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Hyperglycaemia blocks sevoflurane-induced postconditioning in the rat heart *in vivo*: cardioprotection can be restored by blocking the mitochondrial permeability transition pore

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Background. Recent studies showed that hyperglycaemia (HG) blocks anaesthetic-induced preconditioning. The influence of HG on anaesthetic-induced postconditioning (post) has not yet been determined. We investigated whether sevoflurane (Sevo)-induced postconditioning is blocked by HG and whether the blockade could be reversed by inhibiting the mitochondrial permeability transition pore (mPTP) with cyclosporine A (CsA).

Methods. Chloralose-anaesthetized rats (n=7–11 per group) were subjected to 25 min coronary artery occlusion followed by 120 min reperfusion. Postconditioning was achieved by administration of 1 or 2 MAC sevoflurane for the first 5 min of early reperfusion. HG was induced by infusion of glucose 50% (G 50) for 35 min, starting 5 min before ischaemia up to 5 min of reperfusion. CsA (5 or 10 mg kg^{-1}) was administered i.v. 5 min before the onset of reperfusion. At the end of the experiments, hearts were excised for infarct size measurements.

Results. Infarct size (% of area at risk) was reduced from 51.4 (5.0)% [mean (SD)] in controls to 32.7 (12.8)% after sevoflurane postconditioning (Sevo-post) ($P<0.05$). This infarct size reduction was completely abolished by HG [51.1 (13.2)%, $P<0.05$ *vs* Sevo-post], but was restored by administration of sevoflurane with CsA [35.2 (5.2)%, $P<0.05$ *vs* HG+Sevo-post]. Increased concentrations of sevoflurane or CsA alone could not restore cardioprotection in a state of HG [Sevo-post2, 54.1 (12.6)%, $P>0.05$ *vs* HG+Sevo-post; CsA10, 58.8 (11.3)%, $P>0.05$ *vs* HG+CsA].

Conclusions. Sevoflurane-induced postconditioning is blocked by HG. Inhibition of the mPTP with CsA is able to reverse this loss of cardioprotection.

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Hyperglycaemia (HG) correlates with increased mortality after acute myocardial infarction in diabetic patients and in patients without diabetes mellitus.[1 2] HG was shown to abolish cardioprotection induced by ischaemic and anaesthetic preconditioning.[3 4]

Besides preconditioning, postconditioning (i.e. cardioprotection by administration of the substance after ischaemia during early reperfusion) can also be induced by volatile anaesthetics.[5 6] Recent studies demonstrated that the volatile anaesthetic sevoflurane offers cardioprotection by postconditioning.[7 8] In both studies, postconditioning induced a cardioprotective effect that was comparable with the extent of cardioprotection induced by sevoflurane preconditioning. Furthermore, Obal and colleagues[9] showed that sevoflurane induces maximal cardioprotection by postconditioning at a concentration of only 1 MAC. It is not known whether anaesthetic-induced postconditioning can be induced in hyperglycaemic subjects. This question was tested in the initial phase of the study using an *in vivo* rat model.

Recent studies have shown that the mitochondrial permeability transition pore (mPTP) is involved in

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isoflurane-induced postconditioning via phosphorylation and inhibition of GSK3β.[10] Krolikowski and colleagues[11] demonstrated that keeping the mPTP closed with cyclosporine A (CsA) enhanced cardioprotection produced by isoflurane-induced postconditioning. Therefore, in the second phase of the study, we tested if administration of CsA shortly before the reperfusion period could restore the cardioprotection.

We hypothesized that (i) sevoflurane postconditioning is abolished by HG and (ii) cardioprotection can be restored by inhibiting the mPTP in hyperglycaemic animals.

Methods

The study was performed in accordance with the requirements of the Animal Ethics Committee of the University of Amsterdam and was in line with European Union directives on the care and use of experimental animals.

Materials

Sevoflurane was purchased from Abbott (SEVOrane®, Abbott B.V., Hoofddorp, The Netherlands). Cyclosporine A was purchased from Fluka Biochemika (Sigma Aldrich, Steinheim, Germany). Glucose 50% was purchased from B. Braun (B. Braun Melsungen AG, Melsungen, Germany).

Surgical preparation and infarct size measurement

Animals had free access to food and water at all times before the start of the experiments.

Surgical preparation was performed as described previously.[9 12] In brief, male Wistar rats (250–350 g, 7–11 per group) were anaesthetized by intraperitoneal S-ketamine injection (150 mg kg^{-1}); this does not interfere with *in vivo* experimental cardioprotection.[13] Ventilatory frequency was adjusted to maintain P_{CO_2} within physiological limits. Body temperature was maintained at 38°C by the use of a heating pad. Anaesthesia was maintained by continuous α-chloralose infusion. A lateral left-sided thoracotomy followed by pericardiotomy was performed and a ligature (5–0 Prolene) was passed below a major branch of the left coronary artery. All animals were left untreated for 25 min before the start of the respective experimental protocol. Arterial blood gases were analysed at baseline and P_{CO_2} and P_{O_2} were maintained within physiological ranges by adjusting ventilation. Sevoflurane concentration was measured in the expiratory gas (Datex Capnomac Ultima, Division of Instrumentarium Corp., Helsinki, Finland). Aortic pressure and electrocardiographic signals were digitized using an analogue to digital converter (PowerLab/8SP, ADInstruments Pty Ltd, Castle Hill, Australia) at a sampling rate of 500 Hz and were continuously recorded on a personal computer using Chart for Windows v5.0 (ADInstruments).

After 120 min of reperfusion, the heart was excised and infarct size was determined as previously described.[9] The area of risk and the infarcted area were determined by planimetry using SigmaScan Pro 5® computer software (SPSS Science Software, Chicago, IL, USA) and corrected for dry weight of each slice.

Experimental protocol

Rats were divided into 10 groups (Fig. 1A): all animals underwent 25 min of coronary artery occlusion and 2 h of reperfusion (*I/R*).

Control group (Con) (n=9): after surgical preparation, rats received oxygen 30% plus nitrogen 70%. Normal saline was given i.v. over 35 min starting 5 min before ischaemia up to 5 min of reperfusion.

Sevoflurane postconditioned group (Sevo-post) (n=11): rats received sevoflurane with an end-tidal concentration of 1 MAC (≙2.4 vol%) for 5 min starting 1 min before the onset of reperfusion; saline 0.9% was infused i.v. over 35 min starting 5 min before ischaemia up to 5 min of reperfusion.

Glucose 50% group (HG) (n=9): glucose 50% was administered i.v. over 35 min starting 5 min before ischaemia and was continued until 5 min of reperfusion. Target blood glucose level before ischaemia was 22 mmol $litre^{-1}$ or higher and was maintained at this level.

Glucose 50%+sevoflurane postconditioned group (HG+Sevo-post) (n=9): glucose 50% and sevoflurane were both given as described above.

CsA group (CsA) (n=9): CsA (5 mg kg^{-1} in dimethyl sulphoxide 1% aqueous solution)[11] was administered i.v. 5 min before reperfusion; saline 0.9% was infused i.v. over 35 min starting 5 min before ischaemia up to 5 min of reperfusion.

CsA+sevoflurane postconditioned group (CsA+Sevo-post) (n=8): rats received CsA and sevoflurane as described above.

Glucose 50%+CsA group (HG+CsA) (n=8): rats received glucose 50% and CsA (5 mg kg^{-1}) i.v. as described above.

Glucose 50%+CsA+sevoflurane postconditioned group (HG+CsA+Sevo-post) (n=8): rats received glucose 50%, CsA (5 mg kg^{-1}) i.v., and inhaled sevoflurane as described above.

To investigate whether a higher concentration of sevoflurane or CsA alone could restore cardioprotection during HG, we added two more groups with 2 MAC sevoflurane and 10 mg kg^{-1} CsA.

Glucose 50%+sevoflurane postconditioned group (HG+Sevo-post2) (n=9): glucose 50% and 2 MAC sevoflurane were both given as described above.

Glucose 50%+CsA group (HG+CsA10) (n=7): rats received glucose 50% and CsA (10 mg kg^{-1}) i.v. as described above.

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