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Cardiac inotropes inhibit the oedema caused by nifedipine in rabbit skin

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1 We have shown previously that exposing the rat or rabbit microcirculation to nifedipine increases the permeability of the post-capillary venule, the segment of microcirculation that is known to control inflammatory oedema.

2 In the present study modulation by the inotropes isoprenaline, dopexamine and dobutamine of nifedipine-induced oedema was examined in the rabbit skin microcirculation by measuring the localised leakage of ^{125}I-radiolabelled albumin after the i.d. injection of agents.

3 Coinjection of isoprenaline (10^{-11} moles per site), dopexamine (10^{-10} moles per site) or dobutamine (10^{-10} moles per site) suppressed significantly ($P<0.05$) the oedema response to nifedipine ($10^{-7.2}$ moles per site) in the rabbit dorsal skin microcirculation.

4 To confirm the oedema suppresser effect of the inotropes, dopexamine or dobutamine were also coinjected with histamine 10^{-8} + PGE_2 10^{-10} moles per site, or bradykinin 10^{-10} + PGE_2 10^{-10} moles per site. Both inotropes at 10^{-10} moles per site reduced significantly ($P<0.05$) the leakage of albumin caused by bradykinin + PGE_2 and histamine + PGE_2.

5 When measured by laser Doppler, basal local skin blood flow increased at 30 min by $57\pm14\%$ with nifedipine $10^{-7.2}$ moles per site and $15\pm11\%$ with isoprenaline 10^{-11} moles per site. Isoprenaline did not suppress the blood flow response to nifedipine, the response to coinjection being $68\pm11\%$.

6 Oedema caused by nifedipine can be suppressed by low concentrations of β-adrenergic agonists that do not suppress the blood flow response to nifedipine. This suggests that cardiac inotropes can influence non-inflammatory changes in microvascular permeability.

Keywords: Nifedipine; calcium channel antagonists; cardiac inotropes; oedema; post-capillary venule; dopexamine; dobutamine; isoprenaline; permeability

Introduction

The use of calcium antagonists is often limited by the side-effect of peripheral oedema (Lewis, 1983; Murphy *et al*., 1983). We have shown recently that nifedipine can act locally in the microcirculation to cause oedema by increasing the permeability of post-capillary venules (Taherzadeh & Warren, 1997). Although not previously implicated in cardiovascular pharmacology, post-capillary venules are known to control the oedema response to inflammatory stimuli (Majno *et al*., 1961). Agents such as histamine or bradykinin are thought to contract actin and myosin of the endothelial cytoskeleton (Majno *et al*., 1969; Joris *et al*., 1972; Simionescu *et al*., 1978). This opens gaps which appear in the interendothelial junctions and allow the passage of fluid. Stimulation of endothelial cell β-receptors has the opposite effect, relaxing the cytoskeleton, closing intercellular gaps and reducing hydraulic permeability (Baulk & McDonald, 1994).

We postulated that β-adrenergic agonists may suppress oedema caused by stimuli other than inflammation. The infusion of low doses of β-adrenergic agonists can reduce peripheral oedema in severe heart failure. Although this benefit is usually attributed to their inotrope and renal effects it is possible that they could also act on the microvascular permeability barrier. The present experiment tested the hypothesis that the inotropes isoprenaline, dopexamine and dobutamine may act locally and antagonise the effect of nifedipine on the post-capillary venule of an *in vivo* skin model of oedema. Isoprenaline is a non-selective β-adrenergic agonist, whilst dopexamine acts on dopamine receptors as well as β-receptors. Dopexamine is a potent β_2 and weak β_1-adrenergic agonist (Brown *et al*., 1985; Smith, 1988). The pharmacological effects of dobutamine are more complex but it may be more selective for β_1 than for β_2 receptors (Hoffman & Lefkowitz, 1990). We wished to test if low dose β-adrenergic stimulation, known to suppress oedema formation in skin models of inflammation, also suppresses nifedipine-induced oedema.

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Methods

Animals

Male New Zealand white rabbits weighing 2.5–3.0 kg were anaesthetised with 30 mg kg^{-1} i.v. injection of pentobarbitone and the dorsal skin was shaved with electric clippers. During the experiment anaesthesia was maintained with sodium pentobarbitone in an air conditioned room at 20–23°C. All injections into skin sites with test agents were given in 100 μl of buffer via a 27-wire gauge needle.

Measurement of oedema formation

Local oedema formation was measured as the intradermal accumulation of ^{125}I-human serum albumin, 1.5 μCi kg^{-1}, which was injected i.v. 5 min before the test agents were given. Test agents were dissolved in 100 μl of saline and injected intradermally in a balanced site pattern in quadruplet. After 30 min, the animal was killed with an overdose of pentobarbitone and a 5 ml blood sample was taken by cardiac puncture into heparin (10 u ml^{-1} final concentration). The skin was removed and the injection sites excised with a 17 mm diameter punch. Skin and plasma samples were placed in tubes and counted in an automatic γ-counter. Oedema formation was expressed by dividing each skin ^{125}I count by the radioactivity in 1 μl of plasma at death.

Measurement of skin blood flow

The dorsal skin of anaesthetised rabbits was shaved and depilated using a commercial depilating cream. The skin was then

rinsed thoroughly with warm water and the animals left for 1 h before measurements were taken. Circular areas of skin were marked out in the dorsal skin in four quadrants, up to 10 sites per sector. Before the injection of test compounds, baseline blood flow was measured in the marked sites using a Perimed II laser Doppler flow probe (Perimed, Stockholm, Sweden) as described previously (Warren *et al*., 1994). The probe was held at the centre of the marked circle and at right angles to the skin by a 3 cm diameter guide. Results were recorded as red blood cell flux (the number of moving red cells detected by laser beam multiplied by the mean cell velocity) and expressed as a percentage of a standardized signal. The laser Doppler was set at 4 Hz, gain 3, and at a time constant of 1.5 s. The output was recorded on a Maclab analog-digital signal converter and Macintosh Apple computer set at an input of 10 V and a chart speed of 4 mm s^{-1}.

Each reading is the mean of three measurements taken for 15 s, interspersed by a 10 s pause. Test agents were injected in 0.1 ml volumes using a 27-wire gauge needle to raise a bleb in the centre of the marked circle. The percentage increase in flow was calculated by comparing the 15 and 30 min readings with the preinjection basal reading in the same site. The injection site pattern was varied in each sector to avoid the influence of anatomical skin site variation. Injection of each test agent was replicated four times, one per quadrant.

Preliminary experiments showed that measuring responses at 15 and 30 min after injection of the agents helped to avoid the early blood flow response caused by the traumatic effect of injection. Results are expressed as the percentage change from basal and data points are the mean of three rabbits.

Materials

The nifedipine used was the generous gift of Bayer PLC (Berkshire, U.K.). The solution of 2% nifedipine in 100% ethanol was diluted 100-fold with saline. A maximal dose of $10^{-7.2}$ moles per site was used. This dose contained a 1% concentration of ethanol and higher doses were not used so as to avoid the pharmacological effects of ethanol. Nifedipine was stored in the absence of light and all dilutions and experiments were carried out under the illumination of a sodium lamp (580 nm wavelength). This was to avoid radiation mediated degradation of nifedipine which is daylight and UV light sensitive.

For all test agents, dilutions were made with saline. Calcium chloride was added to give a final concentration of 1 mM to minimise an alteration in tissue calcium following dilution by the injected volume.

Dopexamine HCl was the generous gift of Speywood Pharmaceuticals Ltd (Maidenhead, U.K.). Dopexamine was initially dissolved in 0.01% EDTA and further dilutions were made with saline. Dobutamine HCl (Dobutrex) was from Eli Lilly & Co Ltd (Basingstoke, U.K.). ^{125}I-human serum albumin was from Amersham International Ltd, Amersham, U.K., and isoprenaline HCl (Saventrine IV) was from Pharmax Ltd (Bexley, England). Other drugs and chemicals were obtained from Sigma (Poole, U.K.).

Statistical analyses

Numerical results are expressed as mean ± s.e.mean. For the measurement of oedema and blood flow all data points are the mean of 3–6 animals, each experiment performed in quadruplet. Statistical comparisons were made with a two-tailed test using analysis of variance (ANOVA) and taken as significantly different if $P<0.05$

Results

Isoprenaline suppresses the oedemagen action of nifedipine

The intradermal injection of nifedipine ($10^{-7.2}$ moles per site) increased plasma albumin leakage in the dorsal skin of male New Zealand rabbits (2.5–3.0 kg) from 6.2 ± 0.8 μl in control sites (ethanol 1%) to 10.0 ± 2.0 μl (Figure 1). The mean plasma albumin leakage at sites of isoprenaline (10^{-11} moles per site) and saline injection were 5.8 ± 0.6 and 5.8 ± 0.8 μl, respectively. On the other hand, coinjection of isoprenaline and nifedipine at the above doses suppressed the nifedipine induced oedema significantly from 10.0 ± 2.0 to 6.8 ± 0.8 μl ($P<0.05$, $n=6$).

Blood flow changes caused by isoprenaline and nifedipine

Local microvascular blood flow was measured in the shaved dorsal skin of rabbits by laser Doppler flow probe at 15 and 30 min (Figure 2). The changes in flow are expressed as the percentage above basal blood flow. At 15 min nifedipine $10^{-7.2}$, isoprenaline 10^{-11} moles per site, and the two agents coinjected, increased basal blood flow by 32 ± 8%, 68 ± 11%, and 74 ± 13%, respectively. Blood flow changes at sites of saline and ethanol (1%) as controls were 5 ± 8% and 6 ± 10%, respectively. At 30 min basal blood flow increased by 57 ± 14% with nifedipine ($10^{-7.2}$ moles per site) and by 15 ± 11% with isoprenaline (10^{-11} moles per site). The blood flow change with nifedipine and isoprenaline coinjected remained high at 68 ± 11%. Changes in flow at control sites at 30 min were 2 ± 8% and 9 ± 16% for saline and ethanol (1%), respectively.

Modulation of nifedipine induced oedema by dopexamine or dobutamine

The effects of the inotropes dopexamine and dobutamine on the oedema inducing action of nifedipine were examined in the same manner as with isoprenaline (Figure 3). Two doses of both drugs were tested in the dorsal skin of rabbits. The injection of nifedipine ($10^{-7.2}$ moles per site) and its coinjection with dopexamine (10^{-11} or 10^{-10} moles per site) reduced the oedema from 6.0 ± 0.8 μl to 5.2 ± 0.7 and 4.6 ± 0.4 μl, respectively. When nifedipine was injected with dobutamine (10^{-11} or 10^{-10} moles per site), the plasma albumin leakage was reduced from 6.0 ± 0.8 μl to 5.3 ± 0.6 and 5.0 ± 0.7 μl, respectively. The oedema response to the control (ethanol 1%) was

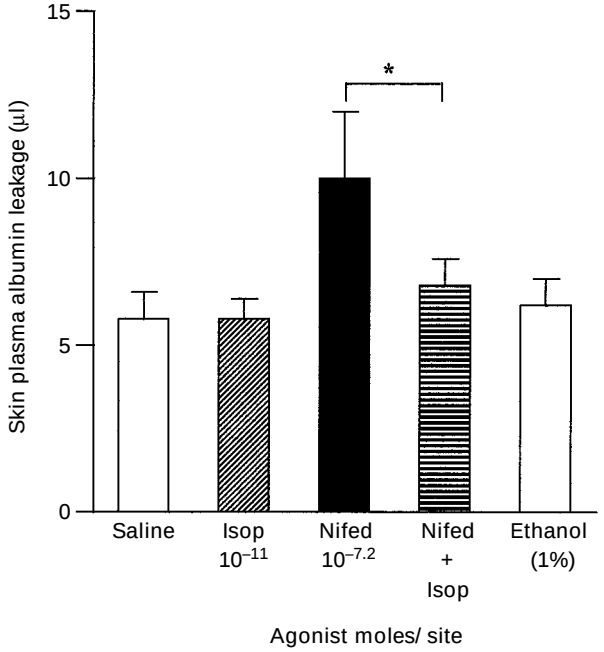

Figure 1 Microvascular plasma albumin leakage (μl) caused by the local injection of $10^{-7.2}$ moles per site nifedipine or the coinjection of nifedipine with 10^{-11} moles per site isoprenaline in rabbit skin. Plasma albumin leakage was measured 30 min after the intradermal injection of agents. Isoprenaline suppressed the oedema induced by nifedipine significantly (*$P<0.05$). Data are mean ± s.e.mean of 6 rabbits, 4 replicates per animal.

4.6 ± 0.4 μl. The effect of coinjection of both dopexamine and dobutamine at 10^{-10} moles per site to suppress the oedema response to nifedipine was significant ($P<0.05$, $n=6$).

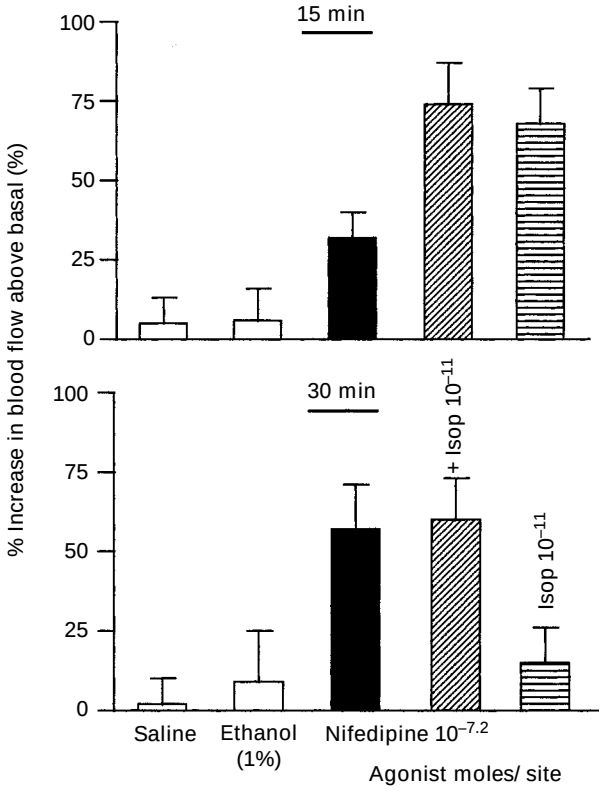

Figure 2 Change in basal blood flow caused by the local injection of nifedipine ($10^{-7.2}$ moles per site) in the rabbit skin microvasculature at 15 and 30 min compared to nifedipine with 10^{-11} moles per site isoprenaline. Coinjection of isoprenaline with nifedipine increased blood flow further at 15 min. Each datum point is the mean $\pm$ s.e.mean of 3 rabbits, 4 replicates per animal.

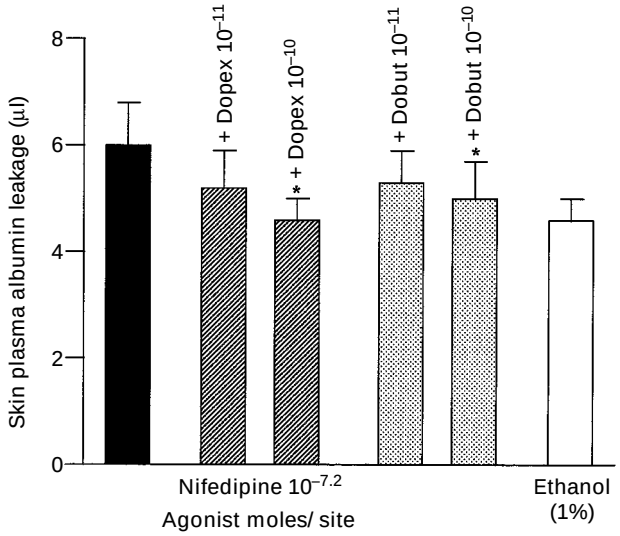

Figure 3 Microvascular plasma albumin leakage (μl) in rabbit skin caused by the local injection of $10^{-7.2}$ moles per site nifedipine, nifedipine with 10^{-11} moles per site dopexamine and nifedipine with 10^{-11} moles per site dobutamine. Both dopexamine and dobutamine suppressed oedema induced by nifedipine significantly (*$P<0.05$). Data are mean $\pm$ s.e.mean of 6 rabbits, 4 replicates per animal.

Modulation of bradykinin + PGE_2 or histamine + PGE_2-induced oedema by dopexamine or dobutamine

This study examined the suppresser action of dopexamine and dobutamine on the oedema response to mediators known to cause large increases in oedema in the model used. The effect of these inotropes was tested on the oedema response to bradykinin + PGE_2 or histamine + PGE_2 in the dorsal skin of rabbits (Figure 4). Coinjection of dopexamine 10^{-11} or 10^{-10} moles per site with bradykinin 10^{-10} moles per site + PGE_2 10^{-10} moles per site, $n=6$ rabbits, reduced the leakage of albumin induced by bradykinin + PGE_2, from 53 ± 8 μl to 51 ± 7 and 44 ± 6 μl ($P<0.05$), respectively. Similarly, coinjection of bradykinin + PGE_2 with dobutamine (10^{-11} or 10^{-10} moles per site, $n=6$) reduced the oedema from 53 ± 8 μl to 52 ± 10 and 46 ± 9 μl ($P<0.05$), respectively. When dopexamine at 10^{-10} or 10^{-11} moles per site was coinjected with histamine 10^{-8} moles per site + PGE_2 10^{-10} moles per site the leakage of albumin induced with histamine + PGE_2 was reduced from 54 ± 12 µl to 40 ± 10 ($n=6$, $P<0.05$) and 34 ± 8 μl ($n=6$, $P<0.05$), respectively. Dobutamine also at the above doses reduced the oedema of histamine + PGE_2 from 54 ± 12 μl to 45 ± 10 and 41 ± 11 μl ($n=6$, $P<0.05$), respectively.

Discussion

The present experiment shows that isoprenaline can suppress the local oedema response to nifedipine when the two drugs are coinjected intradermally. This suppression occurred with a low dose of isoprenaline that has been shown previously to suppress the oedema response to inflammatory mediators (Warren *et al*., 1993; Kreienberg *et al*., 1994; Noel *et al*., 1995).

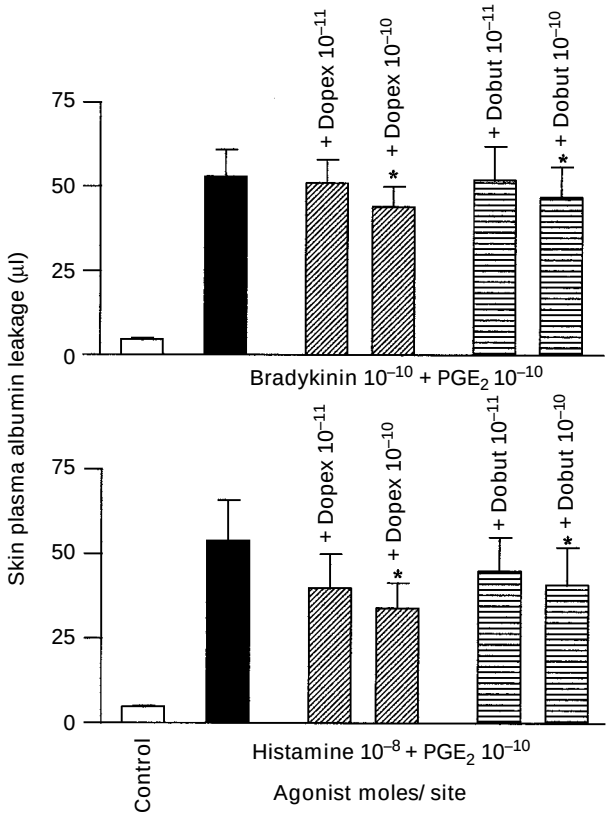

Figure 4 Effects of coinjection of dopexamine or dobutamine on the plasma albumin leakage caused by histamine + PGE_2 or bradykinin + PGE_2 in rabbit skin. Both dopexamine and dobutamine at 10^{-10} moles per site suppressed significantly histamine 10^{-8} moles per site + PGE_2 10^{-10} moles per site or bradykinin 10^{-10} moles per site + PGE_2 10^{-10} moles per site induced oedema (*$P<0.05$). Data are the mean + s.e.mean of 6 rabbits, 4 replicates per animal.

The cardiac inotropes dopexamine and dobutamine also suppressed oedema formation at similar low doses to isoprenaline. This was not restricted to nifedipine-induced oedema, but also occurred with oedema caused by bradykinin or histamine. The oedema suppressor effect of inotropes may be mediated predominantly by β_2-receptor stimulation as β_2-agonists suppress the plasma albumin leakage induced by a variety of inflammatory stimuli (Advenier *et al*., 1992; Underwood *et al*., 1992; Sulakvelidze & McDonald, 1994). This suppression can be explained by the stimulation of β-receptors on the endothelium with the modulation of the endothelial cytoskeleton via an increase in intracellular cyclic AMP. Endothelial cells contain the contractile elements actin and myosin and the main mechanism for inflammatory mediators to elicit oedema was proposed to be through the contraction of these elements leading to the formation of intercellular gaps (Shasby *et al*., 1982; Crone, 1986; Grega *et al*., 1986; Wysolmerski & Langunoff, 1990). These gaps are thought to be the principal site of water transport through the permeability barrier. Stimulation of endothelial adrenergic receptors may relax the actin–myosin of the cytoskeleton and close the intercellular gaps (Minnear *et al*., 1989; Patton *et al*., 1991). An alternative explanation for the anti-oedema action of β-adrenergic agonists is the relaxation of pericytes (Baulk & McDonald, 1994). It has been shown that cultured pericytes can contract in reponse to histamine and relax in response to isoproterenol (Kelley *et al*., 1988).

Vasodilatation alone has been suggested as the sole mechanism by which nifedipine induces oedema (Murad, 1990). It has been propsoed that the effect of calcium channel antagonists in the microcirculation can be explained by their intervention with autoregulation of microvascular blood flow or attenuation of postural vasoconstrictor reflexes (Gustafsson, 1987; Williams *et al*., 1989; Salmasi *et al*., 1991). It was suggested the drug causes post-capillary vasoconstriction and precapillary arterial dilation leading to an excessive rise in capillary hydrostatic pressure causing transcapillary fluid efflux (Gustafsson, 1987). Several lines of evidence now argue against this. Other vasodilators do not cause oedema to the same extent (Agostini *et al*., 1986; Weir *et al*., 1996) and even among the other calcium antagonists the oedema effect does not correlate with vasodilator activity (M. Taherzadeh & J.B. Warren, unpublished results). However, our topographical studies suggest the site of leak is the post-capillary venule and not the capillary (Taherzadeh & Warren, 1997). Although vasodilation can contribute to oedema formation by increasing microvascular hydrostatic pressure this cannot be the sole mechanism by which calcium antagonists induce local oedema.

There is some evidence that microvascular vasoconstrictors, such as endothelin, can suppress local oedema formation (Lawrence *et al*., 1995). For this reason we tested in this experiment if the suppression of oedema by isoprenaline was associated with a suppression of vasodilation. This was not the case. As expected the laser Doppler findings confirm that isoprenaline is a microvascular vasodilator in this model (Warren *et al*., 1993). Indeed, coinjecting isoprenaline with nifedipine slightly increased microvascular blood flow yet still suppressed the oedema response. The independency of the anti-oedema effect of β-adrenergic agonists from changes of blood flow and venous pressure has been reported previously (Beets & Paul, 1980; Erjefält & Persson, 1991).

The topographical location of nifedipine-induced microvascular leakage to the post-capillary venule has several implications. As this is the site that controls inflammatory oedema then the pharmacology of the two types of oedema might have common features. In many models of inflammatory oedema, β-adrenergic agonists or other agents that increase endothelial cell cyclic AMP suppress the oedema response (Suttorp *et al*., 1993; Warren *et al*., 1993). Our results support the hypothesis that topographical similarities between nifedipine-induced oedema and inflammatory mediator-induced oedema are associated with a similarity in their pharmacological suppression by β-adrenoceptor agonists.

In conclusion, we have shown that nifedipine-induced oedema has pharmacological similarities to inflammmatory mediator-induced oedema in that both can be suppressed by low doses of β-adrenoceptor agonists. This suggests that cardiac inotropes can influence non-inflammatory changes in microvascular permeability.

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