Effects of hypoxia and isoflurane on liver blood flow: the role of adenosine

S. H. Cray, M. W. Crawford, N. Khayyam and F. J. L. Carmichael

1Department of Anaesthesia, The Hospital for Sick Children and 2Department of Pharmacology, University of Toronto, 555 University Avenue, Toronto, Ontario, Canada

3Present address: Birmingham Children’s Hospital NHS Trust, Steelhouse Lane, Birmingham B4 6NL, UK

*Corresponding author

We investigated the role of endogenous adenosine in mediating the effects of hypoxia and isoflurane on portal tributary blood flow (PTBF) and hepatic arterial blood flow (HABF) in rats. Liver blood flows were determined using radiolabelled microspheres. Hypoxia resulting from the exposure of rats to an atmosphere containing 15% oxygen for 30 min decreased PTBF (23%) (P<0.05) and cardiac index (15%) (P<0.05), and increased HABF (78%) (P<0.05). Isoflurane (1.4 vol%) increased HABF in both normoxic and hypoxic conditions but did not affect PTBF. The adenosine receptor antagonist 8-phenyltheophylline attenuated the hypoxia-induced increase in HABF but did not affect that resulting from the administration of isoflurane. In conclusion, in contrast to the increase in HABF induced by hypoxia, that induced by isoflurane appears to be independent of endogenous adenosine.

Keywords: liver, blood flow; hypoxia; anaesthetics volatile, isoflurane; receptors, adenosine; rat

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It has been suggested that changes in portal tributary blood flow (PTBF) lead to reciprocal changes in hepatic arterial blood flow (HABF) thereby maintaining total liver blood flow. This response, termed the ‘hepatic arterial buffer response,’ is mediated in part through the action of locally produced adenosine. Published studies have reported that isoflurane increases HABF, an effect that has been attributed to preservation of the hepatic arterial buffer response. However, there are no direct data to substantiate this view.

We have previously reported that hypoxia decreases PTBF and increases HABF, a pattern of change that is consistent with the buffer response. In the present study, we investigated the effects of hypoxia, isoflurane and their combination on blood flows to the liver, and we examined the role of endogenous adenosine in the hypoxia- and isoflurane-induced changes in liver blood flows using the adenosine receptor antagonist 8-phenyltheophylline.

Methods and results

With institutional approval, 60 fasting male Sprague-Dawley rats (Charles River Breeding Laboratories, Quebec, Canada) weighing 260–320 g were anaesthetized with isoflurane. Polyethylene catheters were inserted into:

1. the left femoral artery for arterial pressure monitoring and reference sample withdrawal,
2. the right internal jugular vein for fluid or drug infusion, and
3. the left ventricle via the right carotid artery for injection of radiolabelled microspheres, as we have reported previously.

Animals breathed spontaneously in individual Plexiglas containers through which the inspired mixture was delivered at a rate of 0.2 mg kg⁻¹ min⁻¹ for 60 min or an equal volume of normal saline.

8-Phenyltheophylline was mixed in normal saline at a pH of 11.6 as described previously.

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were infused into the left ventricle over 20 s. A reference sample was drawn from the femoral artery at a rate of 0.6 ml min\(^{-1}\) starting 10 s before the microsphere infusion. The rats were killed and the liver, kidneys, spleen, stomach, small intestine, and large intestine were removed for determination of radioactivity (Nuclear Chicago, model 1185, Chicago, IL, USA). The mixing of microspheres in the circulation was considered adequate if there was less than a 15% difference in the left and right renal blood flows. Cardiac index, liver blood flows and vascular resistances were calculated using standard formulae.\(^4\) Arterial blood gases were determined in separate groups of rats given one of the four inspired gas mixtures. Data are expressed as mean (SD). Two-way ANOVA and the Student Newman–Keuls test were used to compare systemic haemodynamics and liver blood flows. Student’s t-test was used to compare arterial pH and blood gases. \(P<0.05\) was considered statistically significant.

In awake rats, hypoxia decreased PTBF by 23% \((P<0.05)\) but did not change pre-portal arterial pressure or PTBF.\(^6\) We have also shown that this dose of 8-phenyltheophylline completely antagonized the increase in HABF induced by hypoxia in awake rats, but did not affect that resulting from the administration of isoflurane. These data suggest that the hypoxia-induced increase in HABF is mediated in part by endogenous adenosine, whereas that produced by isoflurane is independent of adenosine and is presumably secondary to a direct vasodilator effect of isoflurane upon the hepatic artery. At the dose used in the present study, we have shown that 8-phenyltheophylline does not modify basal mean arterial pressure or PTBF.\(^6\) We have also shown that this increase in splanchnic blood flow induced by administration of adenosine in the rat.\(^6\) These studies support our present findings that a hepatic arterial buffer response to reduced PTBF occurs in the rat and that 8-phenyltheophylline can attenuate this response.

Radiolabelled microspheres were used to determine liver blood flows in the present study. This technique has been used extensively in studies of the splanchnic circulation and yields accurate estimates of cardiac output and liver blood flows.\(^7\) \(^8\) The number of microspheres used in the present study causes minimal haemodynamic disturbance while being sufficient to measure liver blood flows accurately.\(^7\) The validity of our absolute blood flow values is substantiated by previous work from this laboratory and others.\(^7\)

In the present study, rats breathed spontaneously in order to permit valid comparisons among the treatments and avoid the need for interventions such as basal anaesthesia and positive pressure ventilation that can reduce liver blood flow. Accordingly, the hypoxic and isoflurane-anaesthetized rats were mildly hypocapnic and hypercapnic, respectively. These changes in carbon dioxide tension, however, were small relative to those previously shown to influence the splanchnic circulation.\(^9\) \(^10\)

In conclusion, in contrast to the hypoxia-induced increase in HABF that induced by isoflurane appears to be independent of endogenous adenosine. The present results suggest that isoflurane enhances HABF in both normoxic and hypoxic conditions and may thereby confer a protective effect upon the liver.

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**Table 1** Systemic haemodynamics and liver blood flows and vascular resistances in awake and isoflurane-anaesthetized rats. Values are mean(\(\pm\)SD). \(\dagger P<0.05\) compared with awake 30% oxygen, \(\star P<0.05\) compared with isoflurane 30% oxygen, \(\ddagger P<0.05\) compared with corresponding value in awake rats, \(\sharp P<0.05\) compared with awake 15% oxygen+normal saline

<table>
<thead>
<tr>
<th></th>
<th>Awake 30% O(_2) (n=11)</th>
<th>15% Oxygen+saline (n=11)</th>
<th>Isoflurane (1 MAC) 30% Oxygen (n=8)</th>
<th>15% Oxygen+8-PT (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>104 (13)</td>
<td>85 (10)*</td>
<td>98 (15)</td>
<td>91 (10)</td>
</tr>
<tr>
<td>Cardiac index (ml min(^{-1}) kg(^{-1}))</td>
<td>256 (20)</td>
<td>217 (23)*</td>
<td>223 (17)*</td>
<td>239 (20)</td>
</tr>
<tr>
<td>Portal tributary blood flow (ml min(^{-1}) kg(^{-1}))</td>
<td>44.4 (8.4)</td>
<td>34.0 (7.0)*</td>
<td>31.9 (9.6)*</td>
<td>40.6 (10.1)</td>
</tr>
<tr>
<td>Hepatic arterial blood flow (ml min(^{-1}) kg(^{-1}))</td>
<td>11.1 (2.3)</td>
<td>19.8 (6.8)*</td>
<td>13.6 (4.6)</td>
<td>17.6 (9.1)*</td>
</tr>
<tr>
<td>Pre-portal vascular resistance (mm Hg ml(^{-1}) min(^{-1}))</td>
<td>2.4 (0.5)</td>
<td>2.5 (0.5)</td>
<td>3.0 (0.7)</td>
<td>2.1 (0.6)</td>
</tr>
<tr>
<td>Hepatic arterial vascular resistance (mm Hg ml(^{-1}) min(^{-1}))</td>
<td>9.3 (2.0)</td>
<td>4.4 (1.9)*</td>
<td>7.2 (2.3)*</td>
<td>4.9 (1.5)*</td>
</tr>
</tbody>
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Comment

We found that pre-treatment with the non-specific adenosine receptor antagonist 8-phenyltheophylline attenuated the increase in HABF induced by hypoxia in awake rats, but did not affect that resulting from the administration of isoflurane. These data suggest that the hypoxia-induced increase in HABF is mediated in part by endogenous adenosine, whereas that produced by isoflurane is independent of adenosine and is presumably secondary to a direct vasodilator effect of isoflurane upon the hepatic artery. At the dose used in the present study, we have shown that 8-phenyltheophylline does not modify basal mean arterial pressure or PTBF.\(^6\) We have also shown that this dose of 8-phenyltheophylline completely antagonized the increase in splanchnic blood flow induced by administration of adenosine in the rat.\(^6\) These studies support our present findings that a hepatic arterial buffer response to reduced PTBF occurs in the rat and that 8-phenyltheophylline can attenuate this response.

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References


