Delta-opioid receptors modulate remifentanil-induced hyperalgesia by regulating N-methyl-D-aspartate receptor trafficking and function

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Numerous studies have demonstrated that intraoperative remifentanil infusion has been associated with postoperative opioid-induced hyperalgesia (OIH) and tolerance. Activation of delta-opioid receptor (DOP) and augmentation of N-methyl-D-aspartate (NMDA) receptor current may play an important role in the development of OIH. The aim of this study was to investigate the interactions of DOP and NMDA receptors in remifentanil-induced postinfusion hyperalgesia in a rat model of incision pain.

A total of 144 male Sprague–Dawley rats (260–280 g) with an intrathecal catheter sited were randomly divided into six groups (n=24): control (C), Incision pain (I), Remifentanil (R), Incision pain + remifentanil (RI), Incision pain + dextorphin II (RD), and Incision pain + naltrindole (RN). The model of Incision pain was established according to the Brennan method. Remifentanil was infused at a rate of 1 μg kg⁻¹ h⁻¹ for 1 h. Four nanomoles of dextorphin II or 30 nmol naltrindole in a total volume of 10 μl were infused through the intrathecal catheter in the RD and RN groups. Mechanical paw withdrawal threshold (PWT) and thermal withdrawal latency (PWL) were measured at 24 h before (T0) and at 2, 6, 24, and 48 h (T1–T4) after anaesthesia. Each animal was killed after the last measurement of PWT and PWL. Dorsal root ganglia were immediately removed for evaluation of the expression and trafficking of DOP receptors by immunofluorescence, western blot, and immune electron microscopy. Spinal dorsal horns (L4–L6) were prepared for determination of NMDA receptors and NR1, NR2A, and NR2B subunit levels in total and at the cell surface. A further 32 14- to 18-day-old male rats were divided into four groups (n=8): control (C); Remifentanil (R, 4 nmol litre⁻¹); Remifentanil + dextorphin II (RD, 4+10 nmol litre⁻¹); Remifentanil + naltrindole (RN, 4+1 nmol litre⁻¹). The lumbosacral spinal cord (L4–6) was prepared, and transverse sections were cut. Isolated spinal cord slices were moved into artificial cerebrospinal fluid and incubated for 60 min. After incubation, whole cell patch clamp was used to detect changes of the NMDA receptor-induced mEPSCs in dorsal horn neurones. Electrophysiological experiments were used to study whether DOP receptor activation or inhibition would change NMDA currents in dorsal horn neurones.

Compared with Group C, PWT significantly decreased and PWL significantly shortened. Expression and trafficking of DOP were up-regulated. Total and cell surface expression of NR1 and NR2B were significantly increased in Groups I, R, RI, and RD. NMDA receptor-induced mEPSCs in Groups R and RD showed a significant increase in amplitude and frequency compared with Group C in dorsal horn neurones. The amplitude and frequency in Group RN were significantly decreased compared with Group R.

Remifentanil infusion can enhance the expression and trafficking of DOP in DRG neurones, and subsequently enhance protein expression and physiological function of NMDA receptors in the spinal cord dorsal horn neurones. Inhibition of the expression and activity of the DOP receptor can prevent the occurrence of remifentanil-induced hyperalgesia.

Acknowledgement

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References

Spinal cord dorsal horn proteomics in bilateral chronic constriction injury-induced neuropathic pain in rats

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Unilateral chronic constriction injury (uCCI) of rat sciatic nerve is a common neuropathic animal model of pain. However, the extent to which uCCI actually mimics clinical neuropathic pain is uncertain. Recently, CCI of bilateral sciatic nerves in the rat has shown long-lasting increases in nocifensive responses to cold, which is similar to the human experience. In this study, the behavioural changes to mechanical and cold stimuli in bilateral CCI rats were initially verified then followed by a proteomic analysis of lumbar spinal cord dorsal horn.

Experiments were performed with specific pathogen-free female Sprague–Dawley rats. Bilateral CCI of the sciatic nerves was performed under aseptic conditions with three loose ligatures of 4-0 chromic suture placed around the sciatic nerve. Both mechanical hyperalgesia and cold hyperalgesia were evaluated on three consecutive days before surgery and on postoperative days (PODs) 7 and 14, respectively. On POD 14, the nerve tissue of lumbar 4-6 spinal cord dorsal horn was dissected. Total protein were isolated, followed by reduction, alkylation, and trypsin digestion. Liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) was applied to characterize differentially expressed proteins. All proteins were analysed with Protein ANalysis THrough Evolutionary Relationships Version 8.0.

No motor deficit was observed in any bilateral CCI or sham rats. Both mechanical withdrawal threshold and cold hyperalgesia threshold decreased significantly on PODs 7 and 14, when compared with naïve or sham rats. Collectively, 1708, 1547, and 1663 proteins were characterized from the lumbar spinal cord dorsal horn of naïve, sham, and bilateral CCI rats, respectively. Twenty-five differentially expressed proteins associated with bilateral CCI were discovered, with 18 up-regulated and seven down-regulated (Table 1). These differentially expressed proteins are involved in several biological processes, such as apoptosis, cell adhesion, cell communication, cell cycle, cellular component organization, cellular process, developmental process, homeostatic process, immune system process, metabolic process, response to stimulus, system process, and transport. Among these differentially expressed proteins, PPP1CB (serine/threonine-protein phosphatase PP1-β catalytic subunit), is a direct inhibitor of CaM kinase Iα that may act as an inhibitor of long-term potentiation. MicroRNA-203, a modulator of PPP1CB expression, was found to be significantly down-regulated in our previous study, and this correlation between miR-203 and PPP1CB may influence the course of neuropathic pain.

### Table 1 Differentially expressed proteins associated with bilateral CCI

<table>
<thead>
<tr>
<th>Accession</th>
<th>Protein name</th>
<th>Up- or down-regulated</th>
<th>Change folds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acat3</td>
<td>Acetyl-CoA acetyltransferase, cytosolic</td>
<td>Up-regulated</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Actn4</td>
<td>α-Actinin-4</td>
<td>Up-regulated</td>
<td>&gt;10</td>
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<tr>
<td>Aldoa</td>
<td>Fructose-bisphosphate aldolase A</td>
<td>Up-regulated</td>
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<tr>
<td>Atp1a1</td>
<td>Sodium/potassium-transporting ATPase subunit α-1</td>
<td>Up-regulated</td>
<td>&gt;10</td>
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<tr>
<td>Atp1a3</td>
<td>Sodium/potassium-transporting ATPase subunit α-3</td>
<td>Up-regulated</td>
<td>&gt;10</td>
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<tr>
<td>Eno2</td>
<td>γ-Enolase</td>
<td>Up-regulated</td>
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<td>Hsp90a1</td>
<td>Heat shock protein HSP 90-α</td>
<td>Up-regulated</td>
<td>&gt;10</td>
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<tr>
<td>Ncam1</td>
<td>Neural cell adhesion molecule 1</td>
<td>Up-regulated</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Srpβ</td>
<td>Srpb signal recognition particle receptor, B subunit</td>
<td>Up-regulated</td>
<td>&gt;10</td>
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<tr>
<td>Tpm1</td>
<td>Tropomyosin α-1 chain isoform h</td>
<td>Up-regulated</td>
<td>&gt;10</td>
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<td>Tpm2</td>
<td>Tropomyosin α-2 chain</td>
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<td>Tropomyosin α-3 chain</td>
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<tr>
<td>Tpm4</td>
<td>Tropomyosin α-4 chain</td>
<td>Up-regulated</td>
<td>&gt;10</td>
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<tr>
<td>Ywhae</td>
<td>14-3-3 protein epsilon</td>
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<td>&gt;10</td>
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<td>Slc1a2</td>
<td>Isoform Glt1 of excitatory amino acid transporter 2</td>
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<tr>
<td>Ppp1cb</td>
<td>Serine/threonine-protein phosphatase PP1-β catalytic subunit</td>
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<tr>
<td>Ndufa10</td>
<td>NADH dehydrogenase (ubiquinone) 1 α subcomplex subunit 10, mitochondrial</td>
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<td>Hsp90b1</td>
<td>Heat shock protein HSP 90-β</td>
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<td>Pfkb</td>
<td>6-Phosphofructokinase type C</td>
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<tr>
<td>Ttn</td>
<td>Titin</td>
<td>Down-regulated</td>
<td>−1.505</td>
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<tr>
<td>Ap2a2</td>
<td>Adaptor-related protein complex 2, α 2 subunit</td>
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<tr>
<td>Myl1</td>
<td>Isoform MLC1 of myosin light chain 1/3, skeletal muscle isoform</td>
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<td>Myl6l</td>
<td>Myosin light polypeptide 6</td>
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<tr>
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<td>Down-regulated</td>
<td>−10</td>
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<tr>
<td>Tubb4</td>
<td>Tubulin, β 4</td>
<td>Down-regulated</td>
<td>&gt;−10</td>
</tr>
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</table>
In conclusion, bilateral CCI significantly decreased mechanical and cold hyperalgesia threshold. Differentially expressed proteins associated with bilateral CCI are involved in several biological processes that may contribute to the pathogenesis of neuropathic pain. Some of these differentially expressed proteins may become new targets for neuropathic pain therapeutics.

Acknowledgement
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References

Limb remote ischaemic preconditioning for intestinal and pulmonary protection during elective open infrarenal abdominal aortic aneurysm repair: a randomized controlled trial
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Remote ischaemic preconditioning may confer cytoprotection to critical organs. We hypothesized that limb remote ischaemic preconditioning (RIPC) would reduce intestinal and pulmonary injury in patients undergoing open infrarenal abdominal aortic aneurysm repair.

With ethical committee approval and informed consent, 62 patients undergoing elective open infrarenal abdominal aortic aneurysm repair were randomly assigned in a 1:1 ratio by computerized block randomization to receive limb RIPC or conventional abdominal aortic aneurysm repair (control). Three cycles of 5 min ischaemia/5 min reperfusion induced by an arterial pressure cuff placed on the left upper arm served as RIPC stimulus. The primary endpoint was arterial–alveolar oxygen tension ratio (a/A). The secondary endpoints mainly included the intestinal injury markers (serum intestinal fatty acid binding protein, endotoxin levels, and diamine oxidase activity), markers of oxidative stress and systemic inflammatory response, and the scores of the severity of intestinal and pulmonary injury.

In the limb RIPC group, a/A ratio was significantly higher than in control 8, 12, and 24 h after cross-clamp release [66 (4) vs 45 (4), P = 0.003; 60 (6) vs 37 (4), P = 0.002; and 60 (5) vs 47 (6), P = 0.039, respectively]. All biomarkers reflecting intestinal injury increased over time and there were significant differences between limb RIPC and control (P < 0.001). The severity of intestinal and pulmonary injury were decreased by limb RIPC (P = 0.014 and 0.001, respectively).

Limb RIPC attenuates intestinal and pulmonary injury in patients undergoing elective open infrarenal abdominal aortic aneurysm repair without potential risk.

Effects of hydrogen gas inhalation on cerebral oxidative stress and inflammation after intestinal ischaemia/reperfusion in rats
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Intestinal ischaemia/reperfusion (II/R) is associated with high morbidity and mortality, and recent data have shown that hydrogen gas (H2) can neutralize free radicals and reduce oxidative stress and inflammation. This study was performed to investigate the effects of hydrogen gas inhalation on cerebral oxidative stress and inflammation after II/R in rats and to understand the mechanism of neuroprotection.

With animal care committee approval, 54 healthy male Sprague-Dawley rats were randomly allocated to one of the three groups (n = 18 each): sham operation (Sham), II/R (I/R), and II/R plus hydrogen gas inhalation (I/R + H2). The model was produced by occlusion of the superior mesenteric artery for 90 min followed by reperfusion. Inhalation of 2% hydrogen gas was performed immediately after I/R for 3 h. Six animals were killed at each of the following time points: 1, 2, and 5 days after reperfusion in each group. Brain tissue was harvested for detection of microglia by immunohistochemistry (Iba-1). The concentrations of ROS, MDA, SOD, IL-6, and TNF-α in the prefrontal cortex were measured.

The Iba-1, IL-6, and TNF-α staining were negative or light in the Sham group. However, their expression strengthened in the I/R group and H2 improved expression. Compared with the Sham group, the number of Iba-1-positive cells and double-labelled (Iba-1/TNF-α; Iba-1/IL-6) cells increased in the I/R and I/R + H2 groups, the differences were statistically significant. Compared with the I/R group, the number of Iba-1-positive cells and double-labelled cells decreased in the I/R + H2 group, and the differences were statistically significant. Compared with the Sham group, the concentrations of ROS, MDA, IL-6, and TNF-α increased and the activity of SOD decreased significantly in the prefrontal cortex in the I/R and I/R + H2 groups. However, compared with the I/R group, the above parameters were significantly reversed in the H2 group.

Inhalation H2 can inhibit II/R-induced activation of microglia and reduce cerebral oxidative stress and the inflammatory response in rats.
Electroacupuncture reduces myocardial ischaemia–reperfusion injury by down-regulating Egr-1 expression via the ERK1/2 pathway

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Early growth response (Egr)-1 is an upstream master switch in controlling inflammatory responses after myocardial ischaemia–reperfusion (I/R). Activation of extracellular signal-regulated protein kinase-1 and 2 (ERK1/2) signalling is known to up-regulate Egr-1. Considering the previous findings that the ERK1/2 pathway is necessary for the therapeutic action of electroacupuncture (EA), we speculated that EA at Neiguan (PC6) could inhibit Egr-1 expression via the ERK1/2 pathway, and subsequently reduce inflammatory responses and myocardial I/R injury.

Male C57/BL6 mice underwent in vivo I/R by occlusion of the left anterior descending artery for 1 h followed by reperfusion for 3 h. Animals were randomly divided into six groups: (i) SHAM (only received thoracotomy as control), (ii) IR (underwent myocardial ischaemia—reperfusion surgery), (iii) EA+IR (before surgery, received EA treatment at PC6 points for 30 min), (iv) U0126+IR (20 mg kg⁻¹ U0126, resolved in 150 μl 0.1% v/v DMSO; i.p., given 1 h before surgery), (v) DMSO+IR (150 μl 0.1% v/v DMSO, i.p., given 1 h before surgery), and (vi) EA+U0126+IR (both EA pretreatment and U0126 were given before surgery). Protein and RNA expression of Egr-1 in myocardium was assessed. The myocardial inflammatory cytokines (TNF-α, IL-β), serum cTnI, and infarct size were also measured for injury evaluation.

Up-regulation of Egr-1 and p-ERK1/2 after myocardial I/R in mice was suppressed by EA pretreatment, which was accompanied by attenuated myocardial inflammatory cytokines (TNF-α, IL-1β), cTnI release and smaller infarct size (P<0.05). Similar inhibition of Egr-1 up-regulation was observed when an ERK1/2 kinase inhibitor U0126 was used before myocardial I/R (P<0.05). However, pretreatment with EA combined with U0126 did not potentiate the inhibition of myocardial Egr-1 expression, and also its downstream target genes (TNF-α, IL-1β), serum cTnI release, and infarct size (P>0.05).

Inhibition of Egr-1 expression via the ERK1/2 pathway and subsequently reduced proinflammatory mediator release are, at least in part, responsible for cardioprotection of EA pretreatment against I/R injury.

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References


Screening and bioinformatic analysis of specific microRNAs involved in the protective effects of morphine preconditioning of cardiomyocytes in rats with heart failure

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Ischaemic preconditioning (IPC)-mediated cardioprotection has been reported to be impaired in some pathological conditions. Previous studies from our laboratory showed that the cardioprotection of IPC was suppressed in doxorubicin-induced myocardial failure, while morphine preconditioning (MPC), which mimics IPC, conserved the cardioprotective effects. To investigate the potential mechanisms of MPC in heart failure, this study proposed to screen specific microRNAs (miRNAs) in MPC failed cardiomyocytes. In addition, we aim to predict and analyse the target genes regulated by the differentially expressed miRNAs and their functions.

Healthy adult male Sprague–Dawley rats (SCXK: 2009-0002) were injected with doxorubicin via a tail vein to induce heart failure. Cardiomyocytes were isolated from normal and heart failure rats and cultured. The cells were divided into four groups: normal cardiomyocyte control (+CON), normal cardiomyocytes with MPC (+MPC), failed cardiomyocyte control (−CON), and failed cardiomyocytes with MPC (−MPC). The cardiomyocytes in the MPC groups were treated with 0.3 μM morphine for 10 min followed by 30 min incubation in drug-free DMEM. The control groups were cultured under normal conditions. Total RNA was extracted from the cardiomyocytes in each group, and subjected to miRNA microarray to screen for differentially expressed miRNAs, among which the different miRNAs between the −CON and −MPC groups were specifically compared. TargetScan software was used to predict the target genes regulated by the differentially expressed miRNAs. Functional enrichment analysis of target genes was performed by GO (gene ontology) and pathway analysis, and a miRNA-gene network was established.

The results of the miRNA microarray analysis showed that miR-133b-5p, miR-6216, miR-664-1-5p were significantly different in each of the two groups (fold change ≥2 or <0.5). By further comparing Groups −CON and −MPC in failed cardiomyocytes, we found that eight miRNAs were up-regulated while 10 miRNAs down-regulated (P<0.01, signal value>500).

References

GO and Pathway analysis revealed that the target genes regulated by differentially expressed miRNAs induced by – MPC were mainly focused on calcium ion transport, apoptosis, and the MAPK signal pathway. Specifically, miR-133b-5p, miR-664-1-5p, and target genes Fos, Bak1 may participate in apoptosis; miR-125b-5p, miR-664-1-5p, and target gene Atp2b2 may participate in regulating calcium homeostasis; while miR-6216, miR-107-3p, and target gene Stag1 may be closely related to the MAPK signal pathway.

Results of the miRNA microarray and bioinformatics analysis revealed that miRNAs were involved in the cardioprotection of MPC in failed cardiomyocytes, and might play an important role in calcium homeostasis, apoptosis, and MAPK signal pathways.

**Funding**

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**Reference**


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**Electroacupuncture attenuates cerebral ischaemic injury through adiponectin receptor 1-mediated signalling pathway in streptozotocin-induced diabetic mice**

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Both type 1 and type 2 diabetes mellitus substantially increase the risk for cerebral ischaemic reperfusion injury. In addition, cerebral ischaemic reperfusion injury is the major cause of morbidity and mortality in diabetic patients, who demonstrated enhanced vulnerability to ischaemic insult and resultant death.1 2 Electroacupuncture (EA) preconditioning could induce cerebral ischaemic tolerance in normal animal models.3 However, it is unknown whether EA could attenuate cerebral ischaemia reperfusion injury in a diabetic model.

In the current study, male C57BL/6 mice were treated with streptozocin (STZ) to induce diabetes. STZ-induced diabetic mice were either untreated or treated with EA (30 min at acupoint ‘Baihui’ with the intensity of 1 mA and frequency of 2/15 Hz). One hour after the end of EA pretreatment, focal cerebral ischaemia was induced by middle cerebral artery occlusion for 60 min after 24 h reperfusion. Neurobehavioural scores, infarction volumes, and neuronal apoptosis were evaluated after ischaemia injury. Malondialdehyde (MDA), superoxide dismutase (SOD), NADPH oxidase, and reactive oxygen species (ROS) levels were also determined. To probe for possible mechanisms, adiponectin (APN) and its receptors were tested by ELISA, western blot, and immunofluorescence, respectively. To elucidate the role of the AdipoR1 in EA-induced neuroprotection, we investigated the effectiveness of AdipoR1 short-interfering RNA (siRNA) on neuroprotection induced by EA pretreatment in vivo. Phosphorylation of GSK-3β at 9ser [p-GSK-3β (9ser)] was also evaluated.

EA pretreatment reduced infarct size, improved neurological outcome, and inhibited neuronal apoptosis 24 h after reperfusion in diabetic mice. In addition, EA pretreatment decreased cerebral MDA and ROS in diabetic mice compared with control, and also NADPH oxidase activity. While SOD level was up-regulated by EA pretreatment. Plasma and cerebral APN levels were increased accompanied by enhanced AdipoR1. AdipoR1 knockdown attenuated the protective effect of EA pretreatment. For further detecting the downstream molecular targets involved, phosphorylation of GSK-3β was decreased with AdipoR1 siRNA pretreatment in EA-treated diabetic mice. On the other hand, 4-benzyl-2-methyl-1, 2, 4 -thiadiazolidine-3, 5-dione (TDZD-8) simulated EA protective effect while wortmannin (Wort) abolished the neuroprotection of EA.

Our results demonstrated that EA attenuated cerebral ischaemic injury through the APN-AdipoR1-GSK-3β signalling pathway. These results suggest a novel mechanism of EA pretreatment-induced tolerance to diabetic cerebral ischaemia.

**References**


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**HSPA12B protects endothelial cells against endotoxin challenge by inhibiting p38 MAPK phosphorylation**

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Endothelial barrier dysfunction is the hallmark of acute lung injury or acute respiratory distress syndrome, involving complicated inflammatory activation and cellular changes, which are far from clear. HSPA12B is a newly discovered member of the heat shock protein-70 family and is predominantly located in endothelial cells.1 It is required for endothelial functioning and angiogenesis,2 and its overexpression is of benefit for several disease models such as septic cardiomyopathy3 and cerebral ischaemia reperfusion injury.4

In this study, we found that HSPA12B was significantly up-regulated in pulmonary microvascular endothelial cells (PMVECs) by endotoxin stimulation. HSPA12B depletion by siRNAs after endotoxin challenge augmented expression of

† These authors contributed equally to this work.
pro-inflammatory factors including TNF-α and IL-6 while inhibiting IL-10 expression. Endotoxin alone did not cause obvious ultrastructural changes according to electron microscopy, but the absence of HSPA12B led to a much worse outcome of PMVECs. HSPA12B knockdown also resulted in higher apoptotic rate of endothelial cells. HSPA12B is also necessary for maintaining migratory function of PMVECs, which reflected the self-repair ability of endothelial barriers because HSPA12B depletion resulted in poor capacity of endothelial cells migration across Transwell membranes and in wound-healing assays. Furthermore, HSPA12B siRNA transfection in endothelial cells enhanced the endotoxin-induced phosphorylation of p38 mitogen-activated protein kinase (MAPK). Blockade of p38 MAPK with a specific inhibitor SB203580 almost completely reverses the harmful effect of HSPA12B depletion on endothelial cells, suggesting that HSPA12B protected PMVECs against endotoxin by inhibiting p38 MAPK activation. Co-immunoprecipitation shows that HSPA12B and p38MAPK did interact. Immune confocal images further suggest that HSPA12B and p38MAPK are co-expressed in PMVECs, further suggesting that HSPA12B and p38MAPK are capable of direct interaction.

Our findings may provide a new insight to the intracellular protective mechanism of endothelial cells during inflammatory challenges.

Acknowledgements

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Evaluation of a magnet guiding technique in the subclavian vein catheterization

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In this study, we aimed to evaluate the efficacy of a magnet guidance technique to reduce internal jugular misplacement during subclavian venous catheterization (SVC).

A total 160 patients were enrolled into the study and were randomly selected into either a magnet-guided group (n=80, 4500 Oe) or a control group (n=80). All patients received SVC placement. Chest X-ray was used after placement to evaluate the placement of the central venous catheter and assess the incidence of catheter placement into the ipsilateral internal jugular vein.

The magnet guidance significantly reduced the incidence of ipsilateral internal jugular misplacement during SVC. The incidence of ipsilateral internal jugular misplacement in the magnet-guided group was 6.25% compared with 18.25% in the control group (P=0.017).

Magnet guidance can be useful in reducing ipsilateral jugular misplacement during SVC.

Association of glycaemic variability and acute kidney injury in cardiac surgery patients

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Previous clinical studies have demonstrated a strong relationship between sustained chronic hyperglycaemia (measured by HbA1c) and diabetic complications. Now, a growing body of evidence shows that glycaemic variability including both upward and downward short-term glucose changes also contributes to diabetes-related complications.1 However, it remains unknown whether glycaemic variability contributes independently to postoperative acute kidney injury (AKI). In this study, we investigated the correlation between perioperative glycaemic variability and the incidence of AKI in patients undergoing cardiac surgery.

An observational retrospective study was performed on consecutive patients (n=2298) receiving coronary artery bypass grafting (CABG), valve, or CABG plus valve surgery in Thomas Jefferson University hospital (dated 2001–2011). Patients were excluded if <18 yr old or if there was incomplete records of serum creatinine and glucose levels perioperatively. The largest increase or decrease between the glucose levels before and after (during the first 7 days after operation) surgery was taken for assessing inter-day glucose fluctuation or variability. Based on the difference in pre- and postoperative glucose levels, the patients were divided into Groups 1, 2, 3, and 4 with the difference ≤25, 25–50, 51–75, and >75 mg dL⁻¹, respectively. After operation, AKI was defined based on the Acute Kidney Injury Network (AKIN) criteria.2 Statistical analysis was performed using analysis of variance or χ² as appropriate with a significance level set at P<0.05.

Based on the difference in pre- and postoperative glucose levels, there were 442, 664, 616, and 576 patients in Groups 1, 2, 3, and 4, respectively. When comparing these four groups, there were no significant differences in baseline parameters including age, gender, body mass index, history of diabetes, chronic lung disease, cerebrovascular disease, hypertension, heart failure, previous myocardial infarction, preoperative medications, and intraoperative parameters such as perfusion time and cross-clamp time. However, there were more smokers in Groups 4 vs 2. The incidence of postoperative AKI were 6.6% and 8.3% in Groups 1 and 2, respectively (P>0.05). However, as
the difference in pre- and postoperative glucose levels became larger, postoperative incidence of AKI increased significantly to 14.1% and 18.1% in Groups 3 and 4 (P<0.05 vs Groups 1 and 2, respectively). The same trend of these changes was observed in patients with or without diabetes. With multivariate analysis, glucose variability was found to be an independent risk factor for postoperative AKI (odds ratio 1.005, P<0.001). Thus, these results showed a strong correlation between a wide swing in peri-operative glycaemia and markedly increased risk of postoperative AKI in patients undergoing CABG, valve surgery, or both.

The present study showed that a large variability of glycaemia, as defined by the difference of pre- and postoperative glucose levels, was associated with an increased risk of postoperative AKI in patients undergoing CABG, valve surgery, or both, suggesting that glycaemic variability may contribute to AKI in cardiac surgery patients.

References

A serum metabolomic investigation of cholestasis in an experimental model of bile duct ligation in rats using ultraperformance liquid chromatography/tandem mass spectrometry

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Metabolomics follows the changes in concentrations of endogenous metabolites, which may reflect various disease states and systemic responses to environmental, therapeutic, or genetic interventions. In this study, we applied metabolomic approaches to monitor dynamic changes in plasma metabolites, and compared these metabolite profiles in bile duct ligation in rats (an animal model of cholestasis) with those in the parent strain of Sprague–Dawley (SD).

Twenty male Wistar rats were randomly divided into two groups (n=10): Sham group (laparotomy); BDL group (subjected to bile duct ligation). Day 7 after BDL, the animals were killed and serum samples were collected. Then reversed phase chromatography and hydrophilic interaction chromatography (HILIC)/tandem mass spectrometry-based analytical methods were used to assay metabolite levels.

Eighteen metabolites were detected in serum, and metabolite profiles of BDL rats differed from those of sham animals. The levels of 10 metabolites (glutamic acid, phenylalanine, acetylformic acid, alanine, glycine, 3-hydroxybutyrate, succinic acid, malic acid, glucose and lactic acid) were markedly increased in serum of BDL group rats. Levels of eight metabolites (histidine, glutamine, taurine, phosphorylcholine, betaine, palmitic acid, citric acid and arachidonic acid) were greatly decreased in serum of BDL group rats. Glutamic acid, phenylalanine, histidine, glutamine, taurine, alanine, and glycine are metabolic amino acids. Acetylformic acid, succinic acid, malic acid, citric acid, and arachidonic acid belong to the citric acid cycle. Phosphorylcholine, betaine, palmitic acid, and 3-hydroxybutyrate belongs to lipid metabolism. Glucose is related to carbohydrate metabolism and lactic acid is glycolytic.

Our metabolomic data suggest that mechanisms may exist in experimental bile duct ligation-induced cholestasis that compensate for cholestasis-related damage. These results provide new ideas and methods for looking for molecular markers of cholestasis, cholestasis metabolism pathway research, and diagnosis.

Reference

Protective effects of remifentanil preconditioning against hypoxia reoxygenation injury in cultured adult rat ventricular myocytes and their signalling mechanisms

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The cardioprotective effects of remifentanil preconditioning (RPC) against ischaemia reperfusion injury have been demonstrated in intact and isolated rat hearts.1 2 This study aimed to investigate the protective effects of RPC against hypoxia/reoxygenation (H/R) injury in cultured adult rat ventricular myocytes and the involvement of opioid receptors, phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) and extracellular signal-regulated kinase (ERK) signalling pathways.

Adult rat ventricular myocytes were isolated using a Langendorff perfusion system and cultured overnight. The cardiomyocytes were incubated in hypoxic conditions for 90 min in a hypoxia chamber flushed with hypoxic gas mixture of 95% nitrogen and 5% carbon dioxide followed by 120 min normoxia to induce H/R injury. Before H/R injury, the cells were pretreated with different concentrations of remifentanil (0.1–10 μmol litre⁻¹) for 10 min followed by 30 min washout period in order to observe the protective effects of RPC against H/R injury in cardiomyocytes. At the same time, the cardiomyocytes were subjected to 10 min hypoxia followed by 30 min reoxygenation to induce hypoxic preconditioning (HPC) as the positive control. Cell viability was evaluated by MTT assay and trypan blue staining. Lactate dehydrogenase (LDH) released from the cells were measured to assess cardiomyocyte injury. In another series of experiments, δ-opioid receptor antagonist (naltrindole, 5 μmol litre⁻¹), κ-opioid receptor antagonist...
In conclusion, RPC showed significant protective effects against H/R injury in cardiomyocytes. These effects may be achieved mainly via the activation of δ-opioid receptors and partly via κ-opioid receptors, and also involving the activation of ERK and PI3K/AKT signalling pathways.

Funding
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References
1 Zhang Y, Irwin MG, Wong TM. Anesthesiology 2004; 101: 918–23

Table 2 The effects of opioid receptor antagonists, ERK, and PI3K inhibitors on RPC. Data are presented as mean (sd), n = 3. aP < 0.05 vs CON, bP < 0.05 vs H/R, cP < 0.05 vs RPC

<table>
<thead>
<tr>
<th>Groups</th>
<th>Trypan blue exclusion (%)</th>
<th>LDH (units litre⁻¹)</th>
<th>Hoechst staining (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td>85.3 (2.9)</td>
<td>13.4 (0.6)</td>
<td>8.0 (1.5)</td>
</tr>
<tr>
<td>H/R</td>
<td>61.7 (2.3)a</td>
<td>25.5 (1.2)a</td>
<td>21.5 (1.6)a</td>
</tr>
<tr>
<td>HPC</td>
<td>78.3 (3.5)b</td>
<td>15.6 (1.6)b</td>
<td>10.9 (1.5)ab</td>
</tr>
<tr>
<td>RPC</td>
<td>76.8 (4.4)b</td>
<td>15.3 (2.2)b</td>
<td>11.7 (1.6)ab</td>
</tr>
<tr>
<td>NTD + RPC</td>
<td>61.6 (2.3)a,b,c</td>
<td>20.8 (1.0)a,b,c</td>
<td>20.6 (1.3)a,b,c</td>
</tr>
<tr>
<td>Nor-BNI + RPC</td>
<td>70.1 (3.7)a,b,c</td>
<td>18.3 (1.0)a,b,c</td>
<td>16.1 (2.0)a,b,c</td>
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<tr>
<td>CTOP + RPC</td>
<td>78.6 (2.2)b</td>
<td>17.8 (0.8)ab</td>
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<tr>
<td>NTD</td>
<td>62.7 (2.9)a</td>
<td>20.8 (1.0)a</td>
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<tr>
<td>Nor-BNI</td>
<td>62.1 (1.5)a</td>
<td>21.0 (0.8)a</td>
<td>22.0 (1.3)a</td>
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<tr>
<td>CTOP</td>
<td>61.9 (0.9)a</td>
<td>22.0 (0.5)a</td>
<td>21.0 (1.5)a</td>
</tr>
<tr>
<td>PD98059 + RPC</td>
<td>63.6 (6.0)a,b,c</td>
<td>23.4 (1.9)a,b,c</td>
<td>19.3 (1.5)a,b,c</td>
</tr>
<tr>
<td>Wortmannin + RPC</td>
<td>66.4 (5.3)a,b,c</td>
<td>24.0 (2.3)a,b,c</td>
<td>19.6 (2.0)a,b,c</td>
</tr>
<tr>
<td>PD98059</td>
<td>58.6 (1.8)a</td>
<td>23.8 (2.0)a</td>
<td>20.3 (1.2)a</td>
</tr>
<tr>
<td>Wortmannin</td>
<td>60.3 (2.8)a</td>
<td>22.7 (1.8)a</td>
<td>20.8 (1.5)a</td>
</tr>
</tbody>
</table>

Incidence of perioperative arthroplasty complications in elderly patients and feasibility of screening perioperative stroke with NIHSS


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In-hospital strokes account for 6.5–15% of total strokes. Half of them are perioperative. Thrombolysis and new antiplatelet drugs have significantly improved the prognosis of ischaemic strokes, but only 2–15% patients receive thrombolysis in time due to a short time window for use (6–12 h). Diagnosis of in-hospital stroke, especially perioperative, is complex. Non-neurological medical staff lack an identification tool; this results in patients exceeding the thrombolysis time window. NIHSS tests most neurological functions when stroke is first detected.
present. It is easy to learn, quick to administer, and there is good agreement between neurologists and non-neurological medical staff. This study planned to prospectively investigate elderly patients undergoing arthroplasty to detect the incidence of perioperative complications. We evaluated patients using NIHSS to analyse screening feasibility for perioperative stroke and to facilitate a subsequent multi-centre investigation.

We selected patients undergoing arthroplasty >60 yr old in Beijing Jishuitan Hospital. General information, previous history, and lab examination were recorded before operation. Surgery and anaesthesia data during surgery and haemodynamic data were recorded after operation. Medication was recorded before and after surgery and before discharge. NIHSS was evaluated before surgery, on postoperative days 1, 2, and 3, and before discharge. Patients were followed up by phone 6 months after surgery and assessed for independence and life quality using Barthel Index and EQ-5D. Data were analysed with SPSS 17.0.

Average duration of surgery was 107.3 (44.1) min; this was mainly related to type of surgery. Surgeries with longest duration were total knee arthroplasty (TKA), total hip arthroplasty (THA), and shoulder joint replacement because of cancer, with an average duration of 201.2 (31.3) min. Surgeries with shorter duration are bilateral TKA, bilateral THA, knee joint rebuilding, hip joint rebuilding, and middle-size joint replacement of limbs, like shoulder, elbow, and ankle; average duration was 163.2 (40.7) min. Shortest duration surgeries include TKA, THA, and replacement of femoral head, capitulum radius, and metatarsophalangeal joints. Anaesthetic type was mainly related to operative site and patient status. Shoulder replacement and femoral head replacement (in elderly with fractured neck of femur) have the highest proportion of general anaesthesia, 59.2% and 60%, respectively. Hip joint replacement not due to fracture but arthroplasty has the lowest proportion of general anaesthesia. For example, the rate of general anaesthesia of bilateral THA and hip joint rebuilding is 14.3%.

There were two patients who suffered perioperative stroke. The incidence is 0.39%. Referring to the records, patients’ relatives and nurses realized abnormal symptoms at an early stage of stroke. NIHSS score changed on the same day. NIHSS score increased as stroke symptoms worsened and decreased as they improved. For one patient, nurses applied neurological consultation two days later. It took neurologists 2 and 3 days separately from first consultation to confirming diagnosis. The specificity of NIHSS changing one score or one day is 85%. The specificity of changing more than 2 scores is 97%. The specificity of NIHSS changing duration more than 2 days is 95%. The sensitivity of NIHSS changes is 100% (Table 3). Not all NIHSS score changes are stroke-related. Delirium (8 cases), hypoxaemia (2 cases), metabolism encephalopathy, and sedative overdose (1 case) which may change cerebral function are all reasons for NIHSS score changes. Most frequent items for score changes are 1b or 1c (evaluating consciousness); changes in score number are often 1. Many arthroplasty patients suffer symmetrical joints of two limbs. Surgery and anaesthesia may affect the non-surgical limb. There were 33 cases where muscle strength was weaker in the non-surgical limb after surgery. Changes in score number are from 1 to 3. There were also 29 cases that have asymmetric feeling between surgical and non-surgical limbs. However, most of these unspecific NIHSS score changes lasted for 1 day. There were only 28 cases where duration of score changes was more than 2 days.

The incidence of perioperative stroke is 0.39%. NIHSS could be used as a screening tool in perioperative stroke. More score changes, and more duration days of changed scores will increase the possibility of perioperative stroke.

<table>
<thead>
<tr>
<th>mNIHSS</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 score or ≥1 day</td>
<td>100</td>
<td>85</td>
<td>2.5</td>
<td>100</td>
</tr>
<tr>
<td>2 days</td>
<td>100</td>
<td>95</td>
<td>7.4</td>
<td>100</td>
</tr>
<tr>
<td>≥ 2 scores</td>
<td>100</td>
<td>97</td>
<td>12.5</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3. NIHSS scores of two perioperative stroke patients. Preop, preoperative; D, postoperative day; Disc, discharge; Sen, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value

References

Effect of intrathecal injection of staurosporine on spinal microglial activation in rats with bone cancer pain
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We aimed to investigate the effect of intrathecal injection of the PKC inhibitor staurosporine on pain behaviour and spinal microglia activation in rats with shin bone cancer pain.

One hundred and twenty adult male Sprague–Dawley rats weighing 200–250g were randomly divided into five groups (n=24): control (Group C), model (Group M), normal saline (Group N), solvent (Group S), and staurosporine (Group SP). Bone cancer pain was induced by intra-tibial inoculation of Walker256 mammary gland carcinoma cells into M, N, S, and SP groups. Intrathecal injection was used after 10 days, once a day, for 3 days. Group N intrathecal injection of normal saline 10 μL, Group S intrathecal injection of DMSO 10 μL, Group SP intrathecal injection of staurosporine 10 μL. Pain behaviour was assessed 1 day before (T₀) and 1, 3, 5, 7, 10, 14, and 21 days later (T₁–T₇). Three rats were killed at each time point in each group for detection of OX-42 and Iba-1 expression in the spinal dorsal horn by immunofluorescence and the microglia were counted.
Compared with Group C, paw withdrawal mechanical threshold (PWMT) significantly decreased and paw withdrawal thermal latency (PWTL) was shorter in the other four groups ($P<0.05$). Compared with Group M, PWMT was significantly increased, PWTL was prolonged, the expression of OX-42 and Iba-1 in the spinal dorsal horn was decreased, and the microglial count was decreased in the S and SP groups ($P<0.05$). Compared with Group S, PWMT was significantly increased, PWTL was prolonged, the expression of OX-42 and Iba-1 in the spinal dorsal horn was decreased, and the microglial count was decreased in Group SP ($P<0.05$).

In conclusion, intrathecal injection of staurosporine can inhibit spinal microglial activation and reduce bone cancer pain.

Role of p38 mitogen-activated protein kinase and ERK1/2 pathways in the regulation of haem oxygenase-1 in the injured lung during endotoxic shock in rats

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Endotoxic shock is a disease process caused by a severe underlying infection. In the case of Gram-negative bacterial infections, the release of endotoxin or lipopolysaccharide (LPS) from the bacterial cell wall causes a dramatic stimulation of LPS-responsive immune cells in the host.1 Macrophages, which are the cells most sensitive to LPS stimulation, become activated and release a battery of endogenous mediators and defence molecules, including pro-inflammatory cytokines such as interleukin (IL)-1 and it results in activation of the MAPK signalling cascade.2 Although pro-inflammatory cytokines can protect the host against infection, if the infection is left unchecked, this process may progress to refractory hypotension, multiple organ system failure, and death.3 The mortality resulting from endotoxic shock, the most common cause of death in the critical care unit, has not decreased in the past decade. Therefore, suppressing LPS-induced inflammation has been a primary target in pharmacological treatment of acute lung injury/acute respiratory distress syndrome patients.

We previously reported that LPS induces the expression of haem oxygenase-1 (HO-1) during septic shock in rats and we used ZnPP-IX to inhibit HO activity. We also found a down-regulation of HO-1 protein in septic shock in the liver, lung, and kidney resulting in an increase in end-organ dysfunction; CO concentration and SOD activity reduced and MDA contents and pulmonary vascular leakage increased.4,5 HO-1 is the inducible isoform of the first and rate-limiting enzyme of haem degradation6 and its expression can be induced by different stress stimuli including hypoxia,7 heavy metals, UV radiation, and ROS such as H$_2$O$_2$.8 The HO-1 products carbon monoxide and bilirubin not only provide antioxidant cytoprotection, but also have potent anti-inflammatory and immunomodulatory functions.9 10 In HO-1-deficient mice, we can see a disproportional activation of monocytes and the mice are highly vulnerable to endotoxin-mediated toxicity.11 12 Accumulating evidence suggests a vital role for HO-1 in both cell growth and cell death, especially involvement of the enzymes in the regulation of apoptosis.13

HO-1 as a representative mediator of antioxidants and cytoprotectants plays an important role in resistance to various stress stimuli. We have shown an increase in HO-1 expression in injured rat lung in LPS-induced endotoxic shock. The mechanisms of HO-1 expression in injured lung caused by endotoxic shock are still unknown because the induction of HO-1 is cell- and stimulus-specific. The purpose of this analysis was to determine the P38MAPK and ERK1/2 (extracellular signal-regulated kinases) signalling pathways are involved in the induction of HO-1 in the injured lung during endotoxic shock in rats.

The experimental protocol was approved by the local animal care and use committee, and all animals received humane care according to the criteria outlined in the ‘Guide for the Care and Use of Laboratory Animals’ prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication 86-23, revised 1985). Pretreatment of SD rats with the inhibitors of P38MAPK and ERK1/2, and 30 min later LPS i.v. Continuous monitoring of MAP, if an initial 25% decrease in MAP, the model can be put to use. The animals were killed 6 h after LPS. Levels of total and phosphorylated forms of p38MAPK, extracellular signal-regulated protein kinases1/2 (ERK1/2) protein, and HO-1 protein were assessed by western analysis and HO-1 mRNA levels were assessed by quantitative PCR. Microscopic examination, W/D weight ratio, SOD activity, and MDA contents of lung tissue were performed.

We found a clear decrease in phospho-p38 MAPK protein levels after inhibition of p38MAPK activity with the chemical inhibitor SB203580. We also found HO-1 expression was increased. Phospho- and total ERK1/2 were decreased after ERK1/2 inhibitor PD98059 and HO-1 mRNA and protein expression was decreased. HO-1 expression was increased by inhibition of the phospho p38MAPK and lung injury decreased, while the HO-1 expression and lung injury went in the opposite direction with inhibition of ERK1/2.

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National Natural Science Foundation (#81372096), Tianjin Natural Science Foundation (#11JCJJC11000), Plan Key project supported by Tianjin Science and Technology (#12ZZDSY0300).

References

Collegenase for treatment for cervical disc herniation: relationship with disc CT number

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There are three objectives to this study. First, observe the dissolving effects of collagenase on herniated discs with different CT numbers (contrast compared with water). Second, to observe the relationship between the effects of collagenase treatment and hernial disc CT number (to provide an objective basis for predicting the effects of collagenase for treatment). Third, to describe the characteristics of cervical disc herniation when treated with collagenase chemonucleolysis.

We chose 75 patients with cervical disc herniation for collagenase chemonucleolysis treatment. All patients were checked the cervical CT and MRI prior to operation and the CT value of the hernial disc was measured. 75 patients were divided into 4 groups according to CT number, group A CT value <70, group B CT value (70–80), group C CT value (80–90) and group D CT value >90. All the patients received Collagenase chemonucleolysis under C-Arm guidance. Patients were followed-up for one year post procedure by telephone or in clinic. VAS pain scores and sleep hours were evaluated to assess outcome.

There were no differences in age, gender, height, weight, disease course or VAS score before operation between the groups. Pain and sleep quality were relieved to different degrees. Smaller the CT number the more obvious the improvement in pain and sleep quality (P <0.05). VAS score gradually decreased and sleep time gradually increased up to 3 months post procedure at which point there was no further change.

In conclusion, there are three major results of this study. Collagenase chemonucleolysis was effective for treatment of cervical disc herniation. There was a negative correlation between preoperative CT number and treatment effect (CT number can be used to predict the effect of collagenase chemonucleolysis). Pain and sleep quality were improved from 3 months.

References

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Effect of stellate ganglion block on postoperative cognitive function in aged rats

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Stellate ganglion block (SGB) has been widely used in the clinic with efficacy in the treatment of pains in the head, face, upper limbs, and in some vasospastic diseases, moreover, stellate ganglion block has been shown to be capable of improving brain circulation, modulating immunity, and reducing plasma catecholamine content. Many studies have shown SGB has brain protective effects but whether it has a preventive effect on postoperative cognitive function is unknown.

With animal use committee approval, 72 male Sprague–Dawley rats were randomly divided into three groups (n=24 each): control group (Group C), operation group (Group O), and SGB+operation group (Group SGB). Groups C and O had the right cervical sympathetic trunk exposed but not blocked. Group SGB received right SGB with 0.25% bupivacaine 0.15 ml, Groups O and SGB underwent 30 min of exploratory laparotomy starting from 15 min after the end of administration. Morris water-maze test was performed at 1 day (T1), 3 days (T2), and 7 days (T3) after operation in eight rats chosen from each group. The escape latency and frequency of crossing the original platform were recorded. Animals were then killed and the hippocampi were removed for microscopic examination and determination of levels of tau protein phosphorylation.

Compared with Group C, escape latency was significantly prolonged T1–T3 after operation, the frequency of crossing the original platform was decreased (P<0.05) and the phosphorylation levels of tau protein was higher in Groups O and SGB (Table 4). Escape latency and phosphorylation of tau protein at T3 in Group SGB was not significantly different from Group C. Compared with Group O, the escape latency was

<table>
<thead>
<tr>
<th>Groups</th>
<th>Tau(p-Ser396) and Tau(p-Thr231)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1 day (T1)</td>
</tr>
<tr>
<td>Group C</td>
<td>3.40 (1.14)</td>
</tr>
<tr>
<td></td>
<td>3.20 (0.86)</td>
</tr>
<tr>
<td>Group O</td>
<td>69.20 (5.26)</td>
</tr>
<tr>
<td></td>
<td>52.80 (5.93)</td>
</tr>
<tr>
<td>Group SGB</td>
<td>23.00 (5.24)</td>
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<td></td>
<td>24.20 (3.03)</td>
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</table>
significantly shortened, the frequency of crossing the original platform was increased, and phosphorylation levels of tau protein was lower at T1–T3 after operation in Group SGB (P<0.05 or <0.01). The number of hippocampal neurones was significantly greater at T1–T3 in Group SGB than in Group O. SGB can improve postoperative cognitive function in aged rats and a depression of overphosphorylation of tau protein may be a potential mechanism.

References

Feasibility of ultrasound-guided central venous catheterization in a porcine model for simulation of haemodynamic monitoring
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Owing to similar vascular structure, the pig is a suitable model to simulate human haemodynamic monitoring. However, it is difficult to establish central venous catheterization via internal jugular vein in the porcine model. Usually, surgical incision is used to expose the internal jugular vein. B-ultrasound has been used as a non-invasive method to guide central venous catheterization. The purpose of this study is to explore the feasibility of ultrasound-guided central venous catheterization in the porcine model for simulation training.1

This study was conducted with the approval of the animal ethics committee of Xuan Wu hospital. Seventeen trainees, 70.59% of whom were attending or consultant anaesthesiologists, were involved in this training programme. Two female pigs (38.5 kg/6 months, 48.5 kg/6 months) were intubated after ketamine anaesthesia. The internal jugular vein was exposed by surgical incision in one pig.23 All trainees performed internal jugular vein catheterization using ultrasound guidance in the other pig. Simultaneously, the success rate, number of attempts, and duration of catheterization were recorded.

Twenty-five minutes was needed to insert the internal jugular vein catheter by surgical exposure. The success rates of ultrasound-guided puncture and catheterization were 100%. The mean number of attempts and manipulation duration were 1.9 and 17 min, respectively. The whole procedure was performed smoothly without any side-effects.

To conclude, ultrasound-guided central venous catheterization in the porcine model, which is easy and rapid to manipulate, is a minimally invasive way to establish haemodynamic monitoring. Ultrasound-guided catheterization can also increase the success rate. It may play an important role in anaesthesia simulation education.

References