

Category I: Promotion of cell proliferation in CNS

Table S1: Neurogenesis

| Study title | Author s | Publication | Target (receptor/molecule/pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|--|----------|---|------------------------------------|---------|------------------------------|------------------|---------------------|---------|---|-----------|------------|--|--|
| A study on the effect of neurogenesis and regulation of GSK3B/PP2A expression in acupuncture treatment of neural functional damage caused by focal ischemia in MCAO rats | Luo, D | Hindawi Publishing Corporation. Evidence-Based Complementary and Alternative Medicine. Vol. 2014, Article ID 962343 | GSK3β/PP2A (+) | MA | Shuigou (GV26) | Previous studies | Permanent Left MCAO | SD rats | Immediately after MCAO, Duration: Once daily for 3 consecutive days; Stimulation: Thrust/Lifted 3 times per/sec. for 1 min. | Acute | 3 | 1. Ac. Improved CBF, 2. Enhanced neurogenesis by upregulating the expression of GSK 3β and PP2A in cortex, hippocampus and striatum | Ac enhances neurogenesis via regulation of GSK-3 and PP2A expression |
| Electroacupuncture promotes post-stroke functional recovery via enhancing endogenous neurogenesis in mouse focal cerebral ischemia | Kim, Y | Plos One February 2014 Volume 9 Issue 2 e90000 | BDNF/VEGF (+) | EA | Dazhui (GV14), Baihui (GV20) | Not specified | MCAO for 40 min | Mice | 5 days after MCAO; Freq: 2HZ; Int: 2V; Time: 20min; Duration: 10 consecutive days | Sub-acute | 10 | 1. EA increased neuroblasts in the ipsilateral SVZ and hippocampus (Subcallosal zone) and enhanced differentiation into neurons or astrocytes, 2. EA increased activation of BDNF and VEGF-mediated downstream PI3K at SVZ and hippocampus, 3. EA improved division of NSCs | EA enhances proliferation and differentiation of neuronal stem cells via the BDNF and VEGF signaling pathway |

| | | | | | | | | | | | | | |
|---|---------|--|-------------------|----|------------------------------|------------------|-----------------------|---------|--|---------------|----|--|---|
| Electroacupuncture promotes neurological functional recovery via the retinoic acid signaling pathway in rats following cerebral ischemia-reperfusion injury | Hong, J | International Journal of Molecular Medicine 31: 225-231, 2013. | Retinoic Acid (+) | EA | Zusanli (ST36), Quchi (LI11) | Previous studies | Left MCAO for 120 min | SD rats | Freq: 5/20Hz, Int: 2-4mA, Time: 20min, Duration: once a day for 4 weeks | Not specified | 28 | 1. EA decreased infarct volume, 2. promoted neurological functional recovery, and 3. increased RA mRNA and protein expression | EA promotes neurological functional recovery through modulating RA expression and stimulation of neurogenesis |
|---|---------|--|-------------------|----|------------------------------|------------------|-----------------------|---------|--|---------------|----|--|---|

Table S2: Cell proliferation in ischemic tissue

| Study title | Author s | Publication | Target (receptor/molecule/pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|---|----------|---|------------------------------------|---------|--|------------------|------------------------|---------|---|---------------|------------|--|--|
| Electro-acupuncture exerts beneficial effects against cerebral ischemia and promotes the proliferation of neural progenitor cells in the cortical peri-infarct area through the Wnt/ β -catenin signaling pathway | Chen, B | International Journal of Molecular Medicine 36: 1215-1222, 2015 | Wnt/ β catenin (+) | EA | Zusanli (ST36), Quchi (LI11) on the paretic side | Previous studies | Left MCAO for 120 min | SD rats | 1 day after MCAO; Freq: 1-20Hz; Time: 30min; Duration: once daily for 3 days | Acute | 3 | 1. EA improved neurological deficits, 2. reduced infarct volume, 3. promoted proliferation of reactive astrocytes in peri-infarct cortex, 4. enhanced proliferation of neural progenitor cells in peri-infarct cortex, and 5. promoted activation of Wnt pathway in peri-infarct cortex | EA promotes the proliferation of neural stem/progenitor cells via the Wnt/ β -catenin pathway |
| Electroacupuncture improves behavioral recovery and increases SCF/c-kit expression in a rat model of focal cerebral ischemia/reperfusion | Lu, T | Neurological Sciences (2013) 34:487–495 | Stem Cell Factor (+) | EA | Hegu (LI4) bilateral | Not specified | Right MCAO for 120 min | SD rats | Freq: 40/60Hz; Int: 1mA; Time: 15 min; Duration: 7 consecutive days | Not specified | 7 | 1. EA improved behavioral recovery, 2. upregulated positive cells and mRNA expression of SCF, c-kit and MMP-9 after cerebral ischemia/reperfusion. | EA may promote neurobehavioral recovery by increasing the protein and mRNA expression of SCF, c-kit and MMP-9 after cerebral ischemia/reperfusion. |

| | | | | | | | | | | | | | |
|--|----------|---|----------------------------------|----|--|------------------|-----------------------|---------|--|---------------|---|---|---|
| Electroacupuncture promotes neural cell proliferation in vivo through activation of the ERK1/2 signaling pathway | Huang, J | International Journal of Molecular Medicine 33: 1547-1553, 2014 | ERK1/2 (+) | EA | Zusanli (ST36), Quchi (LI11) on the paretic side | Not specified | Left MCAO for 120 min | SD rats | 1 after MCAO; Freq: 1-20Hz; Time: 30min; Duration: once a day for 3 consecutive days | Acute | 3 | 1. EA improved neurological function, 2. reduced infarct volume, and 3. activated the ERK1/2 signaling pathway in ischemic brain cortex. | EA appears to activate the ERK1/2 signaling pathway to protect against brain injury during cerebral ischemia |
| Electroacupuncture at Quchi and Zusanli treats cerebral ischemia-reperfusion injury through activation of ERK signaling | Xie, G | Experimental and Therapeutic Medicine 5: 1593-1597, 2013 | ERK 1/2 (+) | EA | Zusanli (ST36), Quchi (LI11) on the paretic side | Clinical use | Left MCAO for 120 min | SD rats | 2 h after reperfusion; Freq: 1-20Hz; Time: 30min; Duration: single | Acute | 1 | 1. EA improved neurological function, 2. reduced infarct volume, 3. activated the ERK1/2 pathway in ischemic cerebral cortex and striatum, 4. promoted cell proliferation, and 5. EA enhanced expression of cyclin D1 and CDK4 | EA enhances the activation of the ERK1/2 pathway and promotes cell proliferation |
| Electro-acupuncture at LI11 and ST36 acupoints exerts neuroprotective effects via reactive astrocyte proliferation after ischemia and reperfusion injury in rats | Tao, J | Brain Research Bulletin 120 (2016) 14–24 | Cell cycle proteins and BDNF (+) | EA | Zusanli (ST36), Quchi (LI11) on paretic limb | Previous studies | Left MCAO for 120 min | SD rats | Freq: 1-20Hz; Time: 30min; Duration: 3 days | Not specified | 3 | 1. EA improved neurological deficits, 2. reduced infarct volume, 3. improved motor function recovery, 4. promoted reactive astrocyte proliferation in peri-infarct cortex and striatum, 5. enhanced expression of cell cycle associated proteins (cyclin D1, CDK4, phospho Rb), and 6. EA promoted secretion of BDNF from reactive astrocytes | EA promotes the proliferation of reactive astrocytes via enhancement of BDNF and promotes expression of cell cycle proteins |

Category II: Regulation of CBF

Table S3: Angiogenesis

| Study title | Author s | Publication | Target (receptor/molecule/pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|--|----------|--|--|---------|----------------------|------------------|--------------------|-------------|---|-------|------------|--|--|
| Effects of electroacupuncture on expressions of angiogenesis factors and anti-angiogenesis factors in brain of experimental cerebral ischemic rats after reperfusion | Ma, J | Journal of Traditional Chinese Medicine 2008; 28(3): 217-222 | VEGF, Angiogenin 1 (+), Endostatin (-) | EA | Hegu (LI4) bilateral | Not specified | Right MCAO for 1h | Wistar rats | 45 min after MCAO; Freq: 40-60Hz; Int: 1.5V; Time: 15min; Duration: once daily for 7 days | Acute | 7 | <ol style="list-style-type: none"> EA enhanced expression of VEGF and Ang-1 in cortex around the ischemic necrotic region, lateral ventricle and dentate gyrus of hippocampus, and EA reduced expression of endostatin | EA increases the expression of angiogenesis factors and inhibits the expression of anti-angiogenesis factors |

Table S4: Vasoactive modulation

| Study title | Author s | Publication | Target (receptor, molecule, pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|---|----------|---|--|---------|------------------------------|------------------|------------------------|-------------|--|---------------|------------|--|---|
| Electroacupuncture acutely improves cerebral blood flow and attenuates moderate ischemic injury via an endothelial mechanism in mice | Kim, J | Plos One February 2013 Volume 8 Issue 2 e56736 | ACh/ Endothelial nitric oxide synthase (+) | EA | Dazhui (GV14), Baihui (GV20) | Not specified | MCAO for 60 and 90 min | Mice | Immediately after MCAO; Int: 1mA; Freq: 2Hz; Time: 20min; Duration: single | Acute | 1 | 1. EA increased perfusion in the cerebral cortex 2. increased ACh release and mAChR M3 expression in cerebral cortex, 3. perfusion effects of EA were dependent on eNOS, 4. EA decreased infarct volume after moderate ischemic injury | EA in the acute stage improves ACh/eNOS-mediated perfusion augmentation, improving tissue and functional recovery |
| Electroacupuncture improves cerebral blood flow and attenuates moderate ischemic injury via Angiotensin II its receptors-mediated mechanism in rats | Li, J | BMC Complementary and Alternative Medicine 2014, 14:441 | Angiotensin II/AT1R (-), AT2R (+) | EA | Shuigou (GV26) | Previous studies | Right MCAO | Wistar rats | Freq: 15Hz; Int: 1mA, Time: 20min; Duration: single | Not specified | 1 | 1. EA reduced neurological deficits, 2. increased CBF at the ipsilateral and contralateral lesion sites, 3. decreased expression of AngII, AT1R, and 4. EA enhanced expression of AT2R in ischemic core and penumbra regions | EA significantly attenuates MCAO-induced increases in AngII expression and its receptor-mediated IP3 signal transduction pathway, reduces vasoconstriction and improves blood supply in ischemic region |

Category III: Anti-apoptosis

Table S5: Specific apoptotic pathway

| Study title | Author s | Publication | Target (receptor/molecule/pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|--|----------|---|------------------------------------|---------|--|------------------|---|-------------|--|-----------|------------|--|---|
| Acupuncture suppresses ischemia-induced increase in c-Fos expression and apoptosis in the hippocampal CA1 region in gerbils | Jang, M | Neuroscience Letters 347 (2003) 5-8 | Caspase 3 (-) | MA | Zusanli (ST36) bilateral, Hegu (LI4) bilateral | Not specified | Common carotid artery occlusion for 5 min | Gerbils | Starting on the third day of the experiment; Time: 20min; Duration: Twice daily for 8 days | Sub-acute | 16 | 1. Ac. suppressed ischemia-induced increases in c-Fos and caspase 3 TUNEL cells in the hippocampal CA1 region, 2. The most potent inhibitory effect was observed at Zusanli acupoint | Ac. exerts anti-apoptotic effects in the hippocampal CA1 region by suppressing ischemia-induced increments in c-Fos and caspase 3 cells |
| Acupuncture protected cerebral multi-infarction rats from memory impairment by regulating the expression of apoptosis related genes Bcl-2 and Bax in hippocampus | Wang, T | Physiology & Behavior 96 (2009) 155–161 | Bax (-) - Bcl-2 (+) | MA | Tanzhong (CV17), Zhongwan (CV12), Qihai (CV6), Zusanli (ST36), Xuehai (SP10) | Not specified | Right common carotid artery and external carotid artery occlusion | Wistar rats | Starting 16 days after artery occlusion; Stimulation: twisted twice a sec. for 30 sec. in each point; Duration: Once daily for 21 days | Chronic | 21 | 1. Ac improved Morris water maze trial performance, 2. Ac significantly reduced the number of apoptotic cells in hippocampal CA1 region, 3. Ac upregulated Bcl-2 expression, and 4. Ac counter-regulated the expression of pro-apoptotic Bax | Ac improves memory via anti-apoptotic effects in hippocampal CA1 region by downregulating the expression of pro-apoptotic factor Bax and upregulating the expression of anti-apoptotic factor Bcl-2 |

| | | | | | | | | | | | | | |
|--|---------|---|---|----|--------------------------------|------------------|-----------------------|-------------|---|-------|---|---|---|
| Potential of Akt and suppression of caspase-9 activations by electroacupuncture after transient middle cerebral artery occlusion in rats | Wang, S | Neuroscience Letters 331(2002) 115–118 | Akt (+), caspase 9 (-) | EA | Baihui (GV20), Renzhong (GV26) | Not specified | Right MCAO for 90 min | Wistar rats | Just after MCAO; Freq: 20/3Hz; Int: 3mA; Time: 1h; Duration: single | Acute | 1 | <ol style="list-style-type: none"> EA increased expression of AKT mainly in the ischemic penumbra, EA diminished caspase 9 induction, and EA decreased number of TUNEL positive cells in the cortex | EA activates Akt and suppresses caspase 9 inhibiting apoptotic cascade |
| Effects of electroacupuncture on apoptotic pathways in a rat model of focal cerebral ischemia | Kim, Y | International Journal of Molecular Medicine 32: 1303-1310, 2013 | DR5 extrinsic and intrinsic pathway mediators (-) | EA | Baihui (GV20), Qihai (CV6) | Previous studies | Right MCAO for 90 min | SD rats | Immediately after MCAO; Freq: 2Hz; Int: 1mA; Time: 30min; Duration: Twice a day | Acute | 2 | <ol style="list-style-type: none"> EA reduced infarct size, diminished the number of apoptotic cells in ischemic tissue, reversed the increase in expression of DR5, EA enhanced expression of Bcl-2, Bcl-xL, cIAP1 and 2, and EA decreased expression and activities of caspase-3, -8, and -9 | EA neuroprotective effects may be associated with the inhibition of DR and mitochondrial apoptotic pathways |

Table S6: Non-specific apoptotic pathway

| Study title | Author s | Publication | Target (receptor/molecule/pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|--|----------|---|------------------------------------|---------|--|------------------|-----------------------|---------|---|-------|------------|--|--|
| Electroacupuncture at the Quchi and Zusanli acupoints exerts neuroprotective role in cerebral ischemia reperfusion injured rats via activation of the PI3K/Akt pathway | Chen, A | International Journal of Molecular Medicine 30: 791-796, 2012 | PI3K/Akt (+) | EA | Zusanli (ST36), Quchi (LI11) on the non paretic limb | Clinical use | Left MCAO for 120 min | SD rats | 120 min after MCAO; Freq: 1 and 20Hz; Time: 30min; Duration: single | Acute | 1 | 1. EA improves neurological deficits, 2. EA reduces infarct volume, 3. EA activates the PI3K/Akt pathway, 4. EA increases expression of BDNF and GDNF, and 5. EA upregulates anti-apoptotic Bcl-2/Bax ratio in ischemic tissue | EA exerts neuroprotective function in ischemic stroke via activation of the PI3K/Akt anti-apoptotic pathway |
| Electroacupuncture at points of Zusanli and Quchi exerts anti-apoptotic effect through the modulation of PI3K/Akt signaling pathway | Xue, X | Neuroscience Letters 558 (2014) 14– 19 | PI3K/Akt (+) | EA | Zusanli (ST36), Quchi (LI11) on the paretic limb | Clinical use | Left MCAO for 120 min | SD rats | 1 day after MCAO; Freq: 4-20Hz; Time: 30min; Duration: once a day for 2 days | Acute | 2 | 1. EA improved neurological deficit scores, 2. reduced infarct volume, 3. reduced apoptosis in penumbra of cerebral cortex, 4. EA stimulated expression of PI3K and p-Akt in ischemic cortex, 5. EA upregulated levels of p-Akt and Bcl-2, 6. EA weakened the downregulation of p-Bad and Bcl-2, and reduced | EA exerts a neuroprotective effect on cerebral ischemia through the activation of the PI3K/Akt pathway, inhibiting apoptosis in the penumbra of cerebral ischemic cortex |

| | | | | | | | | | | | | | |
|---|----------|--|--------------------------------------|----|------------------------------|--|-----------------------|---------|--|-------|---|--|---|
| | | | | | | | | | | | | the upregulation of Bax, and 7. EA enhanced the ratios of the protein of p-Bad/Bad and anti-apoptotic Bcl-2/Bax | |
| Electroacupuncture-like stimulation at Baihui and Dazhui acupoints exerts neuroprotective effects through activation of the brain-derived neurotrophic factor-mediated MEK1/2/ERK1/2/p90RSK/bad signaling pathway in mild transient focal cerebral ischemia in rats | Cheng, C | Complementary and Alternative Medicine 2014, 14:92 | MEK1/2/ERK1/2/p90RSK/bad pathway (+) | EA | Baihui (GV20), Dazhui (GV14) | Chinese Medicine theory - Previous studies | Right MCAO for 15 min | SD rats | Following MCAO; Freq: 5Hz; Int: 2.7-3mA; Time: 25min; Duration: twice daily for 2 consecutive days | Acute | 4 | 1. EA reduced infarct volume, 2. EA lowered neurological deficit scores, 3. EA enhanced BDNF expression in ischemic cortex, 4. EA suppressed increase of caspase-3, and 5. EA enhanced expression of protein kinases related to the ERK1/2 pathway | EA elicits BDNF-mediated neuroprotective action against caspase-3-dependent neuronal apoptosis through activation of the Raf-1/MEK1/2/ERK1/2 pathway |
| Electroacupuncture-like stimulation at the Baihui (GV20) and Dazhui (GV14) acupoints protects rats against subacute-phase cerebral ischemia-reperfusion injuries by reducing S100B-mediated neurotoxicity | Cheng, C | Plos One March 2014, Volume 9, Issue 3, e91426 | S100B (-) | EA | Baihui (GV20), Dazhui (GV14) | Chinese Medicine theory - Previous studies | Right MCAO for 15 min | SD rats | After MCAO; Freq: 5Hz; Int: 2.7-3mA; Time: 25min; Duration: once daily for 6 consecutive days | Acute | 6 | 1. EA reduced infarct volume, 2. EA improved neurological deficits, 3. EA lowered S100B, p38 MAP kinase-mediated NF-kB, and iNOS expression, 4. EA downregulated TNF- α /TRADD/FADD/cleaved caspase-8/cleaved caspase-3 apoptotic pathway in ischemic cortical penumbra, 5. EA | EA provides neuroprotection by downregulation of astrocytic S100B expression, delaying infarct expansion through the modulation of p38 MAP kinase-mediated NF-kB expression, attenuating oxidative/nitrative stress and downregulating the TNF- |

| | | | | | | | | | | | | | |
|--|----------|--|-------------------|----|------------------------------|--|-----------------------|---------|--|-------|---|--|---|
| | | | | | | | | | | | | downregulated S100B/nitrotyrosine | a/TRADD/FADD/cleaved caspase-8/cleaved caspase-3 apoptotic pathway |
| Electroacupuncture at different frequencies (5Hz and 25Hz) ameliorates cerebral ischemia-reperfusion injury in rats: possible involvement of p38 MAPK-mediated anti-apoptotic signaling pathways | Cheng, C | Complementary and Alternative Medicine 2015 15:241 | p38 MAPK/CREB (+) | EA | Baihui (GV20), Fengfu (GV16) | Chinese Medicine theory - Previous studies | Right MCAO for 30 min | SD rats | 1 day after MCAO; Freq: 5-25Hz; Int: 2.7-3mA; Time: 25min; Duration: once daily for 7 consecutive days | Acute | 7 | <p>1. EA reduced infarct volume, 2. EA reduced neurological deficit scores, 3. EA downregulated GFAP expression, 4. EA activated p38 MAPK/CREB pathway, 5. EA upregulated expression of Bcl-xL and Bcl-1, 6. EA downregulated expression of Bax, 7. EA decreased Smac/DIABLO translocation, 8. EA decreased caspase-3 upregulation, 9. EA enhanced XIAP expression (all the results were shown at</p> | EA downregulates reactive astrocytosis to provide neuroprotection by activating the p38 MAPK/CREB pathway. The modulating effects of EA on Bax-mediated apoptosis are possibly due to the activation of Bcl-xL and Bcl-2 signaling, thereby preventing Smac/DIABLO translocation and restoring XIAP-mediated caspase-3 inhibition |

| | | | | | | | | | | | | | |
|--|---------|---|-------------------|----|--------------------------------|--|-----------------------|---------|---|-------|----|--|--|
| | | | | | | | | | | | | the ischemic cortical penumbra) | |
| Electroacupuncture ameliorates cognitive impairment through inhibition of NF-κB mediated neuronal cell apoptosis in cerebral ischemia-reperfusion injured rats | Feng, X | Molecular Medicine Reports 7: 1516-1522, 2013 | NF-κB pathway (-) | EA | Baihui (GV20), Shenting (GV24) | Chinese Medicine theory - Clinical use | Left MCAO for 120 min | SD rats | 2 h after MCAO; Freq: 1-20Hz; Time: 30min; Duration: daily for 10 days | Acute | 10 | 1. EA improved neurological deficit scores and reduced cognitive impairment (learning and memory), 2. EA reduced infarct volume, 3. EA inhibited apoptosis by blocking NF-κB pathway and downregulating the apoptotic Fas/Bax genes expression in ischemic tissue | EA inhibits NF-κB-mediated neuronal cell apoptosis |

| | | | | | | | | | | | | | |
|---|---------|---|-----------|----|--|------------------------------------|-----------------------|---------|--|---------------|---|--|--|
| Electroacupuncture regulates TRPM7 expression through the trkA/PI3K pathway after cerebral ischemia-reperfusion in rats | Zhao, L | Life Sciences 81 (2007) 1211–1222 | TRPM7 (-) | EA | Renzhong (GV26), Chengjiang (CV24) | Xingnao Kaiqiao acupuncture method | Right MCAO for 30 min | SD rats | Immediately after MCAO; Freq: 16-4Hz; Int: 1-3V; Time: 30min; Duration: single | Acute | 1 | 1. EA reversed TRPM7 over-expression in ischemic cortex and hippocampal CA3 and CA1 regions, 2. EA upregulated the expression of trkA in the same regions, 3. trkA triggered the downstream PI3K pathway, necessary for the effect of EA on TRPM7 | EA can reverse the increase of TRPM7 by enhancing trkA activity, which triggers the downstream PI3K pathway |
| Electroacupuncture effect on neurological behavior and tyrosine kinase-JAK 2 in rats with focal cerebral ischemia | Liu, R | Journal of Traditional Chinese Medicine 2012 September 15; 32(3): 1-2 | JAK2 (-) | EA | Baihui (GV20), Dazhui (GV14) | Not specified | MCAO | SD rats | Freq: 20Hz; Int: 1-2mA; Time: 30min | Not specified | 1 | 1. EA improved neurological deficits, 2. EA lowered the overexpression of JAK2 in the ischemic cortex | EA effectively inhibits the overexpression of JAK2, blocking the signal transduction pathways induced by JAK2 (neuronal apoptosis) |
| Effect of electroacupuncture on cell apoptosis and ERK signal pathway in the hippocampus of adult rats with cerebral ischemia-reperfusion | Wu, C | Evidence-Based Complementary and Alternative Medicine, Volume 2015, Article ID 414965 | ERK (+) | EA | Chize (LU5)+Hegu (LI4); Zusanli (ST36)+ Sanyinjiao (SP6) | Clinical use | Left MCAO for 30 min | SD rats | 1.5 h after MCAO; Freq: 2-15Hz; Int: 2mA; Time: 20min; Duration: once daily for 3 consecutive days | Acute | 3 | 1. EA improved neurological deficits, 2. EA diminished cerebral I/R injury, particularly in the CA1 hippocampus area, 3. EA reduced the apoptosis index, and 4. EA upregulated expression of p-ERK signaling pathway | EA alleviates neurological deficits, reduces the apoptosis index, and simultaneously upregulates the expression of p-ERK signaling pathway in I/R rats |

Category IV: Regulation of neurochemicals

Table S7: Neurotransmitters and receptors

| Study title | Authors | Publication | Target (receptor/molecule/pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|--|-----------|---|------------------------------------|---------|-------------------------------|--|-----------------------|---------|--|-------|------------|---|--|
| Acupuncture stimulation at Baihui acupoint reduced cerebral infarct and increased dopamine levels in chronic cerebral hypoperfusion and ischemia-reperfusion injured Sprague-Dawley rats | Chuang, C | The American Journal of Chinese Medicine, Vol. 35, No. 5, 779–791, 2007 | Dopamine (+) | MA | Baihui (GV20) | Chinese Medicine theory - Previous studies | Right MCAO for 90 min | SD rats | Immediately after MCAO; Time: 20min; Duration: 3 times a week for 4 weeks | Acute | 12 | 1. Ac did not improve cognitive and memory deficits in rats with ischemia reperfusion injury, 2. Ac increased dopamine levels in the right cerebral cortex and hippocampus | Ac increases levels of dopamine reducing the degree of cerebral atrophy after cerebral infarct |
| Role of GABA in electro-acupuncture therapy on cerebral ischemia induced by occlusion of the middle cerebral artery in rats | Gan, P | Neuroscience Letters 383 (2005) 317–321 | GABA (+) | EA | Shuigou (GV26), Baihui (GV20) | Not specified | Left MCAO for 120 min | SD rats | 15 min after MCAO; Freq: 3.58-6.25Hz; Int: 1.4-2mA; Time: 60min with a 10 min pause every 30 min; Duration: single | Acute | 1 | 1. EA increased GABA in cerebral cortex and hippocampus CA1 region, 2. EA reduced infarct size, 3. EA increased the percentage of surviving neurons in the ipsilateral cerebral cortex and striatum | EA up-regulates GABA expression in the ischemic cerebral cortex and CA1 hippocampus area |

| | | | | | | | | | | | | | |
|---|---------|---|--------------------|----|------------------------------------|------------------|---|---------|--|---------------|---|---|---|
| Acupuncture improves locomotor function by enhancing GABA receptor expression in transient focal cerebral ischemia rats | Xu, Q | Neuroscience Letters 588 (2015) 88–94 | GABA receptors (+) | MA | Jiaji (EX-B2) | Previous studies | Right MCAO | SD rats | Stimulation: Rotated clockwise 2-3 times per sec; Time: 30sec; Duration: 7 days | Not specified | 7 | 1. Ac improved performance in behavioral tests, 2. AC reduced infarct volume, 3. AC increased β -endorphin concentrations in striatum and spinal cord, and 4. Ac increased expression of GABA receptors in striatum and spinal cord | AC improves locomotor function by modulating the expression of GABA receptors |
| Electroacupuncture Attenuates Both Glutamate Release and Hyperemia After Transient Ischemia in Gerbils | Pang, J | The American Journal of Chinese Medicine, Vol. 31, No. 2, 295–303, 2003 | Glutamate (-) | EA | Fengfu (GV16), Shendao (GV11) | Not specified | Bilateral common carotid artery occlusion for 5 min | Gerbils | Immediately after ischemia; Freq: 7Hz; Int: 6mA; Time: 30min | Acute | 1 | 1. EA depressed glutamate release in CA1 hippocampal subfield, 2. EA suppressed hyperemia during reperfusion | EA suppresses both hyperemia and excessive glutamate release during and after ischemia |
| Electroacupuncture regulates NMDA receptor NR1 subunit expression via PI3-K pathway in a rat model of cerebral ischemia–reperfusion | Sun, N | Brain Research 1064 (2005) 98–107 | NMDA receptor (-) | EA | Renzhong (GV26), Chengjiang (CV24) | Not specified | Right MCAO for 30 min | SD rats | Immediately after MCAO; Freq: 16-4Hz; Int: 1-3V; Time: 30min; Duration: single | Acute | 1 | 1. EA reduced NR1 levels in ischemic cortical areas through PI3K, 2. EA increased TrkA in cortical ischemic areas | EA prolongs the time windows of the expression of TrkA in ischemic cortex. EA also reverses the expression of the NR1 subunit through the PI3-K pathway |

Table S8: Antioxidant enzymes

| Study title | Author s | Publication | Target (receptor/molecule/pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|--|----------|---------------------------------------|------------------------------------|---------|---|---|---|-------------|---|-----------|------------|--|---|
| Acupuncture prevents cognitive deficits and oxidative stress in cerebral multi-infarction rats | Liu, C | Neuroscience Letters 393 (2006) 45–50 | SOD/ GSH-Px (+) | MA | Tanzhong (REN17), Zhongwan (REN12), Qihai (REN6), Zusanli (ST36), Xuehai (SP10) | Yiqitiaoxue-Fubenpeiyuan acupuncture method | Internal carotid occlusion over 1-2 min | Wistar rats | 9 days after occlusion; Stimulation: twisted twice a sec. for 30 sec. in each point; Duration: Once daily for 21 days (rest every 7 days) | Sub-acute | 18 | 1. Ac significantly increased hippocampal SOD and GSH-Px activity | Ac exerts beneficial effects on spatial memory and antioxidant status of cerebral multi-infarction rats |

| | | | | | | | | | | | | | |
|---|----------|---|---------------------------|----|---|---------------|---------------------------------|-------------|---|-----------|----|--|--|
| Acupuncture elicits neuroprotective effect by inhibiting NADPH oxidase-mediated reactive oxygen species production in cerebral ischemia | Shi, G | Scientific Reports, December 2015, 5:17981, DOI: 10.1038 | NADPH oxidase (-) | MA | Bilateral Zusanli (ST36), Baihui (GV20) | Not specified | Common carotid artery occlusion | Wistar rats | 3 days after occlusion; Stimulation: Twirling manipulation >60 in 30 sec; Duration: once daily for 2 weeks (1 day rest after 6 days of treatment) | Sub-acute | 13 | 1. Ac ameliorated neurological impairment, 2. Ac reduced infarct size, 3. Ac suppressed overproduction of O ₂ via inhibition of NADPH oxidase in the hippocampus, and 4. Ac suppressed expression of NADPH oxidase subunits | Ac plays a neuro-protective effect against cognitive impairment via inhibition of NADPH oxidase-mediated oxidative stress |
| Electroacupuncture reduces the extent of lipid peroxidation by increasing superoxide dismutase and glutathione peroxidase activities in ischemic reperused rat brains | Siu, F | Neuroscience Letters 354 (2004) 158–162 | Antioxidant enzymes (+) | EA | Fengchi (GB20) bilateral | Not specified | Right MCAO for 1h | SD rats | 30 min after MCAO; Freq: 2Hz; Int: 0.7V; Time: 30min; Duration: single | Acute | 1 | 1. EA increased SOD and GSH-Px activity in ischemic brain | EA reduces the extent of lipid peroxidation in ischemic-reperused rat brains, possibly by increasing the activities of SOD and GPx |
| Neurochemical mechanism of electroacupuncture: anti-injury effect on cerebral function after focal cerebral ischemia in rats | Zhong, S | Advance Access Publication 27 October 2007 eCAM 2009; 6(1)51–56 | Respiratory chain enzymes | EA | Renzhong (GV26), Baihui (GV20) | Not specified | Right MCAO for 90 min | SD rats | Immediately after MCAO; Freq: 5/20Hz; Int: 2-4mA; Time: 60min with 15 min rest every 20 min; Duration: single | Acute | 1 | 1. EA reduced neurological deficits, 2. improved mitochondrial respiratory control ratio in penumbra area, and 3. EA increased the activities of succinic dehydrogenas | EA improves respiratory chain function and has an anti-oxidative action in brain tissues at the infarct penumbra zone |

| | | | | | | | | | | | | | |
|--|--------|---------------------------------|-----------------|----|--|--------------|-------------------|---------|--|-------|---|--|--|
| | | | | | | | | | | | | e, NADH dehydrogenase and cytochrome C oxidase in penumbra zone | |
| Electroacupuncture potentiates the disulphide-reducing activities of thioredoxin system by increasing thioredoxin expression in ischemia-reperfused rat brains | Siu, F | Life Sciences 77 (2005) 386–399 | Thioredoxin (+) | EA | Fengchi (GB20), bilateral Zusanli (ST36) | Clinical use | Right MCAO for 1h | SD rats | 30 min after MCAO; Freq: 2Hz; Int: 0.7V; Time: 30min; Duration: single | Acute | 1 | 1. EA increased TR activity with St36, 2. EA upregulated expression of Trx at both acupoints | EA can upregulate the activity of Trx system by increasing the availability of Trx to TR and thereby reduce the ROS-induced formation of disulphides |

Table S9: Inflammatory mediators

| Study title | Authors | Publication | Target (receptor/molecule/pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|--|---------|--|------------------------------------|---------|------------------------------------|--|--------------------|---------|---|-------|------------|--|---|
| Effects of acupuncture at Baihui (DU20) and Zusanli (ST36) on the expression of heat shock protein 70 and tumor necrosis factor α in the peripheral serum of cerebral ischemia- | Xu, H | Chinese Journal of Integrative Medicine 2014 May;20(5):369-374 | HSP70/TNF α (-) | EA | Left Zusanli (ST36), Baihui (GV20) | Chinese Medicine theory - Clinical use | Right MCAO for 2h | SD rats | After 2 h MCAO; Freq: 2Hz; Int: 1mA; Time: 20min; Duration: once a day (7 times in total) | Acute | 7 | 1. Ac reduced the expression of HSP70 and TNF- α protein in the peripheral serum | Ac delays inflammatory injury, which was associated with a reduction in the expression of HSP70 and TNF- α |

| | | | | | | | | | | | | | |
|---|--------|---|----------------|----|--|--------------|-----------------------|---------|---|-------|---|---|---|
| reperfusion-injured rats | | | | | | | | | | | | | |
| Electroacupuncture exerts anti-inflammatory effects in cerebral ischemia reperfusion injured rats via suppression of the TLR4/NF-κB pathway | Lan, L | International Journal of Molecular Medicine 31: 75-80, 2013 | TLR4/NF-κB (-) | EA | Zusanli (ST36), Quchi (LI11) on the paretic limb | Clinical use | Left MCAO for 120 min | SD rats | 2 h after MCAO; Freq: 1-20Hz; Int: 0.01mA; Duration: 1 day | Acute | 1 | <ol style="list-style-type: none"> EA improved neurological function, reduced infarct volume, alleviated cerebral inflammation, suppressed activation of the TLR4/NF-κB pathway by inhibiting NF-κB nuclear translocation, and EA inhibited I/R-induced secretion of TNFα, IL-1β, IL-6 | EA reduces ischemic brain damage, improves neurological deficits and exerts anti-inflammation activity via inhibition of the TLR4/NF-κB pathway |

Table S10: Neurotrophic factors

| Study title | Author s | Publication | Target (receptor/molecule/pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|-------------|----------|-------------|------------------------------------|---------|-----------|------------------|--------------------|--------|-----------|-------|------------|---------|-------------|
|-------------|----------|-------------|------------------------------------|---------|-----------|------------------|--------------------|--------|-----------|-------|------------|---------|-------------|

| | | | | | | | | | | | | | |
|---|--------|---|----------|----|--|---------------|-------------------|---------|--|---------------|---|---|---|
| Electroacupuncture enhances motor recovery performance with brain-derived neurotrophic factor expression in rats with cerebral infarction | Kim, M | Acupuncture in Medicine Journal 2012;30:222–226 | BDNF (+) | EA | Baihui (GV20), on the non paretic side Qubin (GB7) | Not specified | Right MCAO for 2h | SD rats | Freq: 3Hz; Time: 5min; Duration: every 2 days for 2 weeks | Not specified | 6 | 1. EA improved motor recovery, 2. enhanced expression of BDNF in the ischemic lobe, and 3. EA increased TrkB | EA increases the expression of BDNF and improves motor recovery |
|---|--------|---|----------|----|--|---------------|-------------------|---------|--|---------------|---|---|---|

Table S11: Anaerobic metabolism

| Study title | Author s | Publication | Target (receptor/ molecule/ pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|-------------|----------|-------------|--------------------------------------|---------|-----------|------------------|--------------------|--------|-----------|-------|------------|---------|-------------|
|-------------|----------|-------------|--------------------------------------|---------|-----------|------------------|--------------------|--------|-----------|-------|------------|---------|-------------|

| | | | | | | | | | | | | | |
|---|-------|--------------------------------|-------------|----|---|---------------|------|-------------|--|-------|---|--|--|
| Electroacupuncture up-regulates astrocytic MCT1 expression to improve neurological deficit in middle cerebral artery occlusion rats | Lu, Y | Life Sciences 134 (2015) 68–72 | Lactate (+) | EA | Bilateral Neiguan (PC6), bilateral Quchi (LI11) | Not specified | MCAO | Wistar rats | After 2h of MCAO; Freq: 2/15Hz; Int: 1mA; Time: 20min; Duration: once daily for 7 days | Acute | 7 | 1. EA promoted recovery of neurological deficits, 2. increased lactate concentrations in the ischemic brain, 3. enhanced expression of MCT1 in astrocytes, and 4. EA increased GFAP expression in the ischemic area, mainly at the hippocampus | EA improves neurological deficits through activating the lactate metabolism in the ischemic brain area and up-regulating the astrocytic expression of MCT1 to facilitate the transfer of intracellular lactate to the extracellular domain to be used by injured neurons |
|---|-------|--------------------------------|-------------|----|---|---------------|------|-------------|--|-------|---|--|--|

Category V: Memory improvement

Table S12: LTP modulation

| Study title | Author s | Publication | Target (receptor/ molecule/ pathway) | Ac type | Acupoints | Selection reason | Experimental model | Animal | Treatment | Stage | # sessions | Results | Conclusions |
|--|----------|--|--------------------------------------|---------|--------------------------|------------------|----------------------------------|-------------|---|-----------|------------|--|---|
| Hippocampal cAMP/PKA/CREB is required for neuroprotective effect of acupuncture | Li, Q | Physiology & Behavior 139 (2015) 482–490 | cAMP/ PKA/ CREB (+) | MA | Zusanli (ST36) bilateral | Previous studies | Right internal carotid occlusion | Wistar rats | 3 days after occlusion; Stimulation: Turned two spins per second for 30 seconds; Duration: once daily for 14 days (rest every 7 days) | Sub-acute | 13 | 1. Ac improved hippocampal-dependent memory, 2. Ac. reversed impairment of LTP in hippocampal PP-DG by upregulating cAMP/PKA/CREB pathway, 3. Ac. significantly inhibited PDE activity, and 4. Ac. enhanced ERK expression in CA1 and DG regions | Acupuncture improves cognitive hippocampus function by modulating the cAMP/PKA/CREB signaling pathway |
| Electroacupuncture at Baihui acupoint (GV20) reverses behavior deficit and long term potentiation through N-Methyl-D-Aspartate and transient receptor potential vanilloid subtype 1 receptors in middle cerebral artery occlusion rats | Lin, Y | Journal of Integrative Neuroscience. Volume 9, Number 3, September 2010, 269-282 | NR1-TRPV1 (-) | EA | Baihui (GV20) | Previous studies | Right MCAO for 10 min | SD rats | 1 day after MCAO; Freq: 2Hz; Int: 2mA; Time: 20min; Duration: 6 days | Acute | 6 | 1. EA improved behavior deficit, 2. EA restored LTP in hippocampal CA1 areas, 3. EA decreased NR1 and TRPV1 levels in hippocampal CA1 areas (pyramidal neurons) to basal conditions | EA improves vascular dementia by decreasing the expression of NR1-TRPV1 |