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The role of adenosine in the hyperaemic response of the hepatic artery to portal vein occlusion (the 'buffer response')

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1 Adenosine has been shown to be responsible for the hyperaemic response of the hepatic artery to portal vein occlusion (the hepatic arterial 'buffer response').

2 The effect of adenosine receptor blockade and of adenosine uptake inhibition on the hepatic arterial response to portal vein occlusion was investigated in three groups of anaesthetized dogs.

3 Venous return and arterial blood pressure were maintained during periods of portal occlusion by establishing a side-to-side portacaval shunt. Hepatic artery and portal vein blood flows were measured with electromagnetic flowmeters.

4 Hepatic arterial infusions of 8-phenyltheophylline ($500\,\mu g\,kg^{-1}\,min^{-1}$) and 3-isobutyl-1-methylxanthine ($75\,\mu g\,kg^{-1}\,min^{-1}$), doses sufficient to block the vasodilator response of the hepatic artery to exogenously applied adenosine, reduced the magnitude of the 'buffer response' by 50% and 75%, respectively.

5 Intravenous infusion of dipyridamole ($100\,\mu g\,kg^{-1}\,min^{-1}$), a dose sufficient to potentiate the vasodilator response of the hepatic artery to exogenously applied adenosine, had little effect on the 'buffer response'.

6 It is concluded that adenosine is an important, but not the sole, agent responsible for the hepatic arterial 'buffer response'.

Introduction

The compensatory hyperaemic response of the hepatic artery (HA) to portal vein (PV) occlusion (the hepatic arterial 'buffer response': Lautt, 1981) has been the subject of many investigations during the past 20 years, such as those by Kock *et al.* (1972), Lautt (1983) and Mathie & Blumgart (1983).

A putative mediator of the response has recently been identified in studies in the cat by Lautt and his colleagues (Lautt *et al.*, 1985), who have concluded that the 'buffer response is mediated entirely by local adenosine concentration' (Lautt & Legare, 1985). They demonstrated that the adenosine receptor antagonist 8-phenyltheophylline totally blocked, and that the adenosine uptake inhibitor dipyridamole potentiated, both the 'buffer response' and the HA vasodilatation induced by injected adenosine. Our own studies have previously shown that, in the dog, neither an intrinsic neurogenic phenomenon (Mathie *et al.*, 1980) nor an hepatic β-adrenoceptor mechanism is involved in the 'buffer response' (Alexander *et al.*, 1989).

The current investigation was carried out to determine the role of adenosine in the HA 'buffer response' in the dog, by use of the experimental model previously established in our laboratory (Mathie *et al.*, 1980; Mathie & Blumgart, 1983). A pharmacological approach has been adopted, employing two adenosine receptor antagonists and an adenosine uptake inhibitor, in three groups of animals. According to the widely accepted classification of Burnstock (1978), purine receptors comprise two distinct populations: P_1-purinoceptors (mediating responses to adenosine and adenosine 5'-monophosphate (AMP)) located on vascular smooth muscle, and P_2-purinoceptors (mediating responses to adenosine 5'-diphosphate (ADP) and adenosine 5'-triphosphate (ATP)) located on the endothelial cell membrane (Burnstock & Kennedy, 1986). We have used both 3-isobutyl-1-methylxanthine (IBMX) and 8-phenyltheophylline (8-PT) as P_1-purinoceptor antagonists, and the adenosine uptake inhibitor, dipyridamole (DPD), to potentiate the effects of adenosine. The magnitude of the 'buffer response' has been examined before and after administration of each of these agents.

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Methods

Experiments were carried out in a total of 14 greyhounds of either sex, weighing 22.2–32.3 kg (mean 27.8 kg). The animals were deprived of food but not water for 24 h before the operation. Anaesthesia was induced with thiopentone ($25\,mg\,kg^{-1}$) i.v. and maintained with pentobarbitone ($30\,mg\,kg^{-1}$) i.v. After endotracheal intubation, the dogs were ventilated with a 3:1 mixture of nitrous oxide and oxygen by a Starling pump. The minute volume and the inspired oxygen concentration were adjusted to maintain the Po_2 and Pco_2 at normal levels (approximately 100 mmHg (13.3 kPa) and 40 mmHg (5.3 kPa), respectively). The base deficit was maintained at $4\,mmol\,l^{-1}$ with sodium bicarbonate i.v. as required. Fluid balance was achieved by infusion of 150 mM sodium chloride i.v.; haematocrit remained above 40% throughout each experiment. Body temperature remained at 36–38°C, assisted when necessary by means of radiant heat lamps.

Operative procedures

The experimental model has been described in detail elsewhere (Mathie *et al.*, 1980; Mathie & Blumgart, 1983). After right femoral artery cannulation (for blood pressure measurement), a mid-line laparotomy was performed. A precalibrated electromagnetic flow probe (Statham) was applied to both the HA and the PV (3 mm and 6 mm diameter respectively). The HA probe was positioned about 2 cm from the coeliac axis while the PV probe was placed mid-way between the gastroduodenal and splenic veins (see illustration in Alexander *et al.*, 1989).

The gastroduodenal artery and vein were then ligated and cannulated, the former to allow injections into the HA and the latter for PV pressure measurement. Hepatic vein (HV) cannulation was achieved via the right external jugular vein, the location of the catheter tip being confirmed by direct palpation; the catheter was withdrawn about 5 mm from a 'wedged' position for 'free' HV pressure measurement.

A side-to-side mesocaval shunt was performed, with 5/0 silk suture, by the construction of an anastomosis between the inferior vena cava and the superior mesenteric vein, just below the entry of the splenic vein. After haemostasis had been achieved, the shunt was closed by means of a small bulldog clip placed along the suture line, thus restoring normal PV flow to the liver until the start of the experimental measurements.

Experimental protocol

The effect of PV flow interruption was investigated in all dogs approximately 1 h after the completion of the operative procedures. Measurements were made of the basal HA and PV blood flows and of the pressures in the femoral artery, PV and HV, before any alterations in blood flow. The PV was then cross-clamped just proximal to the flow probe, and the shunt immediately opened to divert PV blood into the vena cava. The PV occlusion was maintained for 5–10 min, at which time blood flow and pressure measurements were repeated. PV flow was then restored by re-closing the shunt with the bulldog clip after release of the cross-clamp on the PV. These manoeuvres were repeated in order to obtain duplicate information on the magnitude of the normal 'buffer response' for every animal; the value ascribed to each dog was the arithmetic mean of the two measurements, the second measurement showing, on average, a 1.7% greater response than the first (range: −25% to +37%).

Drug administration

The effect of intra-portally injected adenosine (Sigma, A-9251) was then investigated to establish the normal response of the HA circulation. Five doses in the range (50 ng–0.5 mg kg^{-1}) were employed. The peak of the HA hyperaemic response to adenosine injection was plotted against the dose given in each case.

One of 3 agents was then administered as follows: 3-isobutyl-1-methylxanthine (IBMX, Sigma I-5879; $n = 5$) was infused into the HA at a rate of 50–100 (mean 75) $\mu g\,kg^{-1}\,min^{-1}$; 8-phenyltheophylline (8-PT, Sigma P-2278; $n = 4$) was infused into the HA at 250–750 (mean 500) $\mu g\,kg^{-1}\,min^{-1}$; dipyridamole (DPD, Sigma D-9766; $n = 5$) was infused i.v. at 50–150 (mean 100) $\mu g\,kg^{-1}\,min^{-1}$, following a bolus i.v. injection of 400 $\mu g\,kg^{-1}$. In general, the rate of infusion of a drug was reduced from the higher to the lower value of the stated range during the course of an experiment.

After 20–30 min, the potency of the blockade or potentiation was established by the construction of a further dose-response curve to exogenously applied adenosine. Good repetition of responses to adenosine over a similar duration of experiment was confirmed in a pilot series of animals.

When maximal blockade or potentiation had been achieved, two further 'buffer responses' were then elicited over the subsequent 15–20 min, and the mean response compared with that of the control (normal) response. Repetition for 'buffer responses' after drug administration was similar to that in the normal situation (mean difference between first and second measurement: −3.6%; range: −17% to +14%), except for two dogs in the 8-PT series and for one dog in the IBMX series in which the second 'buffer response' was less than half the magnitude of the first; the 'buffer response' was completely eliminated in both measurements in another of the dogs given IBMX.

Calculations

Blood flows were recorded on the flowmeters in ml min^{-1} and subsequently recalculated in ml min^{-1} 100 g^{-1} by relating the readings to the wet weight of the liver, determined at the end of each experiment. Total liver blood flow was calculated by addition of the individual HA and PV flows.

The 'buffering capacity' of the HA was calculated as the increase in HA flow/decrease in PV flow, expressed in %.

Statistics and presentation of data

Student's paired t test was used to test the significance of differences in: (a) measured indices before and after PV occlusion; (b) measured indices due to drug administration alone; (c) the magnitude of responses either to adenosine injection or to PV occlusion before and after drug administration. All results are quoted as mean ± s.e.mean.

Results

Dose-response to adenosine

The changes in HA blood flow produced by intraportal injections of adenosine before and after IBMX, 8-PT or DPD are shown in Figure 1(a–c). Increasing doses of adenosine caused increasing dilatation of the HA up to the maximum dose

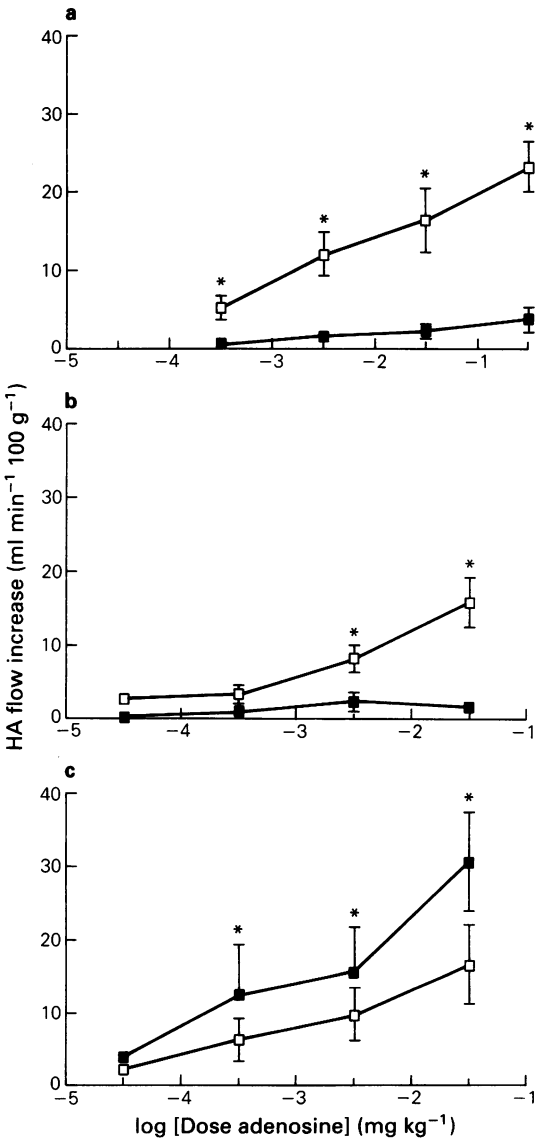

Figure 1 Hepatic arterial (HA) blood flow response to increasing doses of adenosine injected intraportally, before (□) and during (■) drug administration in 3 groups of dogs: (a) IBMX (3-isobutyl-1-methylxanthine); (b) 8-PT (8-phenyltheophylline); (c) DPD (dipyridamole). All values are mean and vertical lines represent s.e.mean. * Significant difference between responses before and during drug adminstration ($P < 0.05$).

injected; an ED_{50} for adenosine could therefore not be calculated. IBMX and 8-PT produced a similar degree of attenuation of the response ($P < 0.05$), while DPD produced a potentiation which was statistically significant at adenosine doses from 0.5–50 $\mu g\,kg^{-1}$ ($P < 0.05$).

Selection of the appropriate infusion rate for each of the three drugs proved somewhat difficult. In each case, the infusion rate often had to be altered by a factor of about 2 around the mean level quoted above, in order to achieve the desired effect on the response to injected adenosine, but with minimal detrimental effect on other haemodynamic indices: IBMX caused a decrease in arterial blood pressure; 8-PT tended to diminish PV blood flow; DPD reduced basal HA blood flow (see below).

Hepatic arterial 'buffer response'

The changes in the 'buffer response' induced by IBMX, 8-PT and DPD are illustrated in Figure 2. In the normal situation, PV occlusion caused HA blood flow to increase, on average over the three groups, by 19.6 ml min^{-1} 100 g^{-1}. Both IBMX and 8-PT reduced the magnitude of the 'buffer response' significantly, though 8-PT was noted to cause a less pronounced mean inhibition of the response (49%) than IBMX (71%). However, the inhibition was much more reproducible with 8-PT than with IBMX (coefficients of variation: 59% and 104% respectively). DPD produced little or no change in the magnitude of the response.

There was a statistically significant increase in HA flow during PV occlusion in all cases, both with and without drug administration, except during infusion of IBMX (see Table 1). Basal HA flow was not altered by either IBMX or 8-PT, but was decreased by DPD. PV flow was increased by IBMX, unaltered by DPD, and decreased (though not in a statistically significant manner) by 8-PT.

'Buffering capacity' was reduced by IBMX from 24.2 ± 4.2% to 6.4 ± 3.2% ($P < 0.05$). 8-PT also reduced 'buffering capacity', from 26.4 ± 5.8% to 18.4 ± 3.7%, but the difference was not statistically significant. DPD caused a non-significant reduction in 'buffering capacity', from 24.5 ± 6.2% to 20.9 ± 4.0%.

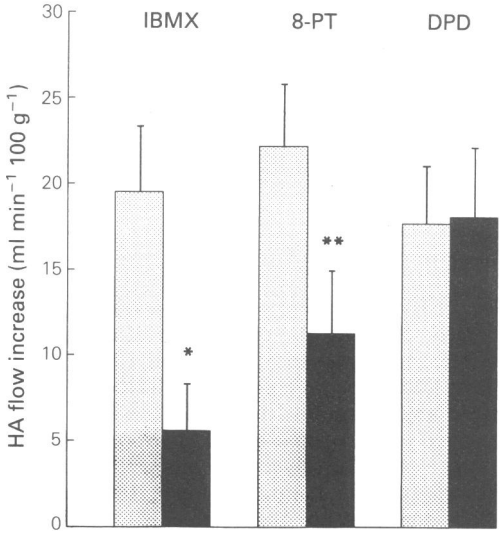

Figure 2 Hepatic arterial (HA) blood flow increase ('buffer response') before (stippled columns), and during (solid columns) drug administration in 3 groups of dogs: IBMX (3-isobutyl-1-methylxanthine); 8-PT (8-phenyltheophylline); DPD (dipyridamole). All values are mean and vertical lines represent s.e.mean. Significant differences between response before and during drug administration: * $P < 0.05$, ** $P < 0.01$.

Basal mean arterial blood pressure was significantly decreased by IBMX, but unchanged by either 8-PT or DPD (see Table 1). PV occlusion did not affect arterial pressure on any occasion. HV pressure was not changed by any procedure. Basal PV pressure was increased by approximately 1.0 mmHg by all 3 drugs, significantly in the cases of IBMX and DPD. The effects of PV occlusion on true pre-hepatic PV

Table 1 Haemodynamic indices before and during hepatic artery (HA) 'buffer response' to portal vein occlusion (PVO) in 3 groups of dogs

	Normal		*Drug*	
	Before PVO	*During PVO*	*Before PVO*	*During PVO*
(a) IBMX ($n = 5$)				
HA flow (ml min^{-1} 100 g^{-1})	35.5 ± 9.3	55.0* ± 11.4	36.2 ± 4.8	41.8 ± 4.4
PV flow (ml min^{-1} 100 g^{-1})	83.3 ± 12.4	0 ± 0	107.4‡ ± 12.4	0 ± 0
Total LBF (ml min^{-1} 100 g^{-1})	118.8 ± 17.0	55.0* ± 11.4	143.6‡ ± 15.1	41.8* ± 4.4
Blood pressure (mmHg)	122.6 ± 7.0	119.0 ± 9.6	68.0‡ ± 6.5	68.4 ± 6.0
PV pressure (mmHg)§	7.2 ± 1.2	(5.5)* ± (1.1)	8.1‡ ± 1.3	(5.0)* ± (1.0)
HV pressure (mmHg)	3.0 ± 1.1	3.1 ± 1.0	2.7 ± 1.0	2.8 ± 0.8
(b) 8-PT ($n = 4$)				
HA flow (ml min^{-1} 100 g^{-1})	31.7 ± 5.7	53.9* ± 5.8	27.6 ± 14.3	38.9* ± 17.1
PV flow (ml min^{-1} 100 g^{-1})	90.2 ± 13.4	0 ± 0	58.8 ± 7.1	0 ± 0
Total LBF (ml min^{-1} 100 g^{-1})	121.9 ± 13.4	53.9* ± 5.8	86.4 ± 20.5	38.9* ± 17.1
Blood pressure (mmHg)	152.0 ± 7.6	152.3 ± 8.6	159.3 ± 6.2	162.8 ± 6.2
PV pressure (mmHg)§	7.3 ± 0.5	(4.5) ± (0.3)	8.0 ± 0.3	(4.9)* ± (0.4)
HV pressure (mmHg)	2.7 ± 0.9	3.1 ± 0.9	1.9 ± 1.1	2.1 ± 1.1
(c) DPD ($n = 5$)				
HA flow (ml min^{-1} 100 g^{-1})	61.9 ± 13.1	79.6* ± 12.5	41.3‡ ± 12.6	59.4* ± 13.3
PV flow (ml min^{-1} 100 g^{-1})	77.7 ± 7.4	0 ± 0	85.4 ± 9.5	0 ± 0
Total LBF (ml min^{-1} 100 g^{-1})	139.6 ± 19.4	79.6* ± 12.5	126.7 ± 19.1	59.4* ± 13.3
Blood pressure (mmHg)	147.8 ± 12.5	146.8 ± 12.6	136.0 ± 9.2	133.5 ± 8.9
PV pressure (mmHg)§	7.6 ± 0.8	(5.8)* ± (0.8)	8.7‡ ± 0.9	(6.0)* ± (0.5)
HV pressure (mmHg)	3.1 ± 0.4	3.2 ± 0.4	3.0 ± 0.4	3.1 ± 0.3

PV: portal vein; LBF: liver blood flow; HV: hepatic vein. IBMX: 3-isobutyl-1-methylxanthine; 8-PT: 8-phenyltheophylline; DPD: dipyridamole.

* Significant difference from baseline value ('Normal, before PVO' or 'Drug, before PVO', as appropriate), $P < 0.05$.

‡ Significant difference from baseline value before drug administration ('Normal, before PVO'), $P < 0.05$.

§ PV pressure measurements during PV occlusion do not represent prehepatic pressure readings, due to the position of the recording catheter (see text).

All values are mean ± s.e.mean.

pressure could not be assessed, due to the absence of a recording catheter below the cross-clamp.

Discussion

The experimental model employed in this study has been used in a number of earlier investigations by the authors: it achieves complete PV occlusion in a repeatable manner without loss of systemic venous return or blood pressure (Mathie *et al.*, 1980; Mathie & Blumgart, 1983; 1987; Alexander *et al.*, 1989). The resultant HA 'buffer response' is highly reproducible both within and between individual animals, as demonstrated by observations in the current and in the previous experiments described by the authors.

The present experiments have demonstrated that blockade of adenosine receptors in the hepatic arterial circulation of the dog reduced, but did not eliminate, the HA 'buffer response' following PV occlusion. In addition, the adenosine uptake inhibitor dipyridamole (DPD) did not potentiate the response, despite potentiating the HA hyperaemia induced by exogenously applied adenosine. We therefore conclude that, while adenosine does exert a significant degree of control over HA blood flow, the 'buffer response' is unlikely to be 'mediated entirely by local adenosine concentration', as proposed by Lautt & Legare (1985).

Effectiveness of adenosine receptor blockade was confirmed in our experiments by the careful measurement of dose-responses to injected adenosine immediately before the time of PV occlusion. 8-Phenyltheophylline (8-PT) and 3-isobutyl-1-methylxanthine (IBMX) had very similar inhibitory effects on the adenosine dose-response curve, though 8-PT caused a less marked (but more reproducible) attenuation of the 'buffer response'.

We found both of these antagonists quite difficult drugs to use: IBMX infusion resulted in progressive systemic hypotension, which necessitated prompt measurement of haemodynamic indices before blood pressure fell below 50% of control. Indeed, it is possible that the profound hypotensive effect of IBMX may have limited the HA 'buffer response'. However, previous studies have shown that the 'buffer response' is unaffected by a 25% reduction in mean arterial blood pressure (Alexander *et al.*, 1989), and it is possible that the 50% reduction in pressure observed with IBMX in the present study may also not have influenced the response, particularly since neither HA nor PV blood flow was reduced by the drug. 8-PT had no effect on blood pressure, even at the dose required to produce virtually complete adenosine blockade, and was therefore considered a preferable drug to use than IBMX. In addition, unlike IBMX, 8-PT is only a very weak phosphodiesterase inhibitor (Smellie *et al.*, 1979), and is a potent and selective P_1-purinoceptor antagonist (Bruns *et al.*, 1988; Collis, 1988). However, 8-PT tended to cause a decrease in PV blood flow.

Lautt & Legare (1985) found the antagonist effect of 8-PT varied considerably between different cats, and they had to administer the drug in the range 1–16 $mg\,min^{-1}\,kg^{-1}$ in order to obtain complete blockade. They also found that the 'buffer response' required a higher dose of 8-PT to achieve the same degree of block as seen with injected adenosine, and that an overdose of 8-PT could produce serious HA vasoconstriction. We found a smaller and much less variable dose of 8-PT produced nearly complete blockade of the response to injected adenosine in our dogs; HA vasoconstriction was never observed. It remains possible that we might have achieved more complete blockade of the 'buffer response' with higher doses of 8-PT, but it seems very unlikely that PV occlusion could stimulate the release of adenosine in amounts exceeding the highest level we administered in our dose-response curves.

DPD significantly potentiated the vasodilator response of the HA to exogenously applied adenosine, but did not alter the magnitude of the 'buffer response'. This finding contrasts with that obtained by Lautt *et al.* (1985), who showed a marked increase in both the response to injected adenosine and the 'buffer response'. We found that potentiation of the hyperaemic response to injected adenosine could only be achieved within a narrow range of DPD infusion rates, and that the measurements of dose-response curves and the 'buffer response' had to be very carefully timed. An additional problem with DPD was its tendency to decrease basal HA blood flow, though to a mean level similar to that in the other two groups. We share Lautt's concern that DPD itself did not dilate the HA, as might be expected if adenosine plays a major role in the control of HA flow. DPD, however, does not have very specific actions: it may block efflux as well as influx of purines (Stone, 1985), and it is a potent inhibitor of some phosphodiesterases (Van Belle, 1988). Results obtained with DPD must therefore be viewed with considerable caution.

Throughout this investigation, we employed the technique whereby adenosine was injected into the PV in order to elicit changes in flow in the HA (Lautt *et al.*, 1984). We have found that this approach provides a highly reproducible vasoactive response in the HA on first pass through the liver. Such a 'transhepatic' mode of drug action is indicative of some form of communication between PV blood and the pre-sinusoidal HA resistance sites. While the mechanism of action is unknown, its existence was used to advantage in the current study, as it enabled the local infusion of blocking agents into the HA to proceed uninterrupted; furthermore, HA rather than PV injection of adenosine was found in pilot experiments to result in a significantly longer duration of response, which would have been incompatible with the precise timing required in our experimental protocol.

The 'buffering capacity' of the HA was significantly reduced by IBMX, but only slightly decreased by 8-PT. The 'buffering capacity' is a useful index of the responsiveness of the HA specifically to abrupt interruption of PV flow, because it accommodates variations in basal PV flow. The absence of a statistically significant decrease in this index with 8-PT may have been due to the decrease in basal PV flow caused by the drug, but this implies an even lesser blocking effect of 8-PT on the 'buffer response' than discussed above. By contrast, the large decrease in 'buffering capacity' with IBMX took place despite an increase in basal PV flow, thus implying a rather greater inhibitory effect of IBMX than previously concluded; the hypotensive effect of IBMX is probably not responsible (see discussion above). DPD did not enhance 'buffering capacity'.

Adenosine has been shown to be an important regulator of blood flow in a number of organs (Berne *et al.*, 1983), including the brain (Phillis *et al.*, 1984; Winn *et al.*, 1985), the coronary circulation (Berne, 1963; Leung *et al.*, 1985; Randall & Jones, 1985), skeletal muscle (Berne *et al.*, 1983), the kidney (Osswald, 1988) and the intestine (Granger & Norris, 1980; Lautt, 1986). It has also been shown to control post-occlusion reactive hyperaemia of the HA (Ezzat & Lautt, 1987). Several mechanisms have been proposed for the release of adenosine from tissue. Its release may be continuous, so that during PV occlusion, for example, it may accumulate and result in HA dilatation (Lautt, 1985; 1988). It may, however, be regulated by tissue hypoxia (Berne *et al.*, 1983), or by an imbalance between oxygen supply and demand (Bardenheuer & Schrader, 1986). The present results do not allow these mechanisms to be separated. Nevertheless, it is important to recognise the fact that the PV normally provides the major supply of oxygen to the liver (Mathie *et al.*, 1988), and that its loss could lead to a degree of hepatic tissue hypoxia.

P_1-purinoceptors in the cardiovascular system comprise two subtypes: A_1 receptors (which mediate the prejunctional inhibition by adenosine of neurotransmitter release) and A_2 receptors (which mediate vasodilatation due to adenosine). They are believed to be present in a number of peripheral vascular beds (Collis, 1985; Burnstock & Kennedy, 1986; Williams, 1987). Evidence also exists to support the existence of P_1-purinoceptors in the HA (A.L. Brizzolara & G. Burnstock, personal communication), and recent work in the rabbit by

the present authors has shown these to include an A_2 receptor subtype (R.T. Mathie, B. Alexander, V. Ralevic & G. Burnstock, unpublished observations).

We therefore suggest that following PV occlusion, adenosine, released from the liver (either from HA endothelial cells or produced from the breakdown of ATP) in response to tissue hypoxia or to diminished oxygen delivery, may act upon P_1 receptors in the HA to result in dilatation of the HA vascular bed. Our results indicate that adenosine is unlikely to be the sole regulator of HA blood flow, and further studies are needed to elucidate the nature of the other mediator(s) of the 'buffer response'.

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