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Regulation of platelet function by catecholamines in the cerebral vasculature of the rabbit

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1 ^{111}In-labelled platelets were monitored continuously in the cerebral and pulmonary vascular beds of anaesthetized rabbits. Dopamine can, depending upon the concentration, either potentiate or inhibit thrombin-induced platelet accumulation in the cerebral vasculature of rabbits by unknown mechanisms. The effects of specific adrenergic and dopaminergic receptor antagonists were tested upon dopamine's actions on intracarotid (i.c.) thrombin-induced (80 u kg^{-1}) platelet accumulation in the cerebral vasculature. The effect of adrenaline on the response to thrombin in this vascular bed was also investigated.

2 Thrombin-induced platelet accumulation was significantly ($P<0.01$) potentiated by dopamine (100 μg kg^{-1} min^{-1}, i.c.) and this effect was significantly inhibited by infusion of the α-adrenoceptor antagonist, phentolamine.

3 A higher dose of dopamine (2 mg kg^{-1} min^{-1}, i.c.) inhibited thrombin-induced platelet accumulation. The β-adrenoceptor antagonist, propranolol, did not significantly alter this inhibitory effect whereas it was abolished by the dopamine D1 selective antagonist, SCH23390.

4 Adrenaline (when administered i.c. by bolus injection or infusion) had no significant effect on thrombin-induced accumulation at any of the doses tested.

5 Potentiation of *in vivo* platelet accumulation by dopamine therefore seems to occur *via* α-adrenergic receptors. However, the inhibitory effect of dopamine appears to be exerted *via* the activation of dopamine D1 receptors and not *via* β-adrenergic receptors. Our findings confirm that dopamine, but not adrenaline, can modify platelet function in the cerebral vasculature and these observations may have implications for current and potential therapeutic uses of dopamine and selective dopaminergic compounds.

Keywords: Thrombin; dopamine; platelets; dopaminergic receptors; adrenergic receptors

Abbreviations: AUC, area under the curve; CFTP, calcium free Tyrode's solution containing prostaglandin E_1; PRP, platelet rich plasma; SCH23390, (R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride

Introduction

Dopamine has been used clinically in the treatment of congestive heart failure, myocardial dysfunction, shock and Parkinson's disease (Goldberg, 1972; Tarazi, 1974), but at high doses causes side-effects such as increased blood pressure and impaired renal function (Lorenz *et al*., 1995). Specific dopamine agonists have been shown to elicit the beneficial effects of dopamine (Frederickson *et al*., 1985; Hughes *et al*., 1986; Elliott *et al*., 1990) without the associated side-effects (Shusterman *et al*., 1993).

It has been shown that dopamine can both potentiate (Ahtee & Michal, 1972) and inhibit (Braunstein *et al*., 1977) ADP-induced platelet aggregation *in vitro*. The potentiating effect of dopamine was shown to occur *via* α-adrenoceptor stimulation and the inhibitory effect was suggested to occur *via* dopamine D1-like receptors (De Keyser *et al*., 1988).

We have recently extended these *in vitro* findings and shown that, *in vivo*, dopamine can exert both potentiating and inhibitory actions upon thrombin-induced platelet accumulation in the cerebral vasculature of the rabbit (Emerson *et al*., 1997). Our previous findings, together with those of De Keyser *et al*. (1988), suggested that specific dopamine D1 agonists might have potential clinical uses as anti-thrombotics by inhibiting platelet aggregation. However, a variety of selective dopamine agonists, including specific D1 agonists, failed to modify platelet accumulation in the rabbit cerebral vasculature *in vivo* (Emerson *et al*., 1997). Thus, the mechanisms by which dopamine affects platelet accumulation *in vivo* are unknown.

We have shown previously that adrenaline can potentiate collagen-induced platelet accumulation in the pulmonary vasculature of the rabbit (Emerson *et al*., 1996), although the ability of adrenaline alone to induce platelet activation directly has been the subject of extensive debate. It has been reported that adrenaline *per se* is not a true platelet agonist but acts to enhance aggregation induced by other agonists (Steen *et al*., 1993; Lanza & Cazenave, 1985). Although other authors have observed that adrenaline can induce platelet aggregation in the absence of other agonists (Shattil *et al*., 1989), the concentrations required are not found physiologically (Roizen *et al*., 1975), but could account for the ability of adrenaline to act synergistically with other platelet agonists (O'Brien, 1963; Packham *et al*., 1973; Mills & Roberts, 1967; Ahtee & Michal, 1972). The mechanisms by which such synergism occurs are unclear and very little is known about such interactions of adrenaline with other platelet agonists *in vivo*.

In the experiments presented here, we have investigated (a) the effects of α- and β-adrenergic antagonists and a dopaminergic antagonist upon the enhancing and inhibitory effects of dopamine and (b) the effect of adrenaline on platelet responses to thrombin in the cerebral vasculature.

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Methods

Animals

These experiments were carried out on New Zealand White, male rabbits weighing 2.0–2.75 kg (Froxfield, Petersfield, Hampshire U.K.). Animals were fed a normal diet and received water *ad libitum*. All procedures reported were subject to Home Office approval and were carried out under the Animal (Scientific Procedures) Act, 1986.

Reagents

ADP, bovine plasma thrombin, citric acid, dopamine, phentolamine, propanolol and prostaglandin E_1 (Sigma); trisodium citrate (BDH Chemicals Ltd); Ca^{2+}-free Tyrode solution (Gibco); Diazepam (Valium, Roche); Hypnorm (fentanyl citrate 0.315 mg ml^{-1} and fluanisone 10 mg ml^{-1}, Janssen Pharmaceuticals Ltd.); ^{111}Indium oxine (Amersham International); SCH23390 (R(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, RBI).

^{111}In labelling of platelets

Full details of the protocol for the isolation and radiolabelling of rabbit platelets have been described elsewhere (May *et al*., 1990). Briefly, 9 ml blood was collected from the right ear artery into 1 ml 3.8% (w v^{-1}) trisodium citrate and centrifuged (225 × *g* for 15 min) to obtain platelet-rich plasma (PRP). PRP was buffered in Ca^{2+}-free Tyrode solution containing prostaglandin E_1 (300 ng ml^{-1}) (CFTP) and centrifuged at 675 × *g* for 15 min. After removal of the supernatant, the surface of the platelet pellet was washed with CFTP. The platelets were gently resuspended in 1 ml of CFTP and incubated for 2 min at 37°C with 1.8 MBq ^{111}Indium oxine. After a further centrifugation (675 × *g* for 15 min) the supernatant containing free ^{111}In oxine was removed and the platelets resuspended in 2 ml CFTP.

Experimental procedure

Animals were anaesthetized with diazepam (4 mg kg^{-1}, i.p.) followed 10 min later by Hypnorm (0.4 ml kg^{-1}, i.m.). Neuroleptic analgesia was maintained by supplemental i.m. injections of Hypnorm (0.1–0.2 ml kg^{-1}) as necessary (approximately 30 min intervals). The left common carotid artery was cannulated in the direction of blood flow for intracarotid (i.c.) bolus injections and infusions. ^{111}In-labelled platelets were administered *via* the left marginal ear vein and allowed to equilibrate in the circulation for 40 min before challenge with thrombin (80 u kg^{-1}, i.c.).

Circulating ^{111}In-labelled platelets were continuously monitored in the pulmonary and cerebral circulations with 1 inch crystal scintillation probes placed over the thorax and against the head. Counts were estimated with a dual-channel gamma spectrometer (Nuclear Enterprises NE461) and logged with the aid of a special application interface (AIMS 8000, Mumed Ltd.) by a microcomputer.

Drugs

All drugs were dissolved in saline and infused by the i.c. route. Bolus injections of antagonists were given at the beginning of the infusion period and infusions began 20 min before injection of thrombin and continued for the duration of the recording period. Bolus injections of adrenaline were given by the i.c. route 1 min prior to thrombin.

Statistics

All values are expressed as mean ± s.e.mean (n = at least 4). Responses to thrombin are expressed as maximum percentage increase in counts above the baseline values recorded immediately prior to injection of thrombin (max % increase) or the area under the curve (AUC) of the plot of percentage increase in counts against time. Control and experimental values were compared using one-way ANOVA followed by a multiple comparison t-test. A P value less than 0.05 was considered significant throughout.

Results

Dopamine potentiation of platelet accumulation

Infusion of dopamine (100 μg kg^{-1} min^{-1}) caused a change in baseline ^{111}Indium platelet counts in the cerebral vasculature of −4.0 ± 1.6% (n = 5) immediately prior to injection of thrombin. Dopamine infusion (100 μg kg^{-1} min^{-1}) significantly (P < 0.01) increased thrombin (80 u kg^{-1}, i.c.)-induced platelet accumulation in the cerebral vasculature to 145.8 ± 14.4% compared to saline infused (control) values of 99.6 ± 8.0% (Figure 1). Pre-treatment with the α-adrenoceptor antagonist, phentolamine (0.5 mg kg^{-1} + 20 μg kg^{-1} min^{-1}) had no significant (P > 0.05) effect on thrombin-induced platelet accumulation (97.7 ± 7.1%; Figure 1). However, this dose of phentolamine, when co-administered with dopamine, reduced the response to a level not significantly different to control values (102.5 ± 10.1%; Figure 1).

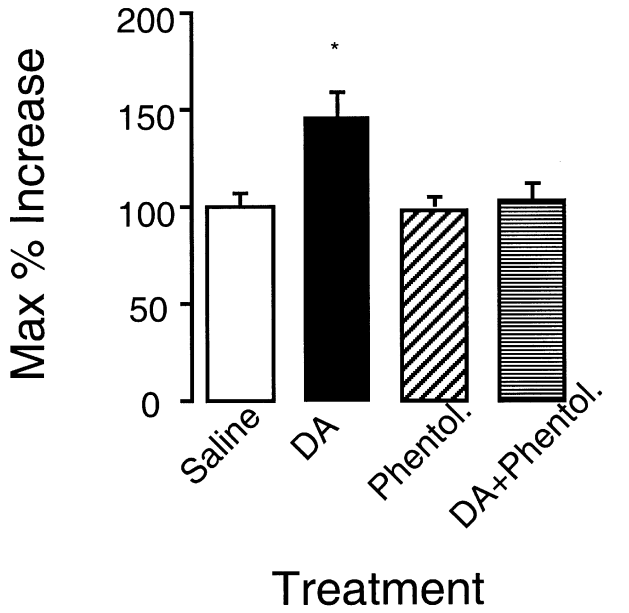

Figure 1 Effect of phentolamine (Phentol: 0.5 mg kg^{-1} + 20 μg kg^{-1} min^{-1}) on dopamine (DA: 100 μg kg^{-1} min^{-1}) potentiated responses to thrombin in the cerebral vasculature of rabbits. Changes in ^{111}In-labelled platelet accumulation were recorded following intracarotid injection of thrombin (80 u kg^{-1}). Responses are expressed as maximum percentage increase in ^{111}In counts in the cerebral vasculature and mean ± s.e.mean values are shown, n = 5. *P < 0.01 vs saline control responses; one-way ANOVA and Dunnett's test.

Dopamine inhibition of platelet accumulation

Infusion of dopamine (2 mg kg^{-1} min^{-1}) caused a change in ^{111}Indium platelet counts in the cerebral vasculature of $-10.6\pm2.9\%$ ($n=5$) immediately prior to injection of thrombin. Dopamine (2 mg kg^{-1} min^{-1}) significantly ($P<0.01$) reduced thrombin-induced platelet accumulation to $62.3\pm7.6\%$ compared to saline infused control values of $120.0\pm10.8\%$ (Figure 2). Pre-treatment with the β-adrenoceptor antagonist, propranolol (0.5 mg kg^{-1}) alone had no significant ($P>0.05$) effect on platelet accumulation ($106.7\pm8.5\%$; Figure 2). This dose of propranolol had no significant effect on the ability of dopamine to inhibit platelet accumulation ($74.9\pm4.1\%$; Figure 2). A higher dose of propranolol (0.5 mg kg^{-1} + 20 μg kg^{-1} min^{-1}) also had no significant action on dopamine's inhibitory effect ($55.2\pm8.0\%$; Figure 2).

The dopaminergic D1 receptor antagonist, SCH23390 (0.25 mg kg^{-1} + 7.5 μg kg^{-1} min^{-1}) blocked the inhibitory effect of dopamine on thrombin-induced responses such that accumulation was not significantly different from saline infused control values ($106.1\pm8.5\%$; Figure 2).

Effect of adrenaline on platelet accumulation

Changes in ^{111}Indium platelet counts in the cerebral vasculature immediately prior to injection of thrombin were $-7.3\pm1.0\%$ following bolus adrenaline (14 μg kg^{-1}) and $-5.0\pm1.9\%$ following adrenaline infusion (10 μg kg^{-1} min^{-1}). Pre-treatment with adrenaline, either as a bolus injection (14 μg kg^{-1}) or as an infusion (0.25–10 μg kg^{-1} min^{-1}), had no significant effect on thrombin-induced platelet accumulation in the cerebral vascular bed, although there was a non-significant fall in platelet accumulation at the highest dose tested (Table 1). It should be noted that, in these experiments, infusion of adrenaline increased the initial accumulation of platelets in the pulmonary vascular bed, which occurs prior to accumulation in the cerebral vasculature, although, once again, these effects were not significant (Table 2).

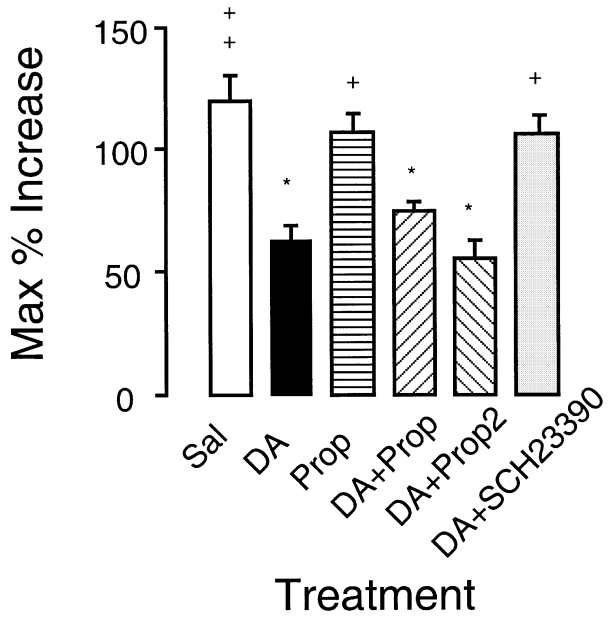

Figure 2 Effect of propranolol (Prop: 0.5 mg kg^{-1} or Prop2: 0.5 mg kg^{-1} + 20 μg kg^{-1} min^{-1}) and the dopamine D1 antagonist SCH23390 (0.25 mg kg^{-1} + 7.5 μg kg^{-1} min^{-1}) on dopamine (DA: 2 mg kg^{-1} min^{-1}) inhibited responses to thrombin in the cerebral vasculature of rabbits. Changes in ^{111}In-labelled platelet accumulation were recorded following intracarotid injection of thrombin (80 u kg^{-1}). Responses are expressed as maximum percentage increase in ^{111}In counts in the cerebral vasculature and mean ± s.e.mean values are shown, $n=5$. $^{*}P<0.01$ vs saline control responses, $^{+}P<0.05$ and $^{++}P<0.01$ vs dopamine responses; one-way ANOVA and Tukey test.

Discussion

Dopamine can exert effects *via* α- and β-adrenergic receptors as well as *via* specific dopaminergic receptors. Platelets express α-adrenergic receptors (principally α_2) as well as β-adrenergic receptors (Grant & Scrutton, 1979; Kerry & Scrutton, 1983). More recently, dopaminergic D1 and D2 receptors have been shown to be present on platelet surface membranes (De Keyser *et al*., 1988; Dean *et al*., 1992). Dopamine may, therefore, modify platelet function *via* a number of receptor mechanisms although the role of dopamine in the regulation of physiological platelet function is unknown.

The results presented here suggest that *in vivo* potentiation of platelet accumulation by dopamine occurs *via* α-adrenergic receptors since this effect of dopamine is inhibited by phentolamine. We are not aware of any evidence to suggest that phentolamine might be able to block dopaminergic receptors directly. Furthermore, since phentolamine *per se* had no significant effect on thrombin-induced platelet accumulation, it is unlikely that it was exerting a non-adrenergic inhibitory effect akin to that reported in stenosed

Table 1 Effect of adrenaline on thrombin-induced platelet accumulation in the cerebral vasculature of the rabbit

		Cerebral platelet accumulation	
Treatment	n	*Max % increase*	*AUC*
Saline bolus	4	92.5±6.4	6285±454
Adr. (14 μg kg^{-1})	4	75.0±12.3	5439±906
Saline infusion	8	93.6±4.7	5739±448
Adr. (0.25 μg kg^{-1} min^{-1})	5	84.2±10.5	5344±686
Adr. (1 μg kg^{-1} min^{-1})	5	99.1±11.2	6429±764
Adr. (10 μg kg^{-1} min^{-1})	5	73.2±7.6	5084±542

Results are expressed as the maximum percentage increase in cerebral counts above basline values (Max % increase) or as the area under the curve of the percentage increase in counts plotted against time (AUC, arbitary units) following injection of thrombin (80 u kg^{-1}, i.c.). Adrenaline (Adr.) administration had no significant ($P>0.05$) effects at any of the doses tested compared with saline control values.

Table 2 Effect of adrenaline infusion on the initial accumulation of platelets in the pulmonary vasculature following injection of thrombin

		Pulmonary accumulation	
Treatment	n	*Max % increase*	*AUC*
Saline	8	14.7±2.4	44±12
Adr. (0.25 μg kg^{-1} min^{-1})	5	23.1±8.1	103±61
Adr. (1 μg kg^{-1} min^{-1})	5	23.0±4.9	132±43
Adr. (10 μg kg^{-1} min^{-1})	5	33.0±6.8	161±51

Results are expressed as the maximum percentage increase in pulmonary counts above baseline values (Max % increase) or as the area under the curve of the percentage increase in counts plotted against time (AUC, abitrary units) following injection of thrombin (80 u kg^{-1}, i.c.). Adrenaline (Adr.) administration had no significant ($P>0.05$) effects at any of the doses tested compared with saline control values.

canine coronary arteries (Bolli *et al*., 1985). This observation may have important implications when considering the potential clinical uses of dopamine and specific dopamine agonists, all of which exhibit various levels of α-adrenergic activity (Emerson *et al*., 1997).

The inhibitory action of dopamine on platelet accumulation does not occur *via* β-adrenergic receptors, since this effect was not modified by blockade of these receptors with a high dose of propranolol. The D1 antagonist SCH23390, however, was able to abolish the inhibitory effect of dopamine, suggesting that inhibition of platelet accumulation is mediated *via* dopamine D1 receptors. It is, therefore, not clear why selective D1 receptor agonists did not inhibit platelet accumulation in previous *in vivo* experiments (Emerson *et al*., 1997). All of the D1 agonists tested previously, however, had significant α-adrenergic activity and it may be that more selective dopamine agonists with less adrenergic activity will be effective in inhibiting platelet accumulation. Additionally, D1 agonists were found to potentiate platelet accumulation in the pulmonary vasculature by an unknown mechanism (Emerson *et al*., 1997). It is possible that this undesirable effect (which did not occur with dopamine itself) is a dopaminergic effect which may prevent these drugs from inhibiting *in vivo* platelet accumulation in the cerebral vasculature. Such observations, in both the present report and our previous study (Emerson *et al*., 1997), may have implications for the potential clinical uses of dopamine agonists and may have some relevance to the recent reports of increased risk in patients with severe heart failure who were treated with ibopamine (Hampton *et al*., 1997; Feenstra *et al*., 1998).

Adrenaline has been shown to potentiate *in vitro* platelet aggregation induced by a variety of platelet agonists in numerous studies. *In vitro* platelet aggregation is, however, poorly predictive of platelet function *in vivo* (Morley & Page, 1984) and we have shown here that, in our model, there is no significant effect of either pre-treatment with a bolus dose or a prolonged infusion of adrenaline on thrombin-induced platelet accumulation in the cerebral vasculature. This stands in contrast to studies of the rabbit pulmonary circulation, where adrenaline was shown to potentiate collagen-induced platelet accumulation (Emerson *et al*., 1996), and the rat pulmonary vasculature, where adrenaline was shown to cause inhibition of platelet aggregation (Oyekan & Botting, 1986). The inability of adrenaline to potentiate thrombin-induced platelet accumulation in the cerebral circulation implies that the effect of dopamine is not a result of its metabolism to noradrenaline and adrenaline.

The baseline changes in ^{111}Indium levels in the cerebral circulation produced by adrenaline and dopamine were of similar magnitude (see Results). These changes are presumed to reflect cardiovascular changes in this vascular bed. It therefore seems unlikely that the observed effects of dopamine on thrombin-induced cerebral platelet accumulation were due to its circulatory effects.

In conclusion, these experiments demonstrate that, despite the failure of dopamine D1 agonists to inhibit platelet accumulation *in vivo* reported previously, drugs of this class may yet have potential uses as anti-thrombotics since dopamine D1 receptor activation appears to underly the inhibitory effect of dopamine on platelet accumulation in the cerebral vasculature *in vivo*. When investigating the antithrombotic effects of these drugs, however, it will be important to consider their effects upon platelet accumulation and trapping in the pulmonary vasculature. Although dopamine can modify platelet function in the cerebral vasculature *via* α-adrenergic receptor stimulation, no such effects were observed with adrenaline in these experiments. This finding indicates that dopamine may have an important role in regulating physiological platelet aggregation and this activity is distinct from that observed with the adrenergic agonist, adrenaline.

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