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EFFECT OF ADENOSINE ON CAROTID CHEMORECEPTOR ACTIVITY IN THE CAT

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1 The effects of intracarotid (i.c.) injections or infusions of adenosine on chemoreceptor activity recorded from the peripheral end of a sectioned carotid sinus nerve have been studied in cats anaesthetized with pentobarbitone.

2 Adenosine injections (0.1–100 μg) caused a rapid and marked increase of spontaneous chemoreceptor discharge, the intensity, duration and onset of which was dose-dependent. Infusion of adenosine, 50 μg/min, also evoked an increase in discharge which persisted for the duration of the infusion.

3 Both theophylline (1 mg i.c.) and aminophylline (1 mg i.c.) caused short-lasting decreases in spontaneous discharge but did not prevent the excitatory effect of adenosine. Theophylline increased the excitatory action of adenosine.

4 Naloxone (400 μg i.c.) antagonized the depressant effect of morphine on chemoreceptor discharge but not the excitatory action of adenosine.

5 It is concluded that exogenous adenosine can excite the cat carotid chemoreceptors, an effect which is not prevented by theophylline in the doses studied. The physiological significance of the findings is discussed.

Introduction

There do not appear to be any reports concerning the action of adenosine on peripheral arterial chemoreceptors. In view of the suggestions that adenosine may play a role in neurotransmission (e.g. Ribeiro, 1979), it seemed of interest to study the effect of adenosine on cat carotid chemosensory activity. A preliminary account of some of this work has been presented to the Physiological Society (McQueen & Ribeiro, 1981b).

Methods

Experiments were performed on 20 cats of either sex weighing between 2.4 and 3.4 kg (median 3.1 kg). The animals were anaesthetized with pentobarbitone sodium (42 mg/kg i.p. initially, supplemented by i.v. administration of 10% of the initial dose every 1 to 2 h), artificially ventilated and paralysed by gallamine triethiodide (3 mg/kg i.v.). The ganglioglomerular (sympathetic) nerves were usually cut. Full details of the experimental techniques, including the recording of arterial blood pressure and monitoring and regulation of arterial blood gas tensions and pH, have been given previously (McQueen, 1977; Docherty & McQueen, 1978).

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Electrical activity of chemoreceptor units (1 to 6 units) was recorded from filaments of the peripheral end of a sectioned sinus nerve, passed through a pulse height (window) discriminator, and quantified with the aid of a PDP-8 computer.

A catheter was introduced via the lingual artery into the common carotid artery ipsilateral to the sinus nerve from which activity was recorded and advanced until its tip lay about 2 cm caudal to the carotid bifurcation. In some experiments a second catheter was positioned in the same common carotid artery, this time via the superior thyroid artery, and used for infusing drug solutions (0.1 ml/min).

Drugs were dissolved in modified Locke solution (McQueen, 1977) or 0.9% w/v aqueous sodium chloride (saline). Drug solutions (0.1 ml, except adenosine 100 μg which was in 0.2 ml) were injected into the common carotid artery and washed in with 0.2 ml Locke solution which had been bubbled with 5% CO_2: 95% air in a water bath at 37°C; injections were made over 2 s.

Results obtained from different experiments were pooled and expressed as the mean ± s.e. mean of the absolute values, which varied from experiment to experiment according to the number of units recorded. In order to determine whether changes observed were statistically significant, particularly when such changes were small, responses to particular drug

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doses in the different experiments were compared with the corresponding responses to the drug vehicle in the same experiments using either the Wilcoxon signed ranks test (when the number of pairs >7) or Student's paired t test (for <6 pairs, and assuming Gaussian distribution). The null hypothesis was rejected if $P<0.05$ and the difference between groups was considered statistically significant.

Drugs used were: adenosine, theophylline, aminophylline (Sigma); morphine sulphate, pentobarbitone sodium, gallamine triethiodide (May & Baker); naloxone hydrochloride (Endo).

Results

Injections of adenosine

The effects of intracarotid injection of different doses of adenosine on spontaneous chemoreceptor discharge in one experiment are illustrated in Figure 1. Discharge for each test was averaged over 10 s periods starting 10 s before and continuing for 60 s after the injection. As can be seen from either the neurograms or the averaged discharge, the main effect of adenosine was a dose-dependent increase in the frequency of discharge. No tachyphylaxis to the action of adenosine was observed. Thus, when injected at intervals of 5 min over a period of 1 h, there was no diminution of the effect on spontaneous chemoreceptor discharge.

Low doses of adenosine (0.001 to 0.01 μg) caused a decrease in chemoreceptor discharge during the first 10 s following the injection (see Figure 1), an effect which appeared to be most pronounced for the lowest dose. However, an inhibition of spontaneous discharge was also usually associated with injection of the same volume of drug vehicle, Locke solution

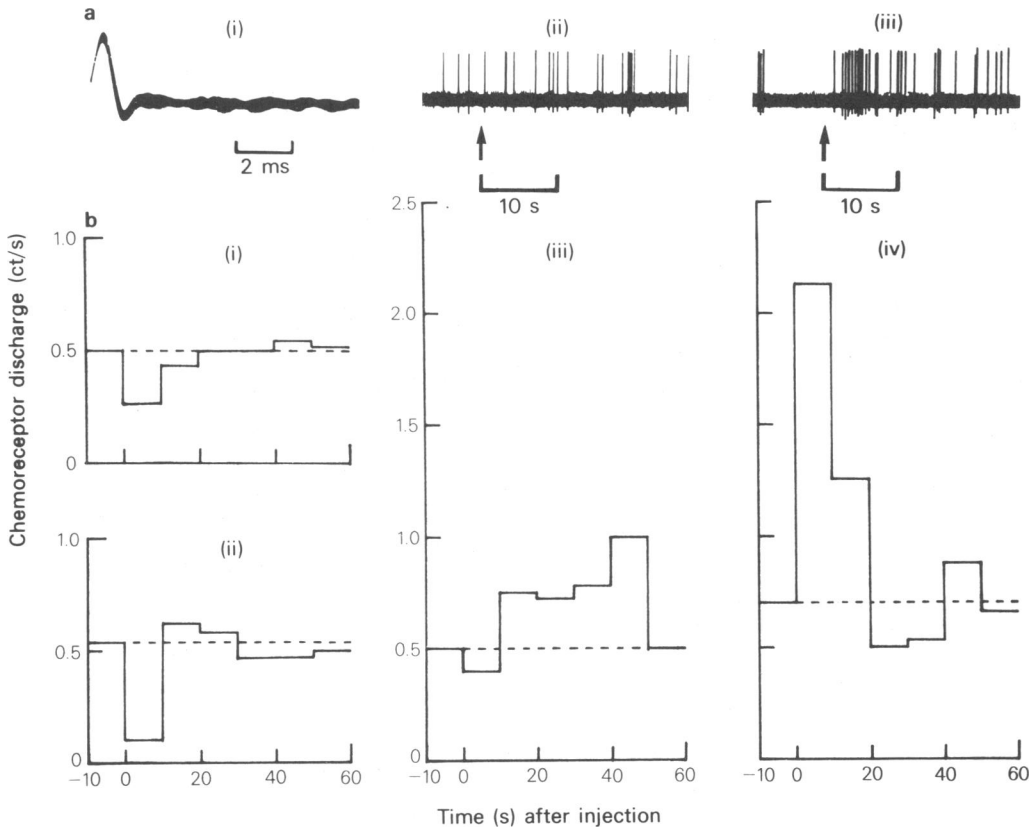

Figure 1 Effects of intracarotid (i.c.) injections of adenosine on the frequency of spontaneous chemoreceptor discharge. (a) Neurograms taken from one experiment show the increase in the discharge of a single unit (insert, i) caused by injecting (arrow) adenosine 0.1 (ii) and 1 μg (iii); in (i) the duration of the action potential is shown, the trace being of 10 consecutive superimposed spikes. (b) Responses of the chemoreceptor unit to i.c. injection of (i) 0.3 ml of the Locke solution and to adenosine: 0.001 μg (ii); 0.1 μg (iii) and 1 μg (iv). The graphs show the amplitude and duration of the responses averaged over 10 s periods following the injections.

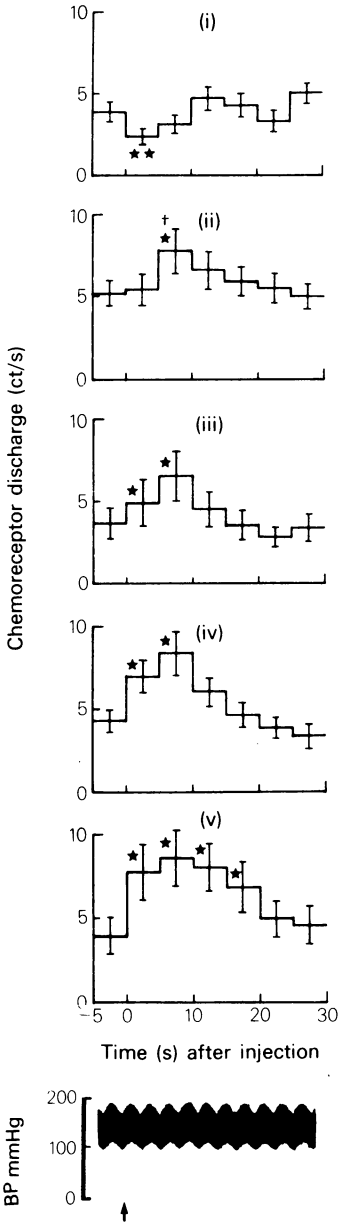

Figure 2 Effects on spontaneous chemoreceptor discharge of injecting Locke solution 0.3 ml (i) and adenosine 0.1 μg (ii); 1 μg (iii); 10 μg (iv) and 100 μg (v). Discharge was averaged over 5 s periods following the injection. Data obtained from tests in 8–10 cats were pooled and presented as the mean with vertical bars indicating s.e.mean. The lower panel shows the effect on arterial blood pressure (BP) of injecting (arrow) 100 μg of adenosine in one experiment. $*P<0.05$ compared with Locke solution injections; $**P<0.05$ compared with pre-injection control discharge; $\dagger P>0.05$ compared with adenosine 100 μg.

(see Figures 1 and 2), so responses to the low doses of adenosine were studied in five cats (results not shown) and compared with responses to injections of Locke solution (0.3 ml). There was no significant difference ($P>0.05$) between the responses to adenosine and Locke solution in these experiments.

Data obtained from ten experiments were averaged over 5 s periods for 30 s after the injection, pooled and plotted against time (Figure 2). This quantitative evidence confirmed that the increase in both amplitude and duration of the discharge were dose-related. The peak of the discharge, averaged over 5 s periods, for all doses (0.1–100 μg) occurred between 5 and 10 s after the injections, and that caused by 0.1 μg was not significantly different from that caused by the highest dose studied, 100 μg ($P>0.05$, $n=8$ pairs). Injections of Locke solution were also made in these experiments and the results obtained are summarized in Figure 2. They confirm the transient inhibitory effect of Locke solution illustrated in Figure 1. A significant decrease in discharge occurred during the first 5 s following the injection ($P<0.05$, $n=10$, compared with the pre-injection averaged discharge). This was less marked and not statistically significant in the next 5 s ($P>0.05$), and thereafter discharge returned to the pre-injection control levels.

Results from four experiments in which both average discharge and maximum discharge, expressed as ct/s, were obtained for different doses of adenosine are compared and summarized in Table 1. The average spontaneous chemoreceptor discharge was determined in the 15 s pre-injection control period immediately preceding each injection and in the 15 s post-control period commencing 45 s after the injections. Responses to adenosine were evaluated by determining the average discharge in the period during which discharge was increased above control frequency. Apart from increasing the average discharge, adenosine also increased the maximum discharge frequency. This latter increase, however, was not so marked as that averaged over the whole period, showing that the overall increase in discharge caused by adenosine resulted from a sustained increase throughout the response rather than from a sudden transient increase, such as occurs with acetylcholine (ACh) (cf. McQueen, 1977). The duration of the adenosine response was dose-dependent, and the delay to onset of the response was inversely related to dose.

The effects obtained were not related to changes in systemic blood pressure since adenosine in the doses studied (0.001 to 100 μg) did not cause any consistent or substantial changes in arterial blood pressure, as can be seen from Figure 2. There were no changes in arterial blood gas tensions or pH following administration of adenosine.

Table 1 Effect of adenosine on chemoreceptor discharge in the cat

	Chemoreceptor discharge					Response	
	Pre-control* (= 100%)	Average discharge Effect of adenosine	Post-control** (= 100%)	Pre-control† (= 100%	Maximum discharge Effect of adenosine	Post-control‡ (= 100%)	Duration	Delay To onset
Adenosine (μg) (No. of expts)	(ct/s) Mean, range	(% of control) Mean, range	(ct/s) Mean, range	(ct/s) Mean, range	(% of control) Mean, range	(ct/s) Mean, range	(s) Mean, range	(s) Mean, range
0.1 (4)	6.1	156	5.1	12	135	11	8.0	7.1
	5.2–6.9	108–184	3.9–5.8	11–14	73–181	8–13	6.0–11.7	3.2–10.1
1 (3)	4.9	181	5.0	10	142	11	12.7	5.4
	3.6–6.2	172–191	3.7–7.1	8–12	70–206	8–12	9.0–15.4	2.1–11.3
10 (4)	4.0	209	3.6	9	175	10	13.8	4.7
	1.9–5.1	195–218	1.3–4.7	5–12	143–196	6–13	12.1–14.6	2.1– 8.2
50 (3)	3.6	248	3.8	7	209	9	15.1	3.6
	1.9–5.1	247–249	2.1–4.7	5–10	183–223	6–11	13.7–16.5	0.7– 8.4
100 (3)	5.5	229	5.5	13	209	12	19.8	1.7
	1.8–7.6	221–243	2.8–6.9	5–17	180–240	7–15	14.3–25.4	0.5– 3.0

*Discharge averaged during the 15 s immediately before injecting adenosine.
**Discharge averaged during the 15 s period commencing 45 s after the injection, by which time the discharge had usually returned to pre-injection levels. There was no significant difference between pre- and post-control values ($P > 0.05$).
†Maximum discharge in 1 s observed during the pre-control period.
‡Maximum discharge in 1 s observed during the post-control period.

Theophylline and aminophylline

Theophylline (1 mg) was given as an intracarotid (i.c.) injection in five cats and caused a decrease in spontaneous chemoreceptor discharge, an effect which lasted for about 30 s. The integrated response ($\Delta\Sigma x$) showed that the depression was significantly greater ($P < 0.05$) than that caused by injecting Locke solution. Although theophylline transiently decreased spontaneous chemoreceptor discharge (Figure 3), it did not prevent the excitatory action of adenosine, and as can be seen in Figure 4, the log dose-response curve to adenosine was shifted upwards and to the left which is indicative of an increase in the responses after theophylline; the response to adenosine 100 μg was statistically significantly greater after theophylline than it was before ($P < 0.05$, $n = 4$).

Injections of lower doses of theophylline (100–200 μg) did not cause any significant effect on the spontaneous discharge ($P > 0.05$, $n = 3$ pairs), and the excitatory effect of adenosine (1–100 μg) was unaltered by these doses ($P > 0.05$, $n = 3$ pairs).

Aminophylline (1 mg i.c.) was injected in one cat

Figure 3 Effect on spontaneous chemoreceptor discharge of injecting theophylline 1 mg i.c. (heavy line, ——) compared with that of injecting Locke solution (0.3 ml) (thin line, ——). Discharge was averaged over 10 s periods following the injection. *$P < 0.05$, $n = 5$ pairs. The upper panel shows the effect on arterial blood pressure of injecting (arrow) 1 mg of theophylline in one experiment.

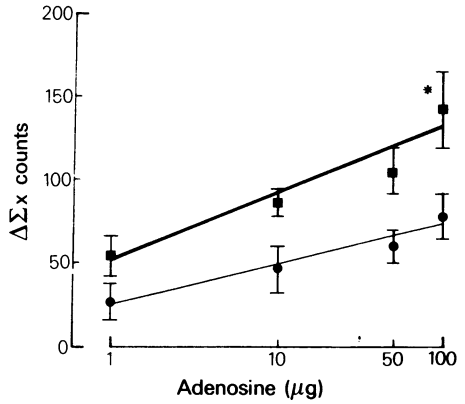

Figure 4 Dose-response data for adenosine obtained before (●) and after (■) theophylline (1 mg i.c.) in four experiments. Doses (μg i.c.) are plotted on a $\log_{10}$ scale and chemoreceptor responses expressed as the mean $\Delta\Sigma x$ for the four experiments; vertical lines show s.e.mean. $\Delta\Sigma x$ was calculated as the response during the 30 s following the injections. ($\Delta\Sigma x = \Sigma x - \bar{x}.t$, where Σx is the number of action potentials counted during the response of duration t s, a 'response' being defined as lasting from the first substantial change from background discharge frequency ($\bar{x}$ ct/s) until return to background level.) Lines were fitted to the data by the method of least squares. Averaged values ± s.e.mean (ct/s) for the pre-injection (15 s) control periods are as follows: adenosine 1 μg 4.5 ± 1.0 before theophylline, 6.5 ± 1.4 after theophylline; adenosine 10 μg 5.5 ± 1.4 before, 7.8 ± 1.7 after, adenosine 50 μg 3.5 ± 1.1 before, 5.2 ± 1.4 after; adenosine 100 μg 3.9 ± 1.7 before, 5.1 ± 2.0 after. * $P < 0.05$.

and the effect of adenosine (1–100 μg) tested before and after the injection. A transient depressant effect similar to that seen with theophylline was observed, and the excitatory action of adenosine was also undiminished after aminophylline.

Neither theophylline (Figure 3) nor aminophylline caused any marked changes in blood pressure and the highest dose of adenosine did not alter arterial blood pressure when injected after theophylline.

Naloxone

Four experiments were performed to investigate the influence of naloxone (0.4 mg i.c.) on chemoreceptor responses to adenosine and morphine. The adenosine results were pooled and are shown in Figure 5. No statistically significant difference was detected between the pre- and post-naloxone response ($P > 0.05$). In two of these experiments morphine (10–100 μg i.c.) was injected before and after naloxone (Figure 5). A chemodepressant effect of morphine was obtained in accordance with previous observations (McQueen & Ribeiro, 1980). This depressant effect of morphine was converted to an excitatory one by naloxone.

Infusions of adenosine

Adenosine, infused at a rate of 50 μg/min for 2 min in two cats, caused a sustained increase in chemoreceptor discharge, which returned to pre-infusion control levels within 30 s of stopping the infusion (Figure 6). The peak response was significantly different from the control, whether this was taken as the pre-infusion discharge or the discharge averaged during an infusion of a Locke solution (0.1 ml/min). The infusion of Locke solution did not affect spontaneous discharge (Figure 6). Adenosine infusions were not

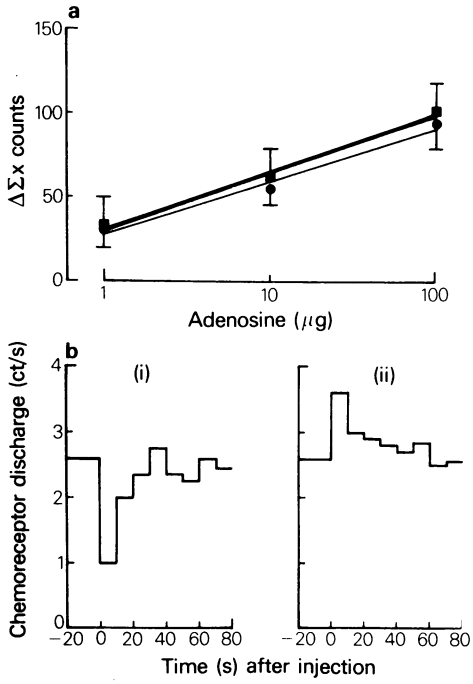

Figure 5 (a) Dose-response data for adenosine obtained before (●) and after (■) administration of naloxone (400 μg i.c.) in four experiments. Doses (μg i.c.) are plotted on a $\log_{10}$ scale and chemoreceptor responses expressed as the mean $\Delta\Sigma x$ for the four experiments; vertical lines show s.e.mean. $\Delta\Sigma x$ was calculated as the response during the 30 s following the injections. For details see Figure 4. Lines were fitted to the data by the method of least squares. Averaged values (ct/s) for the pre-injection (15 s) periods ± s.e.mean were as follows: adenosine 1 μg 4.5 ± 2.1 before naloxone, 5.7 ± 2.6 after naloxone; adenosine 10 μg 4.2 ± 1.4 before, 6.7 ± 1.5 after; adenosine 100 μg 6.5 ± 1.3 before, 5.0 ± 1.9 after. (b) Effects of morphine (100 μg i.c.) on chemoreceptor discharge before (i) and after (ii) naloxone (400 μg i.c.) in one experiment. Discharge was averaged over 10 s periods following the injection.

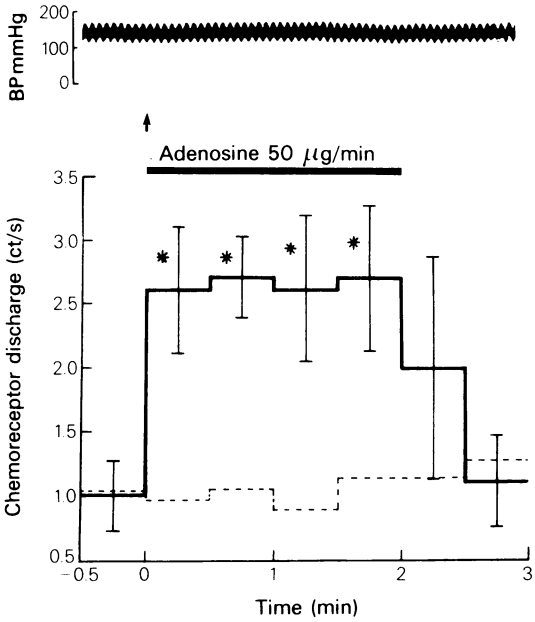

Figure 6 Pooled data from 6 infusions of adenosine (50 μg/min) in 2 cats showing the effect on spontaneous chemoreceptor discharge. The broken line represents the typical discharge during an infusion of Locke solution (0.1 ml/min). The upper panel shows a blood pressure trace recorded during one of the adenosine infusions. * $P < 0.05$.

associated with changes in arterial blood pressure, as can be seen from Figure 6.

Discussion

The results show that the predominant effect of injecting or infusing adenosine close-arterial to the cat carotid chemoreceptors is an increase in spontaneous discharge frequency.

In many preparations exogenous adenosine decreases the release of neurotransmitters (e.g. ACh (Ginsborg & Hirst, 1972; Ribeiro & Walker, 1975; Vizi & Knoll, 1976; Gustafsson, Hedqvist, Fredholm & Lundgren, 1978); noradrenaline (Hedqvist & Fredholm, 1976; Verhaeghe, Vanhoutte & Shepherd, 1977; Wakade & Wakade, 1978), dopamine (Michaelis, Michaelis & Myers, 1979) γ-aminobutyric acid (Hollins & Stone, 1978)). If adenosine exerts a similar action in the carotid body, its excitatory effect could be interpreted as being the consequence of decreased release of an inhibitory transmitter and/or modulator. Dopamine (Chiocchio, Biscardi & Tramezzani, 1966; Zapata, Hess, Bliss & Eyzaguirre, 1969) and enkephalins (Lundberg, Hökfelt, Fahrenkrug, Nilsson & Terenius, 1979; Wharton, Polak, Pearse, McGregor, Bryant, Bloom, Emson, Bisgard & Will, 1980) appear to be present in the cat carotid body and both exogenous dopamine (Zapata, 1975; Docherty & McQueen, 1978) and the enkephalins (McQueen & Ribeiro, 1980; 1981a; McQueen, 1981) depress spontaneous chemoreceptor activity. Osborne & Butler (1975) suggested that tonically released dopamine may suppress chemoreceptor discharge and although evidence which is not in agreement with their hypothesis has been obtained (e.g. Docherty & McQueen, 1978), the present results could be explained in terms of adenosine inhibiting the release of dopamine, or some other substance which is tonically active in inhibiting discharge (? enkephalins).

However, it has also been found that adenosine can excite nerve cells. For example, Siggins, Gruol, Padjen & Forman (1977) showed that adenosine depolarizes neurones of explanted amphibian sympathetic ganglia, and Bleehen & Keele (1977) described algogenic actions of adenosine on the human blister base. It appears that adenosine sensitizes the carotid chemoreceptors to ACh and dopamine (McQueen & Ribeiro, 1981b) which might be construed as evidence that adenosine acts directly on the postsynaptic component of the carotid body chemosensory synapse, i.e. on the sensory nerve ending. An adenylate cyclase-cyclic AMP system is apparently located in the sinus nerve endings (Fitzgerald, Rogus & Dehghani, 1977) and it may be that adenosine interacts with this in a manner similar to that described for the brain (e.g. Davies, Taylor, Gregson & Quinn, 1980). Further investigation is needed to explore this possibility.

Theophylline appears unable to prevent activation of P_2-purinoceptors. These receptors, as so far described, seem to be localized post-junctionally (see Burnstock, 1978). De Mey, Burnstock & Vanhoutte (1979) found that in the canine saphenous vein, theophylline antagonizes the inhibitory effect of ATP on neurogenic responses but not its direct contractile effect. According to these authors this suggests the presence of both inhibitory presynaptic (P_1) and excitatory postsynaptic (P_2) receptors. In the present study the excitatory effect of adenosine was unaffected by low doses of theophylline (0.1–0.2 mg) but potentiated by a slightly higher dose (1 mg), a finding that is compatible with a P_2-excitatory post-junctional effect. However, the potentiation might also have resulted from theophylline antagonizing a chemodepressant component of the adenosine response, which might normally be masked by the excitatory component, or from mechanisms having in common the ability to increase the cyclic AMP concentration (e.g. theophylline by inhibiting phosphodiesterases, and adenosine by activating the adenylate cyclase).

It has also been proposed that the inhibitory action of morphine may involve the release of adenosine as an intermediary (Sawynok & Jhamandas, 1976; Stone & Perkins, 1979), and it has been shown that morphine and enkephalins can inhibit spontaneous carotid chemosensory discharge in the cat (McQueen & Ribeiro, 1980; 1981a; McQueen, 1981). However, naloxone reduces the inhibitory effect of morphine without reducing the excitatory response to adenosine, so the effects of adenosine do not appear to result from actions on naloxone-sensitive opiate receptors in the carotid body.

Adenosine can cause vasodilatation (see Berne, Foley, Watkinson, Miller, Winn & Rubio, 1979) and we cannot, therefore, preclude the possibility that adenosine was changing blood flow in the carotid body and thereby, perhaps, altering chemoreceptor discharge, even though it had little overall effect on the systemic blood pressure. However, other vasodilators (e.g. sodium nitrite, sodium nitroprusside: Docherty, 1980) tend to cause a delayed decrease in discharge, which is the opposite of the main effect obtained following adenosine injections in the present experiments. We consider it unlikely that vascular effects are responsible for the greater part of the response to adenosine, but would wish to investigate this with *in vitro* carotid body studies.

Adenosine is released into the circulation by a number of physiological and pathophysiological processes (e.g. ischaemia; see Winn, Rubio & Berne, 1979), and a correlation between adenosine concentration and oxygen supply in rat brain has been suggested (Rubio, Berne, Bockman & Curnish, 1975). In the present study, low doses of adenosine modified chemoreceptor discharge and it seems reasonable to speculate that adenosine might influence events taking place in the carotid body, perhaps by modulating any putative transmitter(s) which may be released within the carotid body complex, and/or by directly activating sensory nerve endings.

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References

BERNE, R.M., FOLEY, D.H., WATKINSON, W.P., MILLER, W.L., WINN, H.R. & RUBIO, R. (1979). Role of adenosine as a mediator of metabolic vasodilation in the heart and brain: a brief overview and update. In *Physiological and Regulatory Functions of Adenosine and Adenine Nucleotides.* ed. Baer, H.P. & Drummond, G.I. pp. 117–126. New York: Raven Press.

BLEEHEN, T. & KEELE, C.A. (1977). Observations on the algogenic actions of adenosine compounds on the human blister base preparation. *Pain*, **3**, 367–377.

BURNSTOCK, G. (1978). A basis for distinguishing two types of purinergic receptor. In *Cell Membrane Receptors for Drugs and Hormones: A Multidisciplinary Approach.* ed. Straub, R.W. & Bolis, L. pp. 107–118. New York: Raven Press.

CHIOCCHIO, S.R., BISCARDI, A.M. & TRAMEZZANI, J.H. (1966). Catecholamines in the carotid body of the cat. *Nature, Lond.*, **212**, 834–835.

DAVIES, L.P., TAYLOR, K.M., GREGSON, R.P. & QUINN, R.J. (1980). Stimulation of guinea-pig brain adenylate cyclase by adenosine analogues with potent pharmacological activity *in vivo*. *Life Sci., Oxford*, **26**, 1079–1088.

DE MEY, J., BURNSTOCK, G. & VANHOUTTE, P.M. (1979). Modulation of the evoked release of noradrenaline in canine saphenous vein via presynaptic receptors for adenosine but not ATP. *Eur. J. Pharmac.*, **55**, 401–405.

DOCHERTY, R.J. (1980). A quantitative pharmacological study of some putative neurotransmitters in the carotid body of the cat and the rabbit. *Ph.D. Thesis, University of Edinburgh.*

DOCHERTY, R.J. & McQUEEN, D.S. (1978). Inhibitory action of dopamine on cat carotid chemoreceptors. *J. Physiol.*, **279**, 425–436.

FITZGERALD, R.S., ROGUS, E.M. & DEHGHANI, A. (1977). Catecholamines and 3′, 5′ cyclic AMP in carotid body chemoreception in the cat. *Adv. exp. Med. Biol.*, **78**, 245–258.

GINSBORG, B.L. & HIRST, G.D.S. (1972). The effect of adenosine on the release of the transmitter from the phrenic nerve of the rat. *J. Physiol.*, **224**, 629–645.

GUSTAFSSON, L., HEDQVIST, P., FREDHOLM, B.B. & LUNDGREN, G. (1978). Inhibition of acetylcholine release in guinea pig ileum by adenosine. *Acta physiol. scand.*, **104**, 469–478.

HEDQVIST, P. & FREDHOLM, B.B. (1976). Effects of adenosine on adrenergic neurotransmission; prejunctional inhibition and postjunctional enhancement. *Naunyn-Schmiedbergs Arch. Pharmac.*, **293**, 217–223.

HOLLINS, C. & STONE, T.W. (1980). Adenosine inhibition of γ-aminobutyric acid release from slices of rat cerebral cortex. *Br. J. Pharmac.*, **69**, 107–112.

LUNDBERG, J.M., HÖKFELT, T., FAHRENKRUG, J., NILSSON, G. & TERENIUS, L. (1979). Peptides in the cat carotid body (glomus caroticum): VIP-, enkephalin-, and substance P-like immunoreactivity. *Acta physiol. scand.*, **107**, 279–281.

McQUEEN, D.S. (1977). A quantitative study of the effects of cholinergic drugs on carotid chemoreceptors in the cat. *J. Physiol.*, **273**, 515–532.

McQUEEN, D.S. (1981). Effects of some polypeptides on carotid chemoreceptor activity. In *Arterial Chemoreceptors*, ed. Belmonte, C., Pallot, D.J., Acker, H. & Fidone, S. pp. 299–306. Leicester: Leicester University Press.

McQUEEN, D.S. & RIBEIRO, J.A. (1980). Inhibitory actions of methionine-enkephalin and morphine on the cat carotid chemoreceptors. *Br. J. Pharmac.*, **71**, 297–305.

McQUEEN, D.S. & RIBEIRO, J.A. (1981a). Comparison of the depressant effects of leucine- and methionine-enkephalin on spontaneous chemoreceptor activity in cats. *Br. J. Pharmac.*, **72,** 544–545 P.

McQUEEN, D.S. & RIBEIRO, J.A. (1981b). Excitatory action of adenosine on cat carotid chemoreceptors. *J. Physiol.* (in press).

MICHAELIS, M.L., MICHAELIS, E.K. & MYERS, S.L. (1979). Adenosine modulation of synaptosomal dopamine release. *Life Sci., Oxford,* **24,** 2083–2092.

OSBORNE, M.P. & BUTLER, P.J. (1975). New theory for receptor mechanism of carotid body chemoreceptors. *Nature, Lond.*, **254,** 701–703.

RIBEIRO, J.A. (1979). Purinergic modulation of transmitter release. *J. theor. Biol.*, **80,** 259–270.

RIBEIRO, J.A. & WALKER, J. (1975). The effects of adenosine triphosphate and adenosine diphosphate on transmission at the rat and frog neuromuscular junctions. *Br. J. Pharmac.*, **54,** 213–218.

RUBIO, R., BERNE, R.M., BOCKMAN, E.L. & CURNISH, R.R. (1975). Relationship between adenosine concentration and oxygen supply in rat brain. *Am. J. Physiol.*, **228,** 1896–1902.

SAWYNOK, J. & JHAMANDAS, K.H. (1976). Inhibition of acetylcholine release from cholinergic nerves by adenosine, adenine nucleotides and morphine: antagonism by theophylline. *J. Pharmac. exp. Ther.*, **197,** 379–390.

SIGGINS, G.R., GRUOL, D.L., PADJEN, A.L. & FORMAN, D.S. (1977). Purine and pyrimidine mononucleotides depolarise neurones of explanted amphibian sympathetic ganglia. *Nature, Lond.*, **270,** 263–265.

STONE, T.W. & PERKINS, M.N. (1979). Is adenosine the mediator of opiate action on neuronal firing rate? *Nature, Lond.*, **281,** 227–228.

VERHAEGHE, R.H., VANHOUTTE, P.M. & SHEPHERD, J.T. (1977). Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenine nucleotides. *Circulation Res.*, **40,** 208–215.

VIZI, E.S. & KNOLL, J. (1976). The inhibitory effect of adenosine and related nucleotides on the release of acetylcholine. *Neuroscience,* **1,** 391–398.

WAKADE, A.R. & WAKADE, T.D. (1978). Inhibition of noradrenaline release by adenosine. *J. Physiol.*, **282,** 35–49.

WHARTON, J., POLAK, J.M., PEARSE, A.G.E., McGREGOR, G.P., BRYANT, M.G., BLOOM, S.R., EMSON, P.C., BISGARD, G.E. & WILL, J.A. (1980). Enkephalin-, VIP- and substance P-like immunoreactivity in the carotid body. *Nature, Lond.*, **284,** 269–271.

WINN, H.R., RUBIO, R. & BERNE, R.M. (1979). Brain adenosine production in the rat during 60 seconds of ischemia. *Circulation Res.*, **45,** 486–492.

ZAPATA, P. (1975). Effects of dopamine on carotid chemo- and baroreceptors *in vitro*. *J. Physiol.*, **244,** 235–251.

ZAPATA, P., HESS, A., BLISS, E.L. & EYZAGUIRRE, C. (1969). Chemical, electron microscopic and physiological observations on the role of catecholamines in the carotid body. *Brain Res.*, **14,** 473–496.

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