2005). Cerebral preconditioning refers to a process by which a brief exposure of the brain to sublethal or non-injurious stimuli renders it resistant to a subsequent damaging ischemic insult. Ischemic tolerance consists of an early phase that occurs within minutes after induction, followed by a delayed phase that develops many hours or even days later (Orio et al., 2007). EA pretreatment can act as such a preconditioning method.

Mechanisms of action - experimental studies

Anti-inflammatory action of EA

During ischemia, cytokines, such as TNF-α, IL-1β, IL-6, and chemokines such as cytokine-induced neutrophil chemoattractant (CINC) and monocyte chemoattractant protein-1 (MCP-1) are produced by a variety of activated cell types, including endothelial cells, microglia, astrocytes and neurons and contribute to stroke damage (Huang et al., 2006; Doyle et al., 2008). Monocyte chemotactic protein-induced protein 1 (MCPIP1), a recently identified protein in human peripheral blood monocytes treated with monocyte chemotactic protein-1 (MCP-1), can play a significant anti-inflammatory role by inhibiting the production of various proinflammatory cytokines (Matsushita et al., 2009; Liang et al., 2010).

MCPIP1 protein and mRNA levels were significantly increased in mouse brain after EA pretreatment (Jin et al., 2013). MCPIP1 expression was selectively increased in the brain and more specifically, in neurons and to a lesser extent in astrocytes (Jin et al., 2013). Two sessions of EA pretreatment significantly attenuated the infarct volume, neurological deficits, NF-κB signaling activation, expression levels of proinflammatory cytokines TNF-α, IL-1β, IL-6 and leukocyte infiltration in the brain of wild-type mice after middle cerebral artery occlusion (MCAO) for 90 min compared with that of the non-EA control group (Jin et al., 2013). Therefore, MCPIP1 seems to be a mediator of EA pretreatment-induced ischemic tolerance.

EA promotes proliferation and differentiation of neuronal stem cells

The adult brain is capable of replacing some lost neurons after stroke injury via proliferation, migration and differentiation of neuronal stem cells (NSCs) (Iwai et al., 2002). Although newly born cells can be supplied from several origins, including subventricular zone (SVZ) of the lateral ventricle, subgranular zone (SGZ) of the hippocampal dentate gyrus and the neocortical layer in the post-stroke brain, the number is too small for recovery of neurologic functions (Abe et al., 2012), with the fraction of dead striatal neurons replaced by newly born neurons at six weeks after insult being only about 0.2% (Arvidsson et al., 2002). Neuroblasts that have migrated to injury sites show differentiation into a region-appropriate phenotype that becomes functionally integrated into neural networks for participation in brain repair and functional recovery after stroke (Thored et al., 2006).

EA stimulation with 2Hz at bilateral Baihui (GV20) and Dazhui (GV14) acupoints from 5 to 14 days after MCAO in mice, on time with the peak level of proliferated NSCs after ischemic injury (Arvidsson et al., 2002; Abe et al., 2012), resulted in improved neuronal function and cognitive ability and induced proliferation and differentiation of NSCs (Kim et al., 2014). Although very limited survival of newborn neuronal precursors was observed against the total number of BrdU positive proliferated cells (Arvidsson et al., 2002; Kim et al., 2014), the significant increase in the number of proliferative and differentiated cells in the hippocampus and SVZ of the ipsilateral hemisphere compared to control group, indicated that EA stimulation may play beneficial roles in enhancement of proliferation and differentiation of NSCs into neurons or astrocytes (Kim et al., 2014). EA treatment-induced functional recovery after ischemic stroke may be mediated via the brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) signaling pathway, since EA stimulation resulted in significantly increased mRNA expression of BDNF and VEGF in the ipsilateral hippocampus and SVZ after ischemic stroke in mice (Kim et al., 2014). BDNF and VEGF stimulate adult neurogenesis and enhance the appearance and migration of new neurons in the SVZ and dentate gyrus (Jin et al., 2002; Schabitz et al., 2007).

EA inhibits neuronal apoptosis and induces tolerance against focal cerebral ischemia

Several animal studies have shown that EA can reduce neural apoptosis, promote cell proliferation, increase cerebral blood flow (CBF) and improve neurological function after stroke (Tao et al., 2010; Du et al., 2011). It has been proven in experimental studies that acupuncture at the Baihui (GV 20) acupoint after ischemia could attenuate the cerebral ischemic injury in monkey and rat (Gao et al., 2002; Chuang et al., 2007). The involvement of the endocannabinoid system and its role in the rapid ischemic tolerance (tolerance to focal cerebral ischemia) induced by EA pretreatment in rats has been recently reported (Wang et al., 2005, 2009). Particularly, EA pretreatment at Baihui acupoint induced two phases of tolerance to focal cerebral ischemia, a rapid tolerance (2 hours after EA) mediated through cannabinoid receptors type 1 (CB1) and a delayed tolerance (24 h after EA) mediated through cannabinoid receptors type 2 (CB2) (Xiong et al., 2003; Wang et al., 2005, 2009; Ma et al., 2011).

EA has been reported to increase neurotrophic factors such as BDNF, stromal cell derived factor-1α (SDF-1α), insulin-like growth factor 1, basic fibroblast growth factor, glial derived neurotrophic factor or receptors, NMDA NR1 and TRPM7 (Sun et al., 2005; Wang et al., 2005; Gao et al., 2006; Zhao et al., 2007). BDNF and SDF-1α are hypoxia-inducible factor (HIF)-1 target proteins, which have been implicated in mediating neuroprotection after hypoxic preconditioning (Bernaudin et al., 2002; Li et al., 2008). BDNF and SDF-1α can affect both neuronal and vascular function in the ischemic brain. BDNF is a potent growth factor involved in recovery following cerebral ischemia (Kokaia et al., 1996). Focal cerebral

ischemia causes an increase in endothelial SDF-1α expression in regions adjacent to the infarcted area (Stumm et al., 2002). Recently, intracerebral administration of SDF-1α was reported to induce neuroprotection against neurotoxic insult, and induce increased bone marrow-derived cell targeting of the ischemic brain, thereby reducing the volume of cerebral infarction and improving neural plasticity (Shyu et al., 2008). For these reasons, BDNF and SDF-1α are potent candidates in ischemic preconditioning.

Pretreatment of mice with EA for 20 min once a day at the acupoints 'Baihui (GV20)' and 'Dazhui (GV14)' for three days prior to the ischemic event increased the production of BDNF in the cerebral cortex ($P < 0.05$) and SDF-1α in the plasma ($P < 0.01$), which elicited protective effects against focal cerebral ischemia (Kim et al., 2013). Moreover, EA preconditioning reduced the infarct volume by 43.5% when compared to control mice at 24 h after photothrombotic cortical ischemia (Kim et al., 2013). Consistent with a smaller infarct size, EA preconditioning showed prominent improvement of neurological function and motor function such as vestibule-motor function, sensori-motor function and asymmetric forelimb use 24 h after occlusion (Kim et al., 2013).

Activation of Notch signaling has been found to contribute to EA pretreatment-induced tolerance against focal cerebral ischemia in rats (Zhao et al., 2012). Notch is a cell-surface receptor, whose activation eventually regulates transcription of the Notch target genes, such as Hes family, in a process called canonical Notch signaling (Gaiano and Fishell, 2002; Iso et al., 2003). Notch signaling is implicated in neural development, progenitor cell fate determination and induction of differentiation in proliferating cells (Gaiano and Fishell, 2002; Iso et al., 2003). Notch pathway can also be activated in the adult brain after stroke and traumatic brain injury (Wang et al., 2009; Tatsumi et al., 2010). Notch1, Notch4, Jag1 and Hes1 genes (major Notch pathway components in the central nervous system) transcription (mRNA) was up-regulated in the striatum but not in the hippocampus of adult rats after EA pretreatment and ischemia/reperfusion (I/R) (Zhao et al., 2012). Although EA pretreatment could not activate Notch pathway before I/R, it prepared the essential materials for the following Notch pathway activation after I/R, thus facilitating neuronal survival (Zhao et al., 2012). EA pretreatment remarkably improved functional outcome and reduced infarct volume after I/R in rats compared with control group ($P < 0.05$) (Zhao et al., 2012). The neuroprotective effects of EA pretreatment were attenuated after intraventricular administration of MW167 (a γ-secretase inhibitor), suggesting that γ-secretase-mediated Notch signaling is required for the cerebral ischemic tolerance induced by EA pretreatment (Zhao et al., 2012).

EA pretreatment stimulated the release of enkephalins, which may bind δ- and μ-opioid receptors to induce tolerance against focal cerebral ischemia in rats (Xiong et al., 2007). Matrix metalloproteinase 2 (MMP-2), aquaporin (AQP) 4 and AQP9 can disrupt the blood-brain barrier (BBB) and provoke cerebral edema after I/R injury (Fukuda and Badaut, 2012). EA at Baihui (GV20) and Zusanli (ST36) acupoints in a rat model of I/R injury (MCAO) significantly decreased infarct size, improved neurological function and reduced inflammatory cell infiltration (Xu et al., 2014). It also significantly reduced the expression of proinflammatory enzymes MMP-2 and MMP-9 and water channel proteins AQP4 and AQP9, suggesting that the protective mechanism of EA treatment is partially dependent on the reduction of inflammation-related brain edema (Dong et al., 2009; Xu et al., 2014).

EA pretreatment at Baihui acupoint (GV 20) for 30 min reduced infarct size ($P < 0.01$), improved neurological outcome ($P < 0.01$) and inhibited neuronal apoptosis at 24 h or 7 days after focal cerebral I/R in rats (Wang et al., 2009; Du et al., 2010). Furthermore, the number of viable cells in the ischemic penumbra was significantly increased in rats after EA pretreatment ($P < 0.05$) (Wang et al., 2009). The beneficial effects were abolished by AM251 (a selective CB1 receptor antagonist), while given alone, AM251 had no significant effect on ischemia-induced neurological outcome, infarct volume or neuronal apoptosis (Wang et al., 2009). The beneficial effect of EA pretreatment was also reversed by the MEK1/2 inhibitor U0126 given 30 min before the onset of each EA pretreatment ($P <0.01$), while it had no effect on neurological scores or brain infarct volume when administered alone (Du et al., 2010). EA pretreatment upregulated the neuronal expression of CB1 receptor in the ipsilateral hemisphere of rat brains (2 h after the end of EA pretreatment) and elevated the brain tissue content of endocannabinoids 2-AG ($P < 0.01$) and AEA ($P < 0.01$) (Wang et al., 2009). Pretreatment with 2-AG and AEA also reduced infarct size and improved neurological outcome ($P < 0.05$) (Wang et al., 2009).

Extracellular signal-regulated kinase (ERK) signaling is one of the major cell survival and proliferation pathways (Seger and Krebs, 1995). By altering the levels and activities of transcription factors, the activation of ERK pathway regulates the expression of various cell cycle-regulatory genes, including cyclin D1 and cyclin-dependent kinase (CDK)4, thus mediating the promotion of cell proliferation (Lavoie et al., 1996). ERK is activated in cerebral I/R injury and is therefore a key target in the treatment of ischemic stroke. EA at the Quchi (LI11) and Zusanli (ST36) acupoints has been shown to exert a neuroprotective effect in ischemic stroke via the activation of ERK1/2 pathway (Xie et al., 2013). More specifically, EA at these acupoints for only 24 h significantly improved neurological deficits ($P < 0.05$) and reduced cerebral infarct volumes ($P < 0.05$) in an experimental model of cerebral I/R injury in rats (Xie et al., 2013). It also significantly upregulated the protein expression of Ras, cyclin D1 and CDK4 in the ischemic cerebral cortex and striatum of rats and promoted cerebral cell proliferation (Xie et al., 2013).

ERK1/2 is thought to be an early indicator for cellular stress and has been reported to be involved in the development of ischemic preconditioning (Choi et al., 2006; Zuo et al., 2006). Although the role of ERK1/2 activation in cerebral I/R injury remained controversial, most studies have verified the role of ERK1/2 as an important protective signaling pathway in the process of reperfusion (Shamloo et al., 1999). EA pretreatment increased phospho-ERK1/2 expression after reperfusion in rats, suggesting that phosphorylation of ERK1/2 is involved in EA pretreatment-induced cerebral ischemic tolerance (Du et al., 2010). Furthermore, CB1 receptor antagonist AM251 abolished the up-regulation of p-ERK1/2 expression induced by EA pretreatment (Du et al., 2010). These results suggest that EA pretreatment induces cerebral ischemic tolerance through the ERK1/2 pathway which might be mediated by CB1 receptors in rats (Du et al., 2010).

Angiogenesis, the formation of new vessels from pre-existing ones, can play a critical role in neurovascular remodeling, a key component of recovery after stroke (Arai et al., 2009). It is currently believed that angiogenesis promotes neurogenesis (Zhang et al., 2005) since it supports the recovering neural networks (Ohab et al., 2006). The angiopoietin (Ang) family, including Ang-1 and Ang-2, is one of the major effectors of angiogenesis (Zhou et al., 2014). Ang-1 and Ang-2 have been shown to regulate ischemia-induced angiogenesis in rat brains (Zhang et al., 2002).

A number of studies have demonstrated that acupuncture at the Zusanli (ST36) acupoint possesses a neuroprotective effect by suppressing neuronal apoptosis (Wang et al., 2002, 2009), improving neural plasticity (Ren et al., 2008), increasing cerebral blood flow and improving microcirculation (Hsieh et al., 2006) in ischemic rat brains. EA at the Zusanli acupoint has been shown to accelerate intracerebral hemorrhage (ICH)-induced angiogenesis in rats (Luo et al., 2013). After EA to the bilateral Zusanli (ST36) acupoint in adult rats, the expression of Ang-1 (from 3 days to 14 days) and Ang-2 (at 3 days) was upregulated after hemorrhagic

stroke at both the protein and mRNA levels (P<0.05), thus exerting neuroprotective effects (Zhou et al., 2014). Furthermore, EA has also exhibited an anti-inflammatory effect after stroke in rats (Lan et al., 2013).

Pretreatment with a combination of melatonin (a potent antioxidant and free radical scavenger) and EA at ST36 and ST39 acupoints (MEA) significantly improved neurological outcome ($p < 0.05$), decreased brain infarct volume by 25.7% ($p < 0.05$) and inhibited neuronal inflammation as well as apoptosis 24 h after transient MCAO in rats when compared with the control group (Liu et al., 2013). The beneficial effects may derive from downregulation of proinflammatory and proapoptotic mediators and upregulation of antiapoptotic mediators (Liu et al., 2013). When compared with the control group, MEA pretreatment significantly decreased the upregulated protein expression of proinflammatory mediators TNF-α and COX-2 ($p < 0.01$) and the relative expression of proapoptotic protein Bax ($p < 0.05$), while the expression of antiapoptotic protein Bcl-2 was significantly increased in the ischemic cerebral hemisphere 24 h after transient MCAO ($p < 0.01$) (Liu et al., 2013). Many necrotic neurons and infiltrated neutrophils were seen in the infarcted cortex in the control group, while in MEA-pretreated rats neutrophil infiltration within the ischemic cerebral cortex was suppressed (Liu et al., 2013).

Necrotic injury occurs in the brain within minutes after ischemic stroke. However, the ischemic penumbra, the border of the necrotic core, undergoes apoptosis within several hours or days with the activation of multiple death pathways (Love, 2003). Treatment with EA may reverse the damage caused to the ischemic penumbra by inhibiting the activation of apoptotic pathways (Kim et al., 2013). EA treatment at the Baihui and Qihai acupoints (2 Hz to 1 mA) after stroke in rats significantly reduced brain infarct volume and apoptotic cells number and improved neurological outcome (Kim et al., 2013). It also resulted in a higher expression of anti-apoptotic Bcl-2 and Bcl-xL, as well as anti-apoptotic proteins cIAP-1 and -2 in the cortex of the EA-treated rats compared with the control group (Kim et al., 2013). These results suggest that EA treatment exerts anti-apoptotic effects in cerebral ischemia in a rat model of MCAO and that these effects are associated with the inhibition of mitochondrial apoptotic pathways (Kim et al., 2013).

EA treatment at Quchi (LI 11) and Zusanli (ST 36) acupoints, is associated with potential benefits for post-stroke conditions such as spastic paralysis (Yue et al., 2012) and improved stroke patients' symptoms and signs (He et al., 2007). Experimental animal data also support that EA treatment at Quchi (LI 11) and Zusanli (ST 36) have neuroprotective and cerebral protective function exerted via activation of phosphatidylinositol 3-kinase (PI3K/Akt) pathway (Ren et al., 2010; Chen et al., 2012). PI3K/Akt signaling pathway, a critical mediator of cell survival, is suppressed in cerebral I/R injury thereby, increasing the infarct size and promoting cerebral cell death (Gao et al., 2010). Inhibiting cerebral cell apoptosis via activation of PI3K/Akt signaling has been a promising strategy for the treatment of ischemic stroke.

EA for 24 h at Quchi (LI11) and Zusanli (ST36) acupoints on the contralateral paralyzed limb in rats after cerebral I/R injury, profoundly activated PI3K/Akt signaling in ischemic cerebral tissues thus, resulting in the inhibition of cerebral cell apoptosis, and significantly improved neurological deficits and reduced cerebral infarct volumes ($P < 0.05$ vs. control group) (Chen et al., 2012). Moreover, EA increased serum secretion levels of the PI3K activators BDNF and glial cell line-derived neurotrophic factor (GDNF), as well as upregulated the anti-apoptotic Bcl-2/Bax ratio in ischemic cerebrum of rats (Chen et al., 2012). Bcl-2 family proteins are key regulators of apoptosis, functioning as either suppressors such as Bcl-2 or promoters such as Bax (Genovese et al., 2011). Both anti-apoptotic Bcl-2 and pro-apoptotic Bax are important target genes of PI3K/Akt signaling pathway (Genovese et al., 2011).

EA stimulation for 20 min at Baihui (GV20) and Dazhui (GV14) immediately after 60 and 90min MCAO in mice increased perfusion in the cerebral cortex (Kim et al., 2013). Perfusion started to increase 10 s after the onset of EA stimulation, gradually increased to 12.4 ± 1.9% of the baseline during EA stimulation and remained at the increased levels for about 20 min after the end of EA stimulation (Kim et al., 2013). EA stimulation at GV20 and GV14 did not cause mean arterial blood pressure (MABP) responses and no perfusion or MABP responses were seen in the control group (Kim et al., 2013). The increased cerebral perfusion elicited by EA at GV20 and GV14 was significantly attenuated after intravenous injection of a blood brain barrier permeable muscarinic acetylcholine receptor (mAChR) blocker (atropine, 5 mg/kg) ($P < 0.01$), but was not affected after intravenous administration of a b-adrenergic receptor blocker (propranolol), an a-adrenergic receptor blocker (phentolamine) or a nicotinic acetylcholine receptor (nAChR) blocker (mecamylamine) (Kim et al., 2013). In addition, EA increased acetylcholine (ACh) release and mAChR M3 expression in the cerebral cortex (Kim et al., 2013). These data suggest that the cholinergic system activated by EA can contribute to the cortical perfusion response via activation of mAChR but not nAChR (Kim et al., 2013).

Acute EA stimulation significantly reduced infarct volume by 34.5% when compared to the control group mice at 24 h after 60 min MCAO (moderate ischemic injury), but not after 90 min MCAO (severe ischemic injury) (Kim et al., 2013). Consistent with a smaller infarct size, acute EA stimulation led to great improvement of neurological function and vestibule-motor function (Kim et al., 2013). These findings suggest that EA has a therapeutic benefit when administered early after moderate, but not severe ischemic stroke.

EA stimulation at appropriate intensity (~1.0 mA) and frequency (5 to 20 Hz) at Shuigou (Du 26) and Baihui (Du 20) acupoints in rats subjected to MCAO increased cerebral blood flow and perfusion in the ischemic brain region more than 100%, compared to that during the non-EA period ($P < 0.05$), and remarkably reduced neurological deficits ($P < 0.01$), death rate ($P < 0.01$) and infarct volume ($P < 0.01$)(Zhou et al., 2011). EA-induced increase in blood flow was specific in the ischemic brain, since it was not observed in the naive brain and was isochronous to EA stimulation, since it disappeared immediately after its discontinuing (Zhou et al., 2011).

Cerebral blood flow in rats, measured by laser Doppler, increased after EA treatment at Quchi (LI 11) and Zusanli (ST 36) acupoints compared to control group, reaching a peak at 15 min after EA stimulation (Wu et al., 2013). The concentrations of aspirin (which is used for the prevention of stroke recurrence) and its metabolite, salicylic acid were determined by microdialysis after single-dose administration (30 mg/kg, i.v.) in rats (Wu et al., 2013). Acupuncture and EA did not significantly interact with the pharmacokinetics of aspirin in rat blood and brain, supporting in part the safety of combination of aspirin and acupuncture or EA (Wu et al., 2013).

Cognitive impairment is a condition characterized by serious mental deficits that severely affect quality of life of stroke patients. Approximately 25% of patients present with cognitive impairment 3 months after a stroke and when specific types of cognitive impairment such as memory, language, orientation and attention are included this percentage rises up to 75% (Desmond et al., 2000). Acupuncture at the Baihui (DU20) and Shenting (DU24) acupoints is commonly used in China to clinically treat post-stroke cognitive impairment (Zhao et al., 2009). EA treatment at Baihui (DU20) and Shenting (DU24) points significantly reduced cerebral infarct volumes, ameliorated cognitive impairment (improved learning and memory ability) and inhibited neuronal cell apoptosis in a rat model of I/R injury ($P < 0.05$, EA vs. control group) (Feng et al., 2013). Nuclear factor-κB (NF-κB)-mediated neuronal cell apoptosis is involved in the development of post-stroke cognitive

impairment. The anti-apoptotic activity of EA was mediated by inhibition of the NF-κB signaling pathway (suppression of NF-κB protein expression) in ischemic cerebral tissues, as well as by downregulation of Bax and Fas pro-apoptotic protein expression at transcriptional and translational levels in rats (Feng et al., 2013).

In a recent study, EA treatment in a rat model of MCAO was shown to activate lactate metabolism in the resident astrocytes of the ischemic penumbra and up-regulated the expression of lactate transporter (monocarboxylate transporter 1, MCT1) in these astrocytes at both protein and mRNA levels (Lu et al., 2015). This facilitated the transfer of intracellular lactate extracellularly, thus making it available to injured neurons to improve the neurological deficit (Lu et al., 2015).

Clinical studies

In a PET study of 6 patients after ischemic stroke, 2 Hz EA treatment at Baihui (GV20) and right Qubin (GB7, on the affected hemisphere) for 20 min resulted in a significant increase of glucose metabolism on the primary motor area (M1), the precentral gyrus, the supplementary motor area (SMA), the medial frontal gyrus, premotor cortex (PMC), the central frontal gyrus and the superior parietal lobule (Lps) of the unaffected side, while in the affected side glucose metabolism was decreased on M1, PMC and Lps (Fang et al., 2012). Besides these areas related to motion directly, glucose metabolism had also changed in the middle and superior temporal gyrus, putamen and cerebellum. These findings suggested that the contralateral hemisphere played an important role in the stroke recovery process (Pantano et al., 1996) and that EA treatment for stroke patients had played a good role in the recovery of motor function, since it proved very helpful for the cerebral motor plasticity after ischemic stroke (Fang et al., 2012).

A randomized controlled pilot study objectively assessed the efficacy of EA for motor function recovery in patients with acute ischemic stroke using the triple-stimulation technique (TST) (Tan et al., 2013). TST can be used for quantitative evaluation of electroacupuncture for motor function recovery in patients with acute ischemic stroke because it can objectively analyze the injury and recovery of corticospinal tract impairments. The patients received either EA plus western conventional medication (WCM) or single WCM for 14 days. The total clinical effective rate was statistically significantly superior in EA group (93.50%) compared to that in WCM group (73.33%) ($p < 0.01$) (Tan et al., 2013). Fugl-Meyer Assessment Scale (FMA) score, National Institutes of Health Stroke Scale (NIHSS) score, and TST_{ratio} were statistically significantly improved in the EA group compared to those in WCM group after 14 days of treatment ($p < 0.01$), while there was no statistical difference between EA treatment group and WCM control group in NIHSS score, FMA score and TST_{ratio} before treatment ($p > 0.05$) (Tan et al., 2013). Comparing between the two groups or between pretreatment and post-treatment, adverse events, electrocardiogram, liver function, and kidney function showed no statistically significant difference ($p > 0.05$) (Tan et al., 2013). In conclusion, EA was more beneficial for the motor function recovery of patients with first-ever acute ischemic stroke when compared with WCM control alone, using NIHSS score for the neurologic severity assessment and FMA score for the motor-status evaluation, and was generally safe (Tan et al., 2013).

A potential explanation of the beneficial effect of acupuncture on post-stroke rehabilitation is that analgesia achieved through acupuncture may relax muscles allowing for passive motion, an increased range of motion, and ultimately motor impairment rehabilitation (Shin et al., 2007). Another observed physiological effect of acupuncture is increased perfusion within peri-infarcts and low perfusion zones in the affected lobe as observed in MRIs of post-stroke patients receiving acupuncture (Lee et al., 2003). This possible effect could play a role in modifying tissue perfusion within cerebral areas affected by stroke, thus promoting a more rapid and effective recovery (Kim et al., 2006). It has also been suggested that adaptive changes in response to stroke involve neuronal reorganization and increased dendritic volume in the cortical layers and number of synapses in the contralateral hemisphere within 30 days after central nervous system injury (Lee et al., 2003). Acupuncture may offer benefit in this reorganization process by stimulating the peripheral site of the lesion (Wu et al., 2010).

Increased CBF after acupuncture has been demonstrated both in stroke patients using SPECT scanning (Lee et al., 2003) and in patients with vascular dementia using fluorodeoxyglucose positron emission tomography (FDG-PET) (Huang et al., 2007). It is well known that nitric oxide (NO) synthesized by endothelial NO synthase (eNOS) plays a pivotal role in maintaining CBF in the ischemic cortex and under most conditions, stimulation of eNOS activity is protective (Limbourg et al., 2002). Several studies employing human and animal models have shown that acupuncture enhances the generation of NO and increases local circulation (Tsuchiya et al., 2007). EA stimulation at GV20 and GV14 acupoints in eNOS knock out mice did not augment perfusion after moderate ischemic injury, suggesting that the cerebroprotective effects of acute EA are dependent on eNOS (Kim et al., 2013).

Contradicting though, are the data about clinical efficacy of manual acupuncture on post-stroke motor rehabilitation. In a prospective randomized controlled trial, carried out in a stroke rehabilitation unit in Hong Kong among 106 patients with moderate or severe functional impairment 3 to 15 days after acute stroke, no additional improvement was shown in motor impairment or disability over a 10 week period in patients receiving traditional Chinese manual acupuncture as compared with the

control (Sze et al., 2002). Moreover, systematic reviews and meta-analysis of nineteen trials involving 1576 patients did not find a statistically significant therapeutic benefit of traditional acupuncture on motor recovery for patients with subacute or chronic stroke (Sze et al., 2002; Zhang et al., 2005; Wu et al., 2008). However, a more recent comparative study of acupuncture versus EA regarding their effectiveness in treating post-stroke spastic paralysis showed that they were both effective and that EA was superior to traditional acupuncture alone (Yue et al., 2012).

DISCUSSION

Pretreatment with EA has been shown to increase the production of endocannabinoid 2-AG and AEA, which elicit neuroprotective effects against transient cerebral ischemia through CB1 receptors (Wang et al., 2009; Zogopoulos et al., 2013). These results suggest a novel mechanism of EA pretreatment-induced rapid tolerance to focal cerebral ischemia.

EA appears to be beneficial for the motor function recovery of patients with acute ischemic stroke and is generally safe, economical, easily performed and with only rare serious side effects (Zhang et al., 2005; Tan et al., 2013). National Institutes of Health have issued a consensus report stating that one of the advantages of acupuncture is that the incidence of adverse effects is substantially lower than that of many other accepted medical interventions (NIH consensus conference, 1998).

Although, EA does not seem to be an achievable practice in the acute and urgent setting of stroke patients treatment, it could effectively be used as a preventive method of cerebral ischemic injury in high-risk patients (susceptible to stroke)(Xiong et al., 2006).

CONCLUSION

EA has been found in a large number of studies to be beneficial in treating post-stroke motor impairment and consequently, in improving overall neurological status and quality of life. EA may also be a potential therapeutic approach for the treatment of cerebral ischemia and large randomized, controlled trials should be conducted to determine safety profiles and establish treatment protocols (Chen et al., 2014).

Conflicts of interest

The authors have none to declare.

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