

LABORATORY INVESTIGATIONS

Desflurane and isoflurane improve neurological outcome after incomplete cerebral ischaemia in rats**K. Engelhard*, C. Werner, W. Reeker, H. Lu, O. Möllenberg, L. Mielke and E. Kochs***Institut für Anaesthesiologie der Technischen Universität München, Klinikum rechts der Isar, Ismaninger Straße 22, D-81675 München, Germany***Corresponding author*

We have investigated the effects of isoflurane and desflurane on neurological outcome in a rat model of incomplete cerebral ischaemia. We studied 40 non-fasted male Sprague–Dawley rats, anaesthetized, intubated and ventilated mechanically with isoflurane and nitrous oxide in oxygen ($F_{I_{O_2}}$ 0.3). Arterial and venous catheters were inserted for measurement of arterial pressure, drug administration and blood sampling. A biparietal electroencephalogram (EEG) was recorded continuously using subdermal platinum electrodes. At completion of surgery, administration of isoflurane was discontinued (with the exception of those animals receiving isoflurane as treatment) and rats were allowed an equilibration period of 30 min according to the following procedure: group 1 ($n=10$), 66% nitrous oxide in oxygen and fentanyl (bolus $10 \mu\text{g kg}^{-1}$ i.v. followed by infusion at a rate of $25 \mu\text{g kg}^{-1} \text{h}^{-1}$); group 2 ($n=10$), 1.0 MAC of isoflurane in oxygen ($F_{I_{O_2}}$ 0.3) and air; groups 3 and 4 ($n=10$ per group), 1.0 MAC or 1.5 MAC of desflurane in oxygen ($F_{I_{O_2}}$ 0.3) and air, respectively. Ischaemia was produced by combined unilateral common carotid artery ligation and haemorrhagic hypotension to 35 mm Hg for 30 min. Functional neurological deficit was evaluated for 3 days after cerebral ischaemia. At baseline, brain electrical activity was higher with fentanyl–nitrous oxide, 1.0 MAC of isoflurane and 1.0 MAC of desflurane (groups 1–3) compared with 1.5 MAC of desflurane (group 4). Neurological outcome was improved in isoflurane and desflurane anaesthetized animals (groups 2–4), regardless of the concentration used compared with fentanyl–nitrous oxide anaesthesia (group 1). The increase in plasma epinephrine and norepinephrine concentrations during ischaemia was significantly higher in fentanyl–nitrous oxide anaesthetized animals (group 1) compared with animals who received volatile anaesthetics (groups 2–4). These data suggest that cerebral protection produced by isoflurane and desflurane appears to be related to reduction in sympathetic activity rather than suppression of cerebral metabolic rate.

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Several animal experiments have investigated the effects of volatile anaesthetic agents on neurological outcome and infarct size after cerebral ischaemia. While some of these studies showed brain protection with halothane, isoflurane or sevoflurane,^{1–3} others failed to demonstrate improvement in neurological function or histopathology.^{4,5} The variability in results may be related to the differences in the ischaemic models (e.g. focal cerebral ischaemia *vs* forebrain ischaemia *vs* incomplete hemispheric ischaemia) or insufficient maintenance of physiological variables, including brain temperature.

Experiments demonstrating a brain protective effect of volatile anaesthetics have attributed this to suppression of cerebral metabolic rate, thus economizing the balance between cerebral metabolic activity and cerebral blood flow. In addition, volatile anaesthetic agents may inhibit neurotransmitter release (e.g. glutamate, catecholamines) which in turn decreases Ca^{2+} and Na^{+} influx into postsynaptic neurones.^{6–8} This reduces the amount of intracellular catabolic processes (e.g. activation of proteases, lipid peroxidation, nitric oxide). Desflurane is a new volatile anaesthetic agent with a low blood-gas partition coefficient,⁹ and it

reduces neuronal function and metabolism until EEG burst suppression is achieved, similar to isoflurane and sevoflurane.¹⁰ Favourable pharmacokinetic characteristics (e.g. rapid emergence), cerebrovascular effects similar to those of isoflurane¹⁰ and the ability to suppress cerebral metabolism suggest that desflurane could be a good anaesthetic for neurosurgical patients. In this study, we have investigated the effects of desflurane compared with isoflurane and fentanyl–nitrous oxide on neurological outcome in a model of incomplete cerebral ischaemia in rats.

Materials and methods

After obtaining approval from the Institutional Animal Care Committee, we studied 40 non-fasted male Sprague–Dawley rats (weighing 350–430 g), anaesthetized in a bell jar saturated with isoflurane. Their tracheas were intubated and the lungs ventilated mechanically with 1.7% isoflurane (expired concentration) and 66% nitrous oxide in oxygen (Capnomac Ultima, Datex). Catheters were inserted into the right femoral artery and vein, and into the right jugular vein for continuous measurement of mean arterial pressure (MAP), blood sampling and drug administration. The right common carotid artery was isolated for later clamping. Vecuronium was given as a continuous infusion ($0.1 \text{ mg kg}^{-1} \text{ min}^{-1}$) to maintain neuromuscular block. On completion of the surgical preparation, administration of isoflurane was discontinued (with the exception of those animals receiving isoflurane as a treatment) and animals were allowed an equilibration period of 30 min according to one of the following treatments: group 1 ($n=10$) received 66% nitrous oxide in oxygen and fentanyl (bolus $10 \text{ } \mu\text{g kg}^{-1}$ i.v. followed by infusion at a rate of $25 \text{ } \mu\text{g kg}^{-1} \text{ h}^{-1}$); group 2 ($n=10$) received 1.0 MAC of isoflurane (1.4% expired concentration) in oxygen and air ($F_{\text{I}_{\text{O}_2}}$ 0.3); group 3 ($n=10$) received 1.0 MAC of desflurane (5.7% expired concentration) in oxygen and air ($F_{\text{I}_{\text{O}_2}}$ 0.3); and group 4 ($n=10$) received 1.5 MAC of desflurane (8.5% expired concentration) in oxygen and air ($F_{\text{I}_{\text{O}_2}}$ 0.3).

Incomplete hemispheric ischaemia was produced in all animals by a combination of right common carotid occlusion and haemorrhagic hypotension to a target MAP of 35 mm Hg for 30 min. A deviation of 1 mm Hg from the target pressure was tolerated. Pericranial temperature was measured by insertion of a 22-gauge stainless steel needle thermistor (YSI temperature controller, model 73A, OH, USA) beneath the right temporalis muscle and was maintained constant throughout the experiment and recovery at 37°C by Servo control using an overhead heating lamp. Mechanical ventilation was adjusted to maintain P_{aCO_2} at 4.7–5.3 kPa. Arterial pH was adjusted by infusion of sodium bicarbonate. Arterial blood-gas partial pressures and plasma glucose analyses were performed at baseline, at 15 min and 30 min during ischaemia, and after reperfusion. At the beginning and end of the ischaemic period, arterial blood samples were

obtained for measurement of plasma concentrations of catecholamines using high performance liquid chromatography (HPLC). After 30 min, ischaemia was terminated by unclamping the carotid artery and by reinfusion of withdrawn blood within 15 min. During an additional 30-min recovery period, the catheters were removed and the incisions closed. Anaesthesia was discontinued, the trachea was extubated and the animals returned to their cages.

High performance liquid chromatography (HPLC)

Blood samples for measurement of plasma concentrations of catecholamines were obtained using vials containing glutathione (Kabe Labortechnik, Nümbrecht-Elsenroth). All blood samples were transported on ice and centrifuged at 4°C for 10 min. Decanted plasma was stored at –70°C. Plasma samples were processed using a Chromosystem test kit for HPLC analysis of catecholamines (Chromosystems, Munich, Germany). Plasma (1 ml) was mixed with 0.5 ml of aluminium oxide. As an internal standard, dehydroxybenzylamine (DHBA) 600 pg (artificial catecholamine) was added to the sample. The remaining particles of plasma proteins were washed out. Elution of catecholamines was completed by adding 120 μl elution buffer. The vials with the elute were placed into an autoinjector WISP (Model 712, Waters Chromatographie, Eschborn, Germany) and 50 μl were injected into the HPLC circulation system (mobile phase sodium acetate buffer for HPLC analysis of catecholamines, Chromosystems, Munich, Germany). The elute was passed over the analytical column (Chromosystems, Munich, Germany) to the electrochemical detector (Waters 406 Electrochemical Detector, Waters Chromatographie, Eschborn, Germany) by the Waters 600 Multi-solvent Delivery System (flow rate 1 ml min^{-1} , pressure 3000 PSI). The whole system was controlled and data were stored by the Maxima 820 Software (Waters Chromatographie, Eschborn, Germany).

Electroencephalography (EEG)

The EEG was recorded continuously via subdermal platinum needle electrodes placed over both hemispheres at the parietotemporal vs frontal cortex recording sites. Electrode impedances were maintained below 5 kW. Bandpass was set at 0.1–30 Hz. After amplification (AC/AD Strain Gage Amplifier, Model P122, Grass Instruments Division) the EEG signals were digitized (CED 1401 plus, Science Products GmbH, Germany) to 12-bit data with a sample rate of 250 Hz and stored on computer hard disk using the software Spike 2 (Cambridge Electronics). Offline EEG analysis was performed using software based on the Spike 2 program, followed by fast Fourier transformation (FFT: epoch length 2.048 s ($512 \times 0.004 \text{ s}$)). Integrated EEG power ($\mu\text{V}^2 \text{ Hz}^{-1}$) was calculated as absolute values for selected frequency bands: delta 0.45–3.9 Hz, theta 4.0–7.9 Hz, alpha 8.0–12.9 Hz and beta 13.0–30.0 Hz. Furthermore, median frequency (50% percentile) and spectral edge frequency

Table 1 Mean arterial pressure (MAP), plasma glucose concentrations, arterial blood-gas partial pressures and arterial pH during baseline, ischaemia and recovery (mean (SD)). * $P < 0.05$ vs group 1 at each respective treatment; † $P < 0.05$ vs group 2 at each respective treatment

Treatment		MAP (mm Hg)	Glucose (mg dl ⁻¹)	P_{aO_2} (kPa)	P_{aCO_2} (kPa)	pH
Group 1 ($n = 10$) (fentanyl–N ₂ O)	Baseline	127 (4)	65 (4)	16.9 (0.5)	4.9 (0.1)	7.39 (0.01)
	15 min ischaemia	35 (1)	199 (21)	17.5 (0.8)	5.3 (0.1)	7.40 (0.01)
	30 min ischaemia	35 (1)	126 (26)	17.7 (0.9)	5.3 (0.1)	7.41 (0.02)
	Recovery	125 (6)	61 (7)	16.9 (0.8)	5.1 (0.1)	7.42 (0.02)
Group 2 ($n = 10$) (1.0 MAC of isoflurane)	Baseline	71 (5)*	91 (4)*	17.7 (10.5)	4.9 (0.1)	7.40 (0.01)
	15 min ischaemia	35 (1)	164 (13)	16.5 (0.9)	5.3 (0.2)	7.41 (0.02)
	30 min ischaemia	35 (1)	198 (23)	17.6 (10.8)	4.8 (0.1)*	7.42 (0.01)
	Recovery	109 (6)	132 (16)*	16.9 (1.1)	4.8 (0.1)	7.43 (0.01)*
Group 3 ($n = 10$) (1.0 MAC of desflurane)	Baseline	81 (3)*	100 (4)*	18.5 (0.5)	5.1 (0.2)	7.38 (0.01)
	15 min ischaemia	35 (1)	192 (14)	17.9 (0.8)	5.5 (0.1)	7.39 (0.01)
	30 min ischaemia	35 (1)	199 (14)	17.6 (1.1)	5.1 (0.1)	7.40 (0.01)
	Recovery	110 (2)	108 (10)	17.2 (1.1)	4.9 (0.1)	7.40 (0.01)
Group 4 ($n = 10$) (1.5 MAC of desflurane)	Baseline	72 (4)*	113 (7)*	20.5 (0.4)*†	5.0 (0.1)	7.37 (0.01)
	15 min ischaemia	35 (1)	190 (10)	19.7 (0.5)†	5.3 (0.1)	7.38 (0.01)
	30 min ischaemia	35 (1)	220 (11)*	18.4 (0.8)	5.3 (0.1)†	7.39 (0.01)†
	Recovery	96 (5)*	153 (14)*	16.9 (1.9)	5.1 (0.1)	7.40 (0.01)

(95% percentile) were calculated. For EEG recordings with burst suppression, the suppression periods were discarded from the EEG. The suppression epoch fraction was calculated using custom-made burst suppression recognition software. The fraction of electrical silence was expressed as a percentage of the duration of the total epoch (% time).

Neurological outcome

Neurological outcome scores were evaluated at 24, 48 and 72 h after ischaemia by an investigator blinded to the treatment. Neurological outcome was evaluated according to the following scoring system where a score of 0 represented no detectable neurological deficit and a score of 17 stroke-related death: grooming (worst score 1), consciousness (worst score 4), walking performance (worst score 4), ability to climb on a rope platform (worst score 4) and ability to stay on a rotating screen (worst score 3). The diagnosis 'stroke-related death' within the first 24 h was accepted only if the rats developed progressive signs of stroke impairment.

Statistical analysis

Data are reported as mean (SD). Neurological deficit scores and physiological variables were analysed using the H test of Kruskal–Wallis. Critical rank differences for multiple comparisons were determined by the method of Harter. EEG data were compared using the Mann–Whitney U test followed by Bonferroni correction. Significance was assumed at $P < 0.05$.

Results

Table 1 shows the physiological variables during and after incomplete hemispheric ischaemia. At baseline, MAP was significantly lower with isoflurane (group 2) and desflurane (groups 3 and 4) compared with fentanyl–nitrous oxide anaesthesia (group 1). According to the protocol, MAP was 35 mm Hg in all groups during ischaemia. During recovery, MAP was less with 1.5 MAC of desflurane (group 4)

compared with all other groups. The amount of withdrawn blood necessary to induce haemorrhagic hypotension was comparable between groups, with the exception of a difference between 1.0 MAC and 1.5 MAC of desflurane (groups 3 and 4) (group 1: 12.8 (0.39) ml; group 2: 11.8 (0.97) ml; group 3: 13.9 (0.48) ml; and group 4: 10.4 (0.63) ml).

Before ischaemia, plasma concentrations of glucose were significantly lower in the fentanyl–nitrous oxide anaesthetized rats (group 1) compared with the other groups. During ischaemia, there were no differences in plasma concentrations of glucose between the groups with the exception of rats anaesthetized with 1.5 MAC of desflurane (group 4). In these animals, plasma concentrations of glucose increased significantly. During recovery, plasma concentrations of glucose were higher after 1.0 MAC of isoflurane (group 2) and 1.5 MAC of desflurane (group 4) compared with fentanyl–nitrous oxide (group 1).

Figure 1 shows the changes in plasma concentrations of catecholamines. Before ischaemia, there were no significant differences in norepinephrine and epinephrine plasma concentrations between groups. During ischaemia, the increase in plasma concentrations of norepinephrine and epinephrine was less with any volatile anaesthetic compared with animals anaesthetized with fentanyl–nitrous oxide (group 1), with the exception of an increase in plasma concentrations of epinephrine with 1.0 MAC of desflurane (group 3).

Figure 2 shows neurological outcome data, evaluated every 24 h for the 3 days after ischaemia. With fentanyl–nitrous oxide anaesthesia (group 1), 50% of rats died after the first 24 h, and 80% died after 48 h as a result of stroke-related events. After 3 days, all animals had died from severe brain damage. In contrast, all animals anaesthetized with isoflurane (group 2) or desflurane (groups 3 and 4) survived the 3-day examination period. Animals anaesthetized with volatile anaesthetics developed only minor neurological deficits, regardless of the compound or anaesthetic concentration. There was no difference in neurological outcome between isoflurane (group 2) and desflurane (groups 3 and 4) anaesthetized animals.

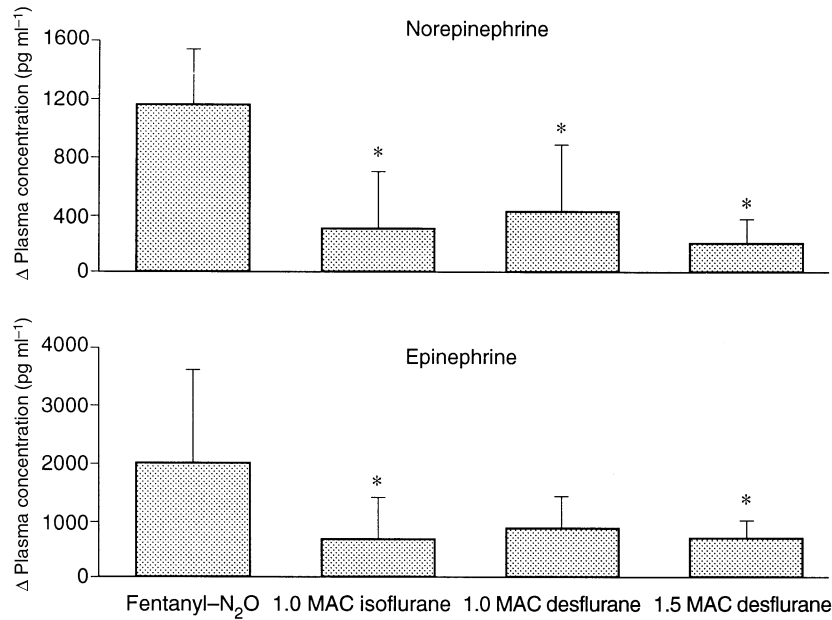


Fig 1 Increase in plasma concentrations of catecholamines (baseline vs 30 min of ischaemia) during incomplete ischaemia in groups 1–4 compared with baseline. Volatile anaesthetics (groups 2–4) significantly depressed the increase in plasma concentrations of norepinephrine and epinephrine compared with the fentanyl–nitrous oxide (N₂O) group (group 1), with the exception of plasma concentrations of epinephrine in the 1.0 MAC of desflurane group (group 3). * $P < 0.05$ compared with the fentanyl–N₂O group.

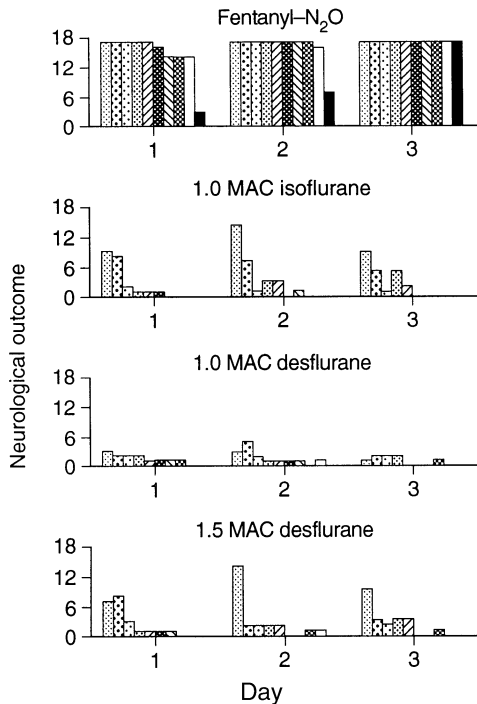


Fig 2 Neurological deficit scores after incomplete cerebral ischaemia in groups 1–4 over a 3-day examination period. A score of 0 represents no neurological deficit and 17 indicates stroke-related death. Desflurane concentration did not significantly influence neurological outcome (groups 3 and 4). Each bar represents a single rat (10 rats per group).

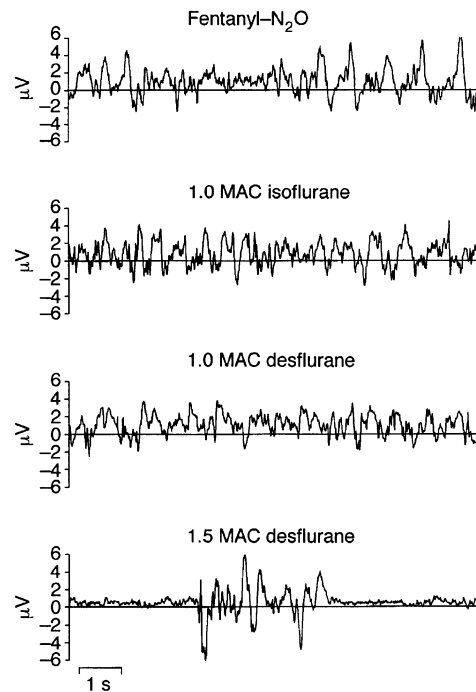


Fig 3 EEG tracings during steady state anaesthesia before incomplete cerebral ischaemia (baseline conditions): slowed EEG with dominant δ activity with fentanyl–nitrous oxide (N₂O), 1.0 MAC of isoflurane and 1.0 MAC of desflurane (groups 1–3); burst suppression with 1.5 MAC of desflurane (group 4).

During baseline, EEG activity decreased to δ frequency in the fentanyl–nitrous oxide, 1.0 MAC of isoflurane and 1.0 MAC of desflurane groups (groups 1–3) (Fig. 3). Desflurane (1.5 MAC) produced EEG burst suppression

with a fraction of electrical silence of 30 (18)% and 32 (17)% during baseline and 38 (15)% and 38 (13)% during reperfusion in the right and left hemispheres, respectively. There was no burst suppression pattern with fentanyl–

nitrous oxide, 1.0 MAC of isoflurane or 1.0 MAC of desflurane (groups 1–3). During ischaemia, reperfusion and recovery, EEG showed dominant δ frequency with fentanyl–nitrous oxide, 1.0 MAC of isoflurane and 1.0 MAC of desflurane (groups 1–3) and burst suppression with 1.5 MAC of desflurane (group 4). The relationship between baseline and recovery for α and β activity, spectral edge frequency and total power of the ischaemic right hemisphere was compared between groups. The control group (group 1) showed a strong decrease in α activity, β activity and spectral edge frequency from baseline to recovery compared with the essentially constant relationship in the volatile anaesthetic groups (groups 2 and 3). From baseline to recovery, an increase in total power was observed in groups 2 and 3 compared with a decrease in the control group (group 1).

Discussion

Our results showed that compared with fentanyl–nitrous oxide anaesthesia, isoflurane and desflurane improved neurological outcome in a rat model of incomplete cerebral ischaemia. Brain protection was similar for the two volatile anaesthetics, regardless of the concentration. During baseline, the EEG was suppressed with fentanyl–nitrous oxide, 1.0 MAC of isoflurane and desflurane, while 1.5 MAC of desflurane induced an EEG burst suppression pattern. Despite these differences in neuronal functional activity and possibly cerebral metabolic rate (CMR), the extent of brain protection was similar in isoflurane and desflurane anaesthetized animals. This and related research suggest that suppression of CMR is not the major mechanism by which volatile anaesthetics mediate brain protection during cerebral ischaemia.^{1 11–15}

Cerebral metabolic suppression has long been thought to be one of the major mechanisms of neuronal protection. By reducing CMR during cerebral ischaemia, volatile anaesthetics adjust cerebral metabolic demand to low energy supply.¹⁶ In our study, we used two different concentrations of desflurane: 1.0 MAC of desflurane (and isoflurane and fentanyl–nitrous oxide) reduced EEG frequency, which relates to slight suppression of CMR.^{17 18} Increasing the concentration of desflurane to 1.5 MAC induced EEG burst suppression which probably relates to near maximal depression of functional CMR. Based on the differences in neuronal activity, 1.5 MAC of desflurane was expected to result in better neurological outcome compared with anaesthetic states with less functional neuronal suppression (i.e. fentanyl–nitrous oxide or 1.0 MAC of volatile anaesthetic). However, while the volatile anaesthetics improved neurological outcome compared with fentanyl–nitrous oxide, there was no difference in the extent of neuronal protection (which was near maximal), regardless of the volatile anaesthetic concentration. This observation is consistent with other studies which failed to demonstrate a relationship between reduction in CMR by anaesthetics and

improved outcome or reduced infarct size. For example, despite comparable depression of CMR (EEG burst suppression) in a rat model of incomplete hemispheric ischaemia, neurological outcome was better with 2.0 MAC of isoflurane compared with high-dose methohexital.¹⁴ In the same ischaemia model, isoflurane suppressed CMR more than halothane, but there was no difference in neuroprotective effects.¹ High concentrations of propofol (1.0–1.5 mg kg⁻¹ min⁻¹) reduced CMR by 50% while halothane at a concentration of 1.0% produced only modest changes in CMR. However, both anaesthetics improved neurological outcome after cerebral ischaemia to a similar extent.¹² In support of this, increasing doses of pentobarbital did not reduce infarct volume further despite a dose-dependent reduction in CMR in a rat model of focal ischaemia.¹⁵ In summary, the lack of neuroprotection by suppression of CMR suggests that other factors appear to be important in the improved outcome produced by anaesthetic agents.^{15 16}

Catecholamines modulate NMDA receptors and thereby affect neuroexcitation.¹⁹ This may be related to potentiation of L-type Ca²⁺ channel conductances which in turn increase NMDA receptor-induced currents.²⁰ It is possible that the concentrations of central and circulating catecholamines affect neurological outcome after cerebral ischaemia. This is consistent with studies in this and other experimental preparations showing substantial neuronal protection with attenuated central sympathetic discharge. During ischaemia, there was an 18-fold increase in norepinephrine and a 500-fold increase in dopamine in cerebral tissue,^{21 22} concentrations which have been shown to have adverse effects on neuronal tissue and biochemical recovery after an ischaemic insult.^{6 22 23} Anaesthetics reduce plasma and central concentrations of norepinephrine and dopamine^{7 24} and it is possible that this effect relates to improved neurological outcome in this study. In rats, ganglionic block before the onset of cerebral ischaemia reduced neurological deficit and histopathological damage from incomplete cerebral ischaemia.²⁵ This effect was partially reversible by infusion of catecholamines. In support of this, administration of the α_2 -adrenoreceptor agonists clonidine and dexmedetomidine reduced sympathetic activity during ischaemia and produced a dose-dependent improvement in neurological outcome in different models.^{26–28} This effect was reversed by the α_2 -adrenoreceptor antagonist atipamezole. As dexmedetomidine does not affect CMR but decreases CBF, the neurological protection seen with this agent is unlikely to be related to a mechanism which involves balancing CMR and CBF. In our study, the increase in plasma catecholamines was attenuated by isoflurane and desflurane, regardless of the inhaled concentration, compared with animals anaesthetized with fentanyl–nitrous oxide and neurological outcome was related to the change in plasma catecholamines. These results support the hypothesis that central and peripheral sympathetic activity mediate neurological outcome after incomplete cerebral ischaemia.

It is also possible that suppression of catecholamine

release occurs secondary to a reduction in presynaptic sodium channel currents in addition to NMDA and kainate receptor activity.²⁹ *In vitro* studies in cerebrocortical synaptosomes, cortical brain slices and CA1 neurones have shown that exposure to volatile anaesthetics decreases glutamate release, glutamate-mediated synaptic transmission and inhibits Ca^{2+} influx.^{30–32} This is consistent with the results in rats subjected to transient near complete forebrain ischaemia, where isoflurane decreased ischaemia-induced glutamate release compared with fentanyl–nitrous oxide anaesthetized controls.⁸ Although glutamate pathways were not studied during our experiments, it is possible that suppression of glutamate turnover produced improved outcome with isoflurane and desflurane.

Changes of physiological variables, including brain temperature, critically influence neurological outcome.³³ In our study, pericranial temperature was maintained at 37.0°C and arterial blood-gas partial pressures and arterial pH were controlled before, during and after ischaemia. In animals anaesthetized with volatile anaesthetics, plasma concentrations of glucose increased before and after cerebral ischaemia compared with animals anaesthetized with fentanyl–nitrous oxide. Although increased plasma glucose concentrations worsen neurological outcome in this and other models,³⁴ this did not reverse the neuroprotective effects of isoflurane and desflurane in our study.

In summary, isoflurane and desflurane improved neurological outcome after incomplete cerebral ischaemia in rats compared with animals anaesthetized with fentanyl–nitrous oxide. This effect was independent of the concentration of volatile anaesthetic and neuronal activity. However, neurological outcome was related to plasma concentrations of catecholamines, which were suppressed by isoflurane and desflurane, but not by fentanyl–nitrous oxide. Although decreased circulating catecholamines and improved neurological outcome may be coincidental, these data suggest that the extent of (peripheral) sympathetic discharge, rather than suppression of CMR, could be associated with neuronal protection produced by volatile anaesthetics.

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