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Bradykinin induced wheal and flare is not mediated by histamine release or cyclooxygenase products

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The wheal and flare response to intradermal bradykinin was studied in man. The possibility that histamine and cyclooxygenase products are involved in the response to bradykinin was examined. Terfenadine given by mouth significantly inhibited the cutaneous response to histamine but the effect of bradykinin was unaltered. Similarly the cutaneous response to bradykinin was unchanged by aspirin.

Keywords wheal flare bradykinin antihistamine cyclooxygenase inhibition

Introduction

Wheal and flare formation in the skin in response to trauma follows both antidromic nerve stimulation, as part of an axon reflex, and local inflammatory mediator formation. The peptide substance P for instance when injected intradermally causes measurable histamine release (Barnes *et al.*, 1986). The size of the flare is reduced by treatment with both an antihistamine, and aspirin suggesting histamine and cyclooxygenase products may be involved (Fuller *et al.*, 1987a). This is also the case for the early flare produced by hCGRP, a substance shown *in vitro* to cause prostacyclin release from human umbilical vein endothelial cells (Crossman *et al.*, 1987). Bradykinin is a more potent stimulant of prostacyclin release from endothelial cells, both *in vitro* and *in vivo*. Further, this release *in vivo* can be blocked by pretreatment with aspirin (Heavey *et al.*, 1985). Therefore, we have examined the effects of the cyclooxygenase inhibitor, aspirin, and an antihistamine, terfenadine, upon bradykinin induced wheal and flare formation.

Methods

Six healthy adult male subjects gave informed consent to take part in the study which had approval from the local Ethics Committee. Bradykinin (1nmol in 50 μl) was injected into the volar surface of each forearm. Histamine (5 nmol in a similar volume) was also injected. One hour prior to the study the subjects had taken either 60 mg terfenadine or placebo in a double-blind, randomized protocol. In a second study the subjects took 600 mg aspirin or placebo 50 min before study.

The wheal and flare area were recorded by tracing over the region involved onto transparent sheets. The areas in sq cm were then measured from the sheets by planimetry using a microcomputer (Hewlett Packard). Flare was recorded at 5 min and wheal formation at 10 min. The data were analysed by analysis of variance.

Results

Histamine caused both flare and wheal. Bradykinin caused little flare formation but did cause a wheal.

Terfenadine (60 mg) reduced histamine induced flare by 80%; the flare area fell from 7.5 ± 2.0 on control to 1.4 ± 1.0 sq cm on terfenadine. Figure 1 shows the wheal areas formed in response to both bradykinin and histamine. Terfenadine caused a 40% reduction in histamine induced wheal area from 0.7 ± 0.2 sq cm on the control day to 0.4 ± 0.1 sq cm on the terfenadine day (significant at $P < 0.05$). Aspirin had no effect upon histamine induced wheal (0.8 ± 0.2 sq cm on aspirin day) nor flare (8.39 ± 2.2 sq cm on aspirin day).

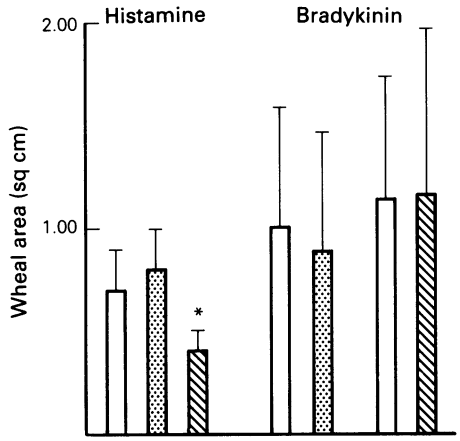

Figure 1 Wheal areas in response to intradermal histamine (5 nmol) and bradykinin (1 nmol) on control days (□), aspirin study days (▨), and on terfenadine study days (▧).
* Significant at $P<0.05$.

Bradykinin's wheal area was unaltered by either drug. On the placebo day the bradykinin induced wheal area was 1.0 ± 0.6 sq cm compared with 0.88 ± 0.6 sq cm on the aspirin study day, and on the terfenadine day the wheal area was 1.16 ± 0.8 sq cm, against the matching control of 1.14 ± 0.6 sq cm (see Table 1).

Discussion

This study has examined the effects of aspirin and terfenadine upon the response to intradermal bradykinin in man. The dose of bradykinin used was 1 nM and this has been seen to be close to the top of the dose-response curve for bradykinin induced wheal in man (Fuller *et al.*, 1987c). It was clear that terfenadine in this study markedly reduced the cutaneous effects of intradermal histamine, and previous studies have shown that antihistamines administered in a similar manner block the cutaneous effects of intradermal substance P, a compound known to release histamine from mast cells (Barnes *et al.*, 1986). The absence of any effect of terfenadine upon bradykinin's wheal response suggests that histamine release is not involved.

The dose of aspirin used in this study has been shown to block the production of the cyclooxygenase product prostacyclin in response to an intravenous infusion of bradykinin (Heavey *et al.*, 1985). The time of inhibition is short, but cyclooxygenase activity as assessed by the prostacyclin response to bradykinin is still very low at 50 min following aspirin administration, as was used in this study. Further, using this dosing schedule it has been seen that aspirin causes significant reduction in the flare response to intradermal substance P and neurokinin A in man (Fuller *et al.*, 1987a). It seems, therefore, that the cutaneous effects of bradykinin in man do not require the formation of cyclooxygenase products. This is in accordance with the observation that co-injected indomethacin did not alter blood flow, or plasma exudation in response to bradykinin in the rabbit (Williams, 1979).

The hypothesis that an acute inflammatory response requires an increase in blood flow and change in permeability is well established (Williams & Peck, 1977). Therefore, it is of importance to examine the possibility that agents which give rise to cutaneous inflammation may produce mediators themselves that bring about all or part of their effect. In the case of bradykinin this report shows that the cutaneous response is not dependent upon the formation of cyclooxygenase products, nor histamine. The former is all the more surprising since it is clear that it is a powerful stimulant of prostacyclin production both *in vitro* and *in vivo*. The two component hypothesis of inflammation would predict that such a vasodilator would potentiate the inflammatory response. Indeed, when PGE_2 is added to bradykinin in the skin of a rabbit, the plasma exudation caused by the latter is increased (Williams & Peck, 1977). It is, therefore, remarkable that an agent known for its power to release cyclooxygenase products

Table 1 The flare areas measured at 5 min and the wheal areas measured at 10 min following 1 nmol of intradermal bradykinin on control days, terfenadine and aspirin study days.

		Flare area (sq cm)	*Wheal area (sq cm)*
Bradykinin	Control	2.26 ± 0.89	1.14 ± 0.6
	Terfenadine	2.18 ± 0.69	1.16 ± 0.8
Bradykinin	Control	1.0 ± 0.9	1.00 ± 0.6
	Aspirin	1.2 ± 0.8	0.88 ± 0.6

when introduced into the skin (or the lungs (Fuller *et al.*, 1987b)) results in a response that is in no way modified by concomitant cyclooxygenase inhibition. The role of the generation of cyclooxygenase products in response to bradykinin remains unclear in the genesis of inflammation.

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References

Barnes, P. J., Brown, M. J., Dollery, C. T., Fuller, R. W., Heavey, D. J. & Ind, P. W. (1986). Histamine is released from skin by substance P but does not act as the final vasodilator in the axon reflex. *Br. J. Pharmac.*, **88**, 741–745.

Crossman, D., Dollery, C. T., MacDermot, J., MacIntyre, I. & McEwan, J. (1987). Effects of human calcitonin gene-related peptide on human endothelial cells. *Br. J. Pharmac.*, **90**, 38P.

Fuller, R. W., Conradson, T.-B., Dixon, C. M. S., Crossman, D. C. & Barnes, P. J. (1987a). Effect of sensory neuropeptides in the human skin. *Br. J. Pharmac.*, **92**, 781–788.

Fuller, R. W., Dixon, C. M. S., Cuss, F. M. & Barnes, P. J. (1987b). Bradykinin-induced bronchoconstriction in humans: Mode of action. *Am. Rev. resp. Dis.*, **135**, 176–180.

Fuller, R. W., Warren, J. B., McCusker, M. & Dollery, C. T. (1987c). Effect of enalapril on the skin response to bradykinin in man. *Br. J. clin. Pharmac.*, **23**, 88–90.

Heavey, D. J., Barrow, S. E., Hickling, N. E. & Ritter, J. M. (1985). Aspirin causes short lived inhibition of bradykinin-stimulated prostacyclin production in man. *Nature*, **318**, 186–188.

Williams, T. J. (1979). Prostaglandin E_2, prostaglandin I_2 and the vesicular changes of inflammation. *Br. J. Pharmac.*, **65**, 517–524.

Williams, T. J. & Peck, M. J. (1977). Role of prostaglandin mediated vasodilatation in inflammation. *Nature*, **270**, 530–532.

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