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Pretreatment with aspirin does not influence the pressor response to α_2-adrenoceptor agonists in conscious rabbits

J. A. M. HANNAH, C. A. HAMILTON*, J. L. REID, *University Department of Materia Medica, Stobhill General Hospital, Glasgow, G21 3UW, UK*

It has proved relatively easy to demonstrate pressor responses mediated via α_2-adrenoceptors in-vivo and in whole blood perfused vascular beds, but not in in-vitro work. The possibility that platelet α_2-adrenoceptor activation, with subsequent release of vasoactive prostanoids, contributes to the pressor response to α_2-adrenoceptor agonists was investigated. The pressor response to the α_2-adrenoceptor agonist BHT 920 (Alefexole) was compared in rabbits pretreated with distilled water or aspirin (3×200 mg kg^{-1} by gavage). Aspirin pretreatment had no significant effect on responses to BHT 920; thus, prostanoid formation does not appear to be an important mechanism contributing to postsynaptic α_2-adrenoceptor activation.

In view of the location of α receptors in a wide range of tissues and sites, the terminology α_1 and α_2 is preferable to previous postsynaptic and presynaptic usage, particularly so as receptors resembling the α_2 subtype, previously called presynaptic, have been demonstrated at postsynaptic sites (Docherty et al 1979) and outwith synapses on platelets (Grant & Scrutton 1979). Postsynaptic or post-junctional α_2 receptors have been proposed to be located on vascular smooth muscle and to contribute to the pressor response to α agonists (Docherty & McGrath 1980).

The initial pressor response to α_2-adrenoceptor agonists has several characteristic features: the maximum response is much smaller, even after high concentrations of agonist, than that seen with α_1-adrenoceptor stimulation; tolerance develops after their repeated administration; there is difficulty in consistently demonstrating a pressor response or a contractile response using in-vitro vascular preparations. The latter observation is confusing since it has been proved relatively easy to demonstrate pressor responses mediated via α_2-adrenoceptors either in-vivo or in whole blood perfused vascular beds (Langer et al 1980; Madjar et al 1980). Postsynaptic α_2-adrenoceptors have been reported only in the dog saphenous vein (Shepperson & Langer 1981). The requirement for perfusion with whole blood raises the possibility that vasoconstriction results indirectly from mediator release from platelets or other elements in blood.

Platelets have α_2-adrenoceptors on their surface stimulation of which leads to aggregation and release of vasoactive agents including thromboxane (Verhaeghe & Janssens 1981) a potent vasoconstrictor (Moncada & Vane 1979).

* Correspondence.

We have investigated the hypothesis that the platelet α_2-adrenoceptor activation with subsequent release of vasoactive prostanoids contributes to the pressor response to i.v. α_2-adrenoceptor agonists in-vivo. The effects of aspirin (salicylic acid) on pressor responses to BHT 920 (Alefexole, Boehinger Ingelheim, Bracknell, Berks, UK) a selective α_2-agonist (Van Meel et al 1981) has been studied.

Methods

Six male New Zealand white rabbits (2·2–2·8 kg) received 10 ml of distilled water by gastric intubation at 10.00 and 17.00 h on the day preceding the study. Each rabbit received a further 10 ml of water the next day at 10.00 h and the experiment was started at 11.00 h. Three days later, the same group of rabbits received the dose regimen as above, but had 200 mg kg^{-1} aspirin added to the 10 ml of water they received by gavage. This dose of aspirin was selected as it has been shown in preliminary experiments to completely inhibit platelet aggregation in response to ADP and collagen in the rabbit.

A second control group of 6 rabbits received no aspirin treatment but were otherwise subjected to the same experimental procedure as the first group of animals.

Under local anaesthetic (2% lignocaine) cannulae were inserted into the central artery and vein of the ear for measurement of mean arterial pressure and injection of drugs (Hamilton et al 1982). After at least 1 h recovery in a quiet room, pressor dose responses to BHT 920 (35, 175, 350 μg kg^{-1}) were investigated. BHT 920 was dissolved in 0·9% NaCl and administered through the venous cannula.

Mean arterial pressure was recorded on a Grass Model 7 polygraph and heart rate counted from the phasic pressure trace. The maximum rise in arterial pressure and change in heart rate after each dose of BHT 920 was recorded for each animal and the results presented as mean ± s.d. for the group of 6. Responses to BHT 920 with and without aspirin pretreatment were compared by analysis of variance.

Results

No significant differences in baseline blood pressure (74 ± 7 mm Hg and 80 ± 4 mm Hg) or heart rate (230 ± 21 and 233 ± 25 beats min^{-1}) were observed when control animals were studied on two occasions three days apart.

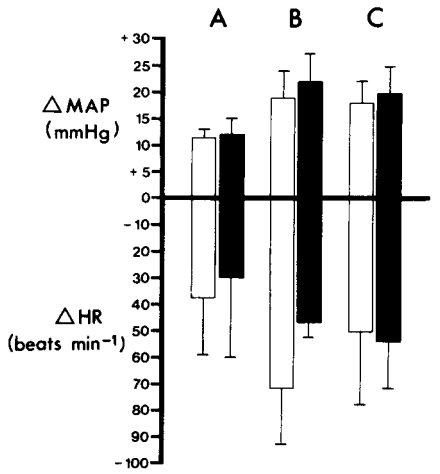

FIG. 1. Changes in mean arterial pressure and heart rate after i.v. BHT 920 (35–350 μg kg^{-1}) A, B, C = BHT 920 at 35, 150 and 350 μg kg^{-1} respectively. □ Saline pretreated group; ■ Aspirin pretreated group. Results are shown as mean ± s.d. n = 6 rabbits per group.

Intravenous BHT 920 caused an immediate dose-related increase in blood pressure and bradycardia in all animals. The rise in mean arterial pressure was similar on the two study days. 35 and 175 μg kg^{-1} BHT 920 caused rises in mean arterial pressure of 9 ± 3 and 14 ± 2 mm Hg on the first day and 11 ± 3 and 15 ± 3 on the second occasion. The fall in heart rate did not differ significantly between study days. In the experimental group of animals aspirin pretreatment did not significantly change baseline blood pressure (82 ± 7 and 75 ± 6 mm Hg after control and aspirin pretreatment) or heart rate (201 ± 24 and 218 ± 35 beats min^{-1} respectively). Similar rises in pressure to BHT 920 were observed after water and aspirin treatment (Fig. 1). In our study no fall in blood pressure was observed after BHT 920.

Discussion

It has been reported that α-receptors may modulate prostaglandin release from the rat mesenteric vascular bed (Pipili & Poyser 1982) and that in-vitro aspirin increased the responses to noradrenaline (Fiotakis & Pipili 1983). In the present study aspirin pretreatment did not alter the pressor response to the α_2-adrenoceptor agonist BHT 920 in-vivo. As this dose of aspirin will substantially block the activity of cyclo-oxygenase and interfere with production of thromboxanes, it is unlikely that a release of a vasoconstrictor prostaglandin-like material from platelets or other sites, is implicated in the pressor response to α_2-agonists.

It is still not clear why it is difficult to demonstrate vascular α_2-adrenoceptors in isolated preparations, but a possible explanation is that they are located predominantly on small resistance vessels, for which there is no suitble in-vitro preparation. This does not, however, explain why α_2-mediated pressor responses can be observed in blood perfused preparations (Langer et al 1980; Madjar et al 1980).

The site and role of vascular α_2-receptors remains to be determined; however, prostanoid formation does not appear to be an important contributory mechanism.

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