Adrenergic antagonist inhibits cerebral cortical oxygen delivery after severe haemodilution in rats

G. M. T. Hare\(^1\)*, J. M. A. Worrall\(^1\), A. J. Baker\(^1\), E. Liu\(^1\), N. Sikich\(^1\) and C. D. Mazer\(^1\)

\(^1\)Department of Anaesthesia and the Cara Phelan Centre for Trauma Research, University of Toronto, St Michael’s Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada. \(^2\)Department of Physiology, University of Toronto, 1 King’s College Circle, Toronto, Ontario, M5S 1A8, Canada

*Corresponding author: Department of Anaesthesia and Physiology, University of Toronto, St Michael’s Hospital, 30 Bond Street, Toronto, ON M5B 1W8, Canada. E-mail: hareg@smh.toronto.on.ca

**Background.** Haemodilution has been associated with neurological morbidity in surgical patients. This study tests the hypothesis that inhibition of cerebral vasodilatation by systemic \(\beta_2\) adrenergic blockade would impair cerebral oxygen delivery leading to tissue hypoxia in severely haemodiluted rats.

**Methods.** Under general anaesthesia, cerebral tissue probes were placed to measure temperature, regional cerebral blood flow (rCBF) and tissue oxygen tension \(\left(\text{P}_{\text{btO}}\right)\) in the parietal cerebral cortex or hippocampus. Baseline measurements were established before and after systemic administration of either a \(\beta_2\) antagonist (10 mg kg\(^{-1}\) i.v., ICI 118, 551) or saline vehicle. Acute haemodilution was then performed by simultaneously exchanging 50% of the estimated blood volume (30 ml kg\(^{-1}\)) with pentastarch. Arterial blood gases (ABGs), haemoglobin concentration (co-oximetry), mean arterial blood pressure (MAP) and heart rate (HR) were also measured. Data were analysed using a two-way ANOVA and post hoc Tukey’s test [mean (SD)].

**Results.** Haemodilution reduced the haemoglobin concentration comparably in all groups [71 (9) g litre\(^{-1}\)]. There were no differences in ABGs, co-oximetry, HR and MAP measurements between control and \(\beta_2\) blocked rats, either before or 60 min after drug or vehicle administration. In rats treated with the \(\beta_2\) antagonist there was a significant reduction in parietal cerebral cortical temperature, regional blood flow and tissue oxygen tension, relative to control rats, 60 min after haemodilution \((P<0.05\) for each). These differences were not observed when probes were placed in the hippocampus.

**Conclusion.** Systemic \(\beta_2\) adrenergic blockade inhibited the compensatory increase in parietal cerebral cortical oxygen delivery after haemodilution thereby reducing cerebral cortical tissue oxygen tension.

**Keywords:** \(\beta_2\) adrenergic blockade; cerebral blood flow; cerebral tissue oxygen tension; cerebral hypoxia; haemodilution

Accepted for publication: June 19, 2006

Acute haemodilution has been associated with cognitive and neurophysiological dysfunction in healthy volunteers\(^1\) and increased neurological injury and mortality in perioperative patients by currently undefined mechanisms.\(^1-6\) Experimental evidence suggests that haemodilution may augment cerebral injury by limiting cerebral tissue oxygen delivery.\(^7\) However, evidence of cerebral tissue hypoxia after severe haemodilution has been difficult to demonstrate,\(^8\)\(^9\) possibly because of the compensatory increase in cerebral blood flow (CBF). The well-characterized increase in CBF after haemodilution is proportional to the reduction in haematocrit and occurs by passive changes in blood rheology and active cerebral vasodilatation.\(^10\)\(^-12\) However, the mechanism by which active cerebral vasodilatation occurs, or its physiological significance, have not been fully defined.

The cerebral vasculature is richly supplied by a variety of different perivascular neurons which release vasodilating...
neurotransmitters including nitric oxide (NO). Several studies have suggested that perivascular NO-producing neurons play a significant role in regulating CBF in response to a variety of physiological and pharmacological stimuli. Experimental evidence suggests that NO released from perivascular cerebral neurons is regulated by stimulation of pre-synaptic β2 adrenergic receptors. Stimulation of these β2 adrenergic receptors releases NO in the region of cerebral blood vessels resulting in cerebral vasodilatation and a regulated increase in CBF. The current study tests the hypothesis that β2 adrenergic mediated cerebral vasodilatation maintains CBF and oxygen delivery after acute haemodilution in rats. Results suggest that systemic β2 adrenergic blockade attenuated the increase in cerebral cortical oxygen delivery which occurs after severe haemodilution, resulting in a reduction in cerebral tissue oxygen tension.

Materials and methods

Animal model

All animal protocols were approved by the Animal Care and Use Committee at St Michael’s Hospital in accordance with the requirements of the Canadian Council on Animal Care. Anaesthesia was induced in male Sprague–Dawley rats (Charles River, St Constant, PQ, Canada) with isoflurane 3–4% in 100% oxygen in an induction chamber and maintained with isoflurane 1–2% (Abbott, St Laurent, PQ, Canada) in 50% oxygen administered via nose cone. After tracheotomy, ventilation was maintained with a pressure-controlled ventilator (Kent Scientific, Litchfield, CT, USA). Cannulation of the right tail vein and tail artery (Angiocath 24G, BD Medical, Oakville ON, Canada) was performed to achieve vascular access for direct measurement of mean arterial blood pressure (MAP) and arterial blood gases (ABGs). After completion of haemodilution, physiological measurements were recorded for an additional 60 min. The total duration of the experiment was 120 min. Brain temperature, brain tissue oxygen tension (PBrO2), CBF, brain temperature, MAP and heart rate (HR) were recorded with a computerized data acquisition system (DASYLab 5.6, Kent Scientific, Litchfield, CT, USA). Animals were sacrificed by anaesthetic overdose (ketamine 100 mg i.v.; Parke-Davis, Toronto, ON, Canada).

Experimental protocol

Two groups of animals were studied to determine the physiological effects of β2 adrenergic antagonism on either hippocampal or parietal cerebral cortical oxygen delivery. Within each group, animals were divided into two arms: the control arm received saline while the experimental arm received the β2 antagonist. In the hippocampal group, the cerebral probe was placed 3–4 mm past the dura into the region of the hippocampus in both control (n=7) and β2 antagonist arms (n=6). In the cerebral cortical group, the probe was placed 1–2 mm past the dura into the region of the parietal cerebral cortex in both control (n=9) and β2 antagonist arms (n=10). These two groups are subsequently referred to as the hippocampal and cerebral cortical groups. Each group contains a saline control and β2 antagonist arm. Rats were randomly assigned to each of the four arms until n=6 successful cerebral tissue oxygen tension measurements were obtained for each arm. Cerebral tissue oxygen tension measurements were excluded if baseline tissue oxygen tension values were below 5 torr. Cerebral tissue oxygen tension measurements were more difficult to obtain in the cerebral cortical group. Therefore, a larger number of rats were required in each arm of this group.

In all arms, an initial 20 min baseline was established (Baseline #1). At 20 min, either the β2 adrenergic antagonist (10 mg kg\(^{-1}\) i.v. in 1 ml saline, ICI 118,551, (±)-1-[2,3-(dihydro-7-methyl-1H-inden-4-yl)oxy]-3-[(1-methylethyl)amino]-2-butanol) hydrochloride) (Biomol Int. obtained from Cedarlane Laboratories Ltd, Hornby, ON) or saline (1 ml) was administered slowly over 10 min. Previous experimental studies demonstrate that the β2 antagonist ICI 118,551 is capable of crossing the blood–brain barrier. After β2 antagonist or saline administration, a second 20 min baseline was established (Baseline #2). All groups were then haemodiluted by simultaneously exchanging 30 ml kg\(^{-1}\) of arterial blood (50% of estimated total blood volume). Blood was withdrawn from the tail artery and replaced with an equivalent volume of warm pentastarch (37°C) via the tail vein (Pentaspan; Bristol-Myers Squibb Canada Co., St Laurent, PQ, Canada). Volume exchange was performed over 10 min using a programmable ‘push-pull’ pump (PHD 2000; Harvard Apparatus, St Laurent, PQ, Canada). After completion of haemodilution, physiological measurements were recorded for an additional 60 min. The total duration of the experiment was 120 min. Brain temperature, brain tissue oxygen tension (PBrO2), CBF, brain temperature, MAP and heart rate (HR) were recorded with a computerized data acquisition system (DASYLab 5.6, Kent Scientific, Litchfield, CT, USA). Animals were sacrificed by anaesthetic overdose (ketamine 100 mg i.v.; Parke-Davis, Toronto, ON, Canada).

Statistical analysis

Data from both arms of the hippocampal or cerebral cortical groups were analysed by two-way ANOVA for
each individual parameter (Sigma Stat Version 2.03S; Chicago, IL, USA). ABG and co-oximetry data were assessed before and after haemodilution (10 and 60 min). Other physiological measurements were assessed at three individual time points including the initial baseline (Baseline #1, 10 min), 10 min after saline or \( \beta_2 \) antagonist administration (Baseline #2, 40 min) and after haemodilution (Haemodilution, 100 min). Assessments were made for any time, arm or interaction effect for each measured parameter. A post hoc Tukey’s test was utilized for post hoc pair-wise comparisons when a significant interaction effect was observed. Statistical significance was assessed at \( P<0.05 \). Data were presented as mean (SD). Laser Doppler flow values were normalized to the first baseline and reported as changes relative to Baseline #1 for each animal.

Results

Co-oximetry and arterial blood gas analysis
At baseline, there were no significant differences between any co-oximetry or ABG measurement between the control and \( \beta_2 \) antagonist arms of the hippocampal or cerebral cortical groups. The baseline haemoglobin concentrations were near 125 \( \text{g litre}^{-1} \) and blood oxygen contents were near 7.5 \( \text{mmol litre}^{-1} \) for all arms (Table 1). After haemodilution, there was a significant reduction in haemoglobin concentration (63–71 \( \text{g litre}^{-1} \)) and estimated blood oxygen content (3.7–4.2 \( \text{mmol litre}^{-1} \)) compared with baseline for all arms (Table 1, \( P<0.001 \)). There was also a small but consistent increase in methaemoglobin concentration by \( \sim 0.3\% \) in all arms after haemodilution (Table 1, \( P<0.001 \)). There were no other significant differences in any other parameter after haemodilution (Table 1).

Haemodynamic and cerebral measurements
Heart rate
Initial baseline HRs (Baseline #1) were not statistically different between control and \( \beta_2 \) antagonist arms for either hippocampal or cerebral cortical groups (Fig. 1). After injection of the \( \beta_2 \) antagonist, the HR tended to be decreased in the \( \beta_2 \) antagonist arm of both hippocampal and cerebral cortical groups, relative to control arms. After haemodilution, there was an increase in HR in both arms of the hippocampal and cerebral cortical groups, relative to baseline (Fig. 1, \( P<0.015 \) and \( P<0.001 \), respectively). However, no significant interaction effect was observed for either group (\( P=0.221 \) and \( P=0.136 \), respectively).

Mean arterial pressure
At Baseline #1 (10 min), Baseline #2 (40 min) and after haemodilution (100 min) there were no differences in mean arterial pressure (MAP) between the control and \( \beta_2 \) antagonist arms in either the hippocampal or cerebral cortical groups (Fig. 1, \( P=0.234 \) and \( P=0.106 \), respectively). Upon administration of the \( \beta_2 \) antagonist, there was a transient decrease in MAP during drug administration (data not shown). The MAP then quickly returned to values near to the initial baseline (Fig. 1, 40 min). In the cerebral cortical group, there was a slight increase in MAP in both arms at 40 and 100 min, relative to Baseline #1 (\( P<0.05 \)). This effect was not observed in the hippocampal group. No significant interaction effect was observed for the control and \( \beta_2 \) antagonist arms of either the hippocampal or cerebral cortical groups.

Cerebral temperature
The initial baseline hippocampal and cerebral cortical temperatures remained near 33–34°C in all study arms. In the hippocampal group, there was a significant time effect, with a tendency for temperature to be increased in both saline control and \( \beta_2 \) antagonist arms at 100 min after haemodilution (Fig. 2, \( P=0.047 \)). No significant group or interaction effects were observed. In the cerebral cortical group, there was a significant time (\( P<0.001 \)), arm (\( P=0.034 \)) and interaction effect (\( P=0.027 \)) when comparing the \( \beta_2 \) antagonist and saline control arms. Post hoc analysis demonstrates that the cerebral cortical temperature was significantly lower in the \( \beta_2 \) antagonist arm, relative to the saline control group, after haemodilution at 100 min (Fig. 3, \( P<0.05 \)).

Table 1 Co-oximetry and arterial blood gases before and after haemodilution. *\( P<0.001 \) vs corresponding baseline measurement

<table>
<thead>
<tr>
<th>Group</th>
<th>Haemoglobin concentration (g litre(^{-1}))</th>
<th>% Saturation (%)</th>
<th>Methaemoglobin (mmol litre(^{-1}))</th>
<th>( \text{O}_2 ) content (mmol litre(^{-1}))</th>
<th>pH</th>
<th>( \text{PaO}_2 ) (torr)</th>
<th>( \text{PaCO}_2 ) (torr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (time=10 min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampal group control arm</td>
<td>129 (8)</td>
<td>99.4 (0.8)</td>
<td>1.0 (0.1)</td>
<td>7.7 (0.5)</td>
<td>7.39 (0.05)</td>
<td>39.9 (3.7)</td>
<td>134.1 (14.3)</td>
</tr>
<tr>
<td>Hippocampal group ( \beta_2 ) antagonist arm</td>
<td>127 (9)</td>
<td>99.5 (1.1)</td>
<td>1.1 (0.1)</td>
<td>7.4 (0.7)</td>
<td>7.44 (0.07)</td>
<td>40.6 (19.3)</td>
<td>155.6 (52.6)</td>
</tr>
<tr>
<td>Cerebral cortical group control arm</td>
<td>127 (11)</td>
<td>99.7 (0.6)</td>
<td>1.1 (0.1)</td>
<td>7.6 (0.7)</td>
<td>7.42 (0.07)</td>
<td>36.1 (7.5)</td>
<td>156.6 (41.2)</td>
</tr>
<tr>
<td>Cerebral cortical group ( \beta_2 ) antagonist arm</td>
<td>125 (8)</td>
<td>99.7 (0.6)</td>
<td>1.1 (0.1)</td>
<td>7.5 (0.5)</td>
<td>7.40 (0.05)</td>
<td>38.7 (7.2)</td>
<td>156.2 (38.3)</td>
</tr>
<tr>
<td>Post-haemodilution (time=60 min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampal group control arm</td>
<td>65 (5)*</td>
<td>99.9 (0.2)</td>
<td>1.4 (0.1)*</td>
<td>3.9 (0.3)*</td>
<td>7.44 (0.03)</td>
<td>37.3 (2.9)</td>
<td>145.5 (48.3)</td>
</tr>
<tr>
<td>Hippocampal group ( \beta_2 ) antagonist arm</td>
<td>70 (6)*</td>
<td>98.8 (1.5)</td>
<td>1.4 (0.2)*</td>
<td>4.1 (0.3)*</td>
<td>7.34 (0.09)</td>
<td>36.3 (14.5)</td>
<td>139.8 (74.8)</td>
</tr>
<tr>
<td>Cerebral cortical group control arm</td>
<td>63 (3)*</td>
<td>99.5 (1.6)</td>
<td>1.5 (0.2)*</td>
<td>3.7 (0.2)*</td>
<td>7.38 (0.06)</td>
<td>38.9 (7.8)</td>
<td>147.5 (39.9)</td>
</tr>
<tr>
<td>Cerebral cortical group ( \beta_2 ) antagonist arm</td>
<td>71 (9)*</td>
<td>99.9 (0.4)</td>
<td>1.4 (0.2)*</td>
<td>4.2 (0.5)*</td>
<td>7.41 (0.05)</td>
<td>39.2 (6.6)</td>
<td>175.0 (32.5)</td>
</tr>
</tbody>
</table>
Cerebral tissue oxygen tension ($P_{BrO_2}$)

There was no significant change in hippocampal $P_{BrO_2}$ values between arms or over time throughout the duration of the experiment (Fig. 2). Baseline cerebral cortical $P_{BrO_2}$ [13.43 (7.49) torr] tended to be below that measured in the hippocampus [20.28 (2.20) torr]. However, there was no difference between baseline measurements of cerebral cortical $P_{BrO_2}$ in saline control or $\beta_2$ antagonist arms, either before (Baseline #1) or after $\beta_2$ antagonist administration (Baseline #2) (Fig. 3). No significant time ($P=0.081$) or arm effects ($P=0.061$) were observed for cerebral cortical $P_{BrO_2}$ measurements. However, a significant interaction effect was observed ($P=0.004$) demonstrating that cerebral cortical tissue oxygen tension was reduced in the $\beta_2$ antagonist arm [7.2 (2.0) torr] relative to the control arm [16.3 (6.4) torr] after haemodilution at 100 min (Fig. 3, $P<0.05$).

Normalized regional cerebral blood flow

In both the hippocampal and cerebral cortical groups, the regional cerebral blood flow (rCBF) remained stable over the initial baseline (Baseline #1) and after administration of $\beta_2$ antagonist or saline (Baseline #2) (Figs 2 and 3). In the hippocampal group, haemodilution resulted in a significant increase in rCBF in both $\beta_2$ antagonist and vehicle arms (Fig. 2, $P<0.001$). However, there was no difference between the control and $\beta_2$ antagonist arms within the hippocampal group at any time (Fig. 2, $P=0.256$). In contrast, significant time ($P<0.001$), arm ($P=0.010$) and interaction effects ($P<0.001$) were observed when comparing control and experimental arms in the cerebral cortical group. Post hoc analysis demonstrated that the relative cerebral cortical blood flow was lower in the $\beta_2$ antagonist arm [1.4 (0.2)] relative to the saline control arm [1.7 (0.2)], after haemodilution at 100 min (Fig. 3, $P<0.05$).

Discussion

The present study supports the hypothesis that $\beta_2$ adrenergic antagonism impairs parietal cerebral cortical oxygen delivery after acute haemodilution. In the $\beta_2$ antagonist treatment arm of the cerebral cortical group, cerebral temperature, tissue oxygen tension and rCBF were all significantly reduced relative to the control arm after haemodilution. These data suggest that the regional cerebral cortical oxygen delivery is maintained by mechanisms which rely upon activation of $\beta_2$ adrenoreceptors. Previous haemodilution studies have demonstrated that cerebral cortical oxygen tension was maintained at similar or lower haemoglobin concentrations.
concentrations, in part because of a regulated increase in CBF.8 9 Our data demonstrate that inhibition of cerebral vasodilatation results in reduced cerebral oxygen delivery under similar conditions. Therefore, β2 adrenoreceptor mediated cerebral vasodilatation likely represents an important regulatory mechanism which acts to maintain adequate cerebral tissue oxygen tension within the cerebral cortex after acute haemodilution.

Interestingly, no effect of β2 antagonism was observed in the region of the hippocampus. This suggests that β2 mediated regulation of CBF may be restricted to specific brain regions. Indeed, regional differences in the CBF response to haemodilution have been reported.11 After severe haemodilution, a much larger absolute increase in blood flow was observed to the visual, auditory, parietal, sensory motor and frontal cortex, relative to that measured in the hippocampus.11 These regional differences in CBF response may explain why we observed a significant effect of β2 blockade in the parietal cerebral cortex, but not in the hippocampus.

**Fig 2** Hippocampal temperature tended to increase after haemodilution (H) in the saline control arm. However, no significant differences in hippocampal temperature, tissue oxygen tension or regional normalized cerebral blood flow were observed between groups before or after administration of the β2 adrenergic antagonist (ICI 118,551) or after haemodilution (H).

**Fig 3** There was no significant difference in parietal cerebral cortical temperature, tissue oxygen tension or regional cerebral blood flow (rCBF) either before (Baseline #1) or after administration of β2 adrenergic antagonist (ICI 118,551) (Baseline #2). After haemodilution (H), the cerebral cortical temperature, tissue oxygen tension and rCBF were all reduced in the β2 adrenergic antagonist arm, relative to controls. *P<0.05, post hoc Tukey’s test between arms.
The systemic effect of ICI 118,551 on HR was similar in both groups of rats which received the drug. The HR in treated animals tended to be lower than controls, after ICI 118,551 administration. This trend was maintained throughout the duration of the experiment and is consistent with the observation that HR is under \( \beta_2 \) adrenergic regulation.\textsuperscript{21 22} After haemodilution, the HR increased comparably over time in the treatment and control arms of both groups, suggesting that \( \beta_2 \) blockade did not completely inhibit the chronotropic response to haemodilution.

There were no significant differences in MAP when comparing the \( \beta_2 \) antagonist and control arms for either hippocampal or cerebral cortical groups. However, there was a slight reduction in MAP (13\%) in both \( \beta_2 \) antagonist treatment arms at 80 min after haemodilution. This could reflect a reduction in cardiac output in the treatment arms of both hippocampal and cerebral cortical groups. Although cardiac output was not measured in the study, previously published experimental studies did not demonstrate a significant impairment in the increase in cardiac output after haemodilution in animals treated with combined \( \beta_1 \) and \( \beta_2 \) antagonists.\textsuperscript{23 24} Furthermore, if a reduction in cardiac output was responsible for the observed changes in cerebral cortical blood flow and tissue oxygen tension, then a similar effect should have been observed within the \( \beta_2 \) antagonist treatment arm of the hippocampal group. Such a generalized effect was not observed suggesting that \( \beta_2 \) adrenergic blockade had a specific effect on the cerebral cortical vasculature. Therefore, systemic haemodynamic factors were not likely responsible for the observed region specific effect of \( \beta_2 \) blockade on parietal cerebral cortical blood flow and oxygen delivery.

Physiological studies have demonstrated that \( \beta_2 \) adrenoreceptors may preferentially mediate cerebral vasodilatation in order to re-direct blood flow to the brain in times of physiological stress.\textsuperscript{25 26} Severe haemodilution may represent such a stress. The well-characterized increase in CBF observed during acute haemodilution has been attributed to passive changes in blood rheology and active cerebral vasodilatation.\textsuperscript{10 11} However, the mechanisms by which cerebral vasodilatation occur have not been fully characterized. The current study has demonstrated that \( \beta_2 \) adrenoreceptors may participate in the regulation of cerebral cortical vasodilatation during severe haemodilution.

Previous experimental studies have provided evidence that the \( \beta_2 \) antagonist ICI 118,551 is capable of crossing the blood–brain barrier and can inhibit the regulated increase in CBF in response to nicotine administration.\textsuperscript{14 19 20} Therefore, potential sites of action of the \( \beta_2 \) adrenergic antagonist in the study include the vascular smooth muscle,\textsuperscript{26 27} vascular endothelium,\textsuperscript{28} cerebral neurons,\textsuperscript{17 29} and astrocytes.\textsuperscript{30} Interestingly, NO can mediate cerebral vasodilation by both endothelial dependent and independent mechanisms.\textsuperscript{14 17 31} Endothelial dependent mechanisms include \( \beta_2 \) adrenoreceptor mediated up-regulation of endothelial nitric oxide synthase (eNOS) expression.\textsuperscript{31} Conversely, endothelial independent mechanisms may regulate CBF by \( \beta_2 \) adrenergic mediated release of NO from perivascular cerebral neurons.\textsuperscript{14 17} Additional experimental studies support the hypothesis that increased cerebral cortical neuronal nitric oxide synthase (nNOS) activity may mediate increases in CBF during haemodilution.\textsuperscript{10 32}

Assessment of relative rCBF utilizing laser Doppler flow probes does not provide an absolute measurement of rCBF. However, laser Doppler has been reported to accurately reflect relative changes in CBF after haemodilution.\textsuperscript{9} Therefore, assessment of relative changes of CBF is valid in this model. Our measurements of hippocampal and parietal cerebral cortical tissue oxygen tension demonstrate a higher tissue oxygen tension in the hippocampus. These measurements are consistent with previously published values using similar methodology and may reflect regional heterogeneity in cerebral tissue oxygen tension and metabolism.\textsuperscript{9 33 34}

The baseline cerebral cortical temperatures tended to be lower than those observed in the hippocampus, possibly because of the closer proximity of the cerebral cortex to the atmosphere. However, no differences were observed between the control and \( \beta_2 \) antagonist arms of the cerebral cortical group at baseline. Immediately after haemodilution with warm pentastarch (37°C), there was a significant increase in brain temperature in the control arms of both the hippocampal and cerebral cortical groups. The maximal temperature was achieved in both groups at about 80 min. The subsequent reduction in temperature may represent redistribution of heat of the infused pentastarch. In the \( \beta_2 \) antagonist arm of the hippocampal group, the increase in brain temperature was blunted but not prevented. However, no increase in brain temperature was observed in the \( \beta_2 \) antagonist arm of the cerebral cortical group. This supports the hypothesis that cerebral cortical vasodilatation was prevented by specific \( \beta_2 \) adrenergic blockade.

In conclusion, our data support the hypothesis that active \( \beta_2 \) mediated cerebral vasodilatation is important in regulating cerebral cortical oxygen delivery in anaesthetized rats after acute haemodilution. Further characterization of the physiological regulation of CBF during haemodilution may help to optimize the management of surgical patients who experience severe acute haemodilution.

Acknowledgements

The authors acknowledge the excellent technical support provided by Rong Qu and Jianli Wang. Preliminary results have been presented at the International Anaesthesia Research Foundation meeting in Honolulu (2004). G.M.T.H. is the recipient of the Bristol-Myers Squibb-Canadian Anesthesiologists’ Society Career Scientist Award. Research support was provided by the Canadian Anesthesiologists’ Society, the Physicians’ Services Incorporated Foundation and the St Michael’s Hospital Department of Anaesthesia.

References

9 Shen H, Greene AS, Stein EA, Hudetz AG. Functional cerebral hyperemia is unaffected by isovolemic haemodilution. Anesthesiology 2002; 96: 142–7
31 Ferro A, Coash M, Yamamoto T, Rob J, Ji Y, Queen L. Nitric oxide-dependent beta2-adrenergic dilatation of rat aorta is mediated through activation of both protein kinase A and Akt. Br J Pharmacol 2004; 143: 397–403
34 Pianadosi CA, Zhang J, Demchenko IT. Production of hydroxyl radical in the hippocampus after CO hypoxia or hypoxic hypoxia in the rat. Free Radic Biol Med 1997; 22: 725–32