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# DORSAL ROOT VASODILATATION IN CAT SKELETAL MUSCLE

BY S. M. HILTON AND JANICE M. MARSHALL
*From the Department of Physiology, The Medical School, Birmingham, B15 2TJ*

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SUMMARY

1. A study has been made, in the cat anaesthetized with chloralose, of the effects of antidromic stimulation of dorsal roots $L_6$–$S_1$ on the blood flow through the gastrocnemius muscle.

2. Stimulation of the peripheral ends of the ligated dorsal roots with current pulses of 0·3–0·5 msec duration and at intensities most effective in activating the smaller afferent fibres, for periods of 15–20 sec, produced a 50–60 % increase in muscle vascular conductance which was slow in onset and long outlasted the stimulus.

3. This muscle vasodilatation could be evoked in the paralysed animal and was unaffected by guanethidine or atropine. It was, however, greatly reduced or even abolished by the prostaglandin synthetase inhibitors, indomethacin or acetylsalicylic acid, in doses which had no effect on the dilatation produced by a local injection of acetylcholine or the functional hyperaemia induced by muscle contraction.

4. It is concluded that activity in the smaller myelinated or unmyelinated afferent fibres of skeletal muscle produces an increase in muscle blood flow which is mediated, at least in part, by prostaglandins locally synthesized within the muscle.

## INTRODUCTION

Application to the skin of various agents, particularly those of a noxious or injurious nature, induces a local flare reaction which is due to dilatation of the smaller blood vessels (Doi, 1920; Krogh, 1920; Langley, 1923; Feldberg, 1926; Lewis, 1927; Hilton & Holton, 1954). This response has generally been found to occur only where there is an intact sensory innervation (Bayliss, 1902; Krogh, 1920; Ranson & Wightman, 1922; Lewis & Grant, 1924; Feldberg, 1926). It is also well known that a similar vasodilatation can be produced in the skin by antidromic stimulation of the sensory nerve supply (Langley, 1923; Feldberg, 1926; Hilton & Holton, 1954). This response is most easily demonstrated when the mode of stimulation is such as to excite the smaller myelinated and unmyelinated afferent fibres (Hinsey & Gasser, 1930; Celander & Folkow, 1953*b*). Considered together, these observations have long been taken to suggest that activity in the smaller sensory nerve fibres of cutaneous tissue initiates release of a substance which acts locally as a vasodilator.

Lewis (1927) proposed that such a response would be functionally advantageous in promoting the movement of nutrients and metabolites in regions of tissue damage. If this were so, there would be every reason to suppose that such a reaction would

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not be restricted to the skin, yet there is very little evidence for its existence in other tissues. Ebbecke (1917) was unable to reproduce the phenomenon on the surface of the spleen or liver, and Florey (1925) could not detect signs of local flare around sites of damage in the pia overlying the cerebral cortex. Bayliss found that antidromic stimulation of dorsal roots evoked a substantial increase in tissue volume of the skinned hind limb with paw ligated (1901) and of the intestine (1902) which he took to indicate vasodilatation in skeletal muscle and intestinal vasculature respectively. But Celander & Folkow (1953*a*, *b*) reported that, though heating or electrical stimulation of mixed peripheral nerves or dorsal roots produced a substantial increase in the venous outflow from the hind paw, it had no effect on venous outflow from a loop of the jejunum or from the hind limb when the paw and skin were excluded. This led them to refute the suggestion made by Bayliss (1901, 1902) and to conclude that antidromic vasodilatation was only of functional importance in superficial tissues. The only contrary result which remains undisputed is that of Duke-Elder & Duke-Elder (1931), who demonstrated that a local dilatation could be produced in the cornea, iris and conjunctiva by antidromic stimulation of the trigeminal, which is a pure sensory nerve. This has been confirmed by many workers, including Maurice (1954) and Ambache (1955).

Thus, the evidence, such as it is, tends to support Lewis's original concept that antidromic vasodilatation 'forms a mechanism of defense peculiar to superficial and sensitive structures such as the skin and conjunctival sac'. However, in view of the rather crude stimulating and recording techniques used in the earlier studies, further investigation seemed justified before the possibility of antidromic dilatation in other tissues was to be finally excluded. Accordingly we carried out experiments in which the venous outflow from the gastrocnemius muscle was isolated and continuously recorded, and electrical stimuli of various parameters were applied to the peripheral ends of the appropriate dorsal roots. In such a preparation, changes in blood flow can be elicited in the absence of changes in arterial blood pressure which demonstrates a response in the vascular bed of skeletal muscle, as already briefly reported (Hilton & Marshall, 1975).

## METHODS

Experiments were performed on thirty female cats anaesthetized with an intravenous injection of $\alpha$-chloralose (British Drug Houses Ltd.) 70–75 mg/kg after anaesthesia had been induced with ethyl chloride and halothane. The trachea was cannulated and arterial blood pressure monitored from a carotid artery via a cannula connected to a pressure transducer (Bell and Howell Ltd). Laminectomy was performed to expose the lumbar and sacral segments $L_4$–$S_1$. The gastrocnemius muscle was prepared for registration of changes in muscle blood flow as described previously (Hilton, 1953). The femoral venous outflow was passed via polyethylene cannulae through a photoelectric drop-counter and returned to the femoral vein more centrally. The saphenous artery was cannulated retrogradely for close arterial injection into the muscle. Heparin, 1000 $\mu$g/kg, was injected 1 hr after all dissection had been completed and before the femoral vein was cannulated.

The animal was then moved to the prone position and a paraffin pool was made around the exposed vertebral column. The dura was incised lengthwise and the dorsal roots $L_6$, $L_7$ and $S_1$ on the side ipsilateral to the isolated gastrocnemius were carefully dissected and sectioned close to the cord. The peripheral ends of one or more roots were arranged over bipolar silver wire electrodes and stimulated with rectangular pulses of 0·1–0·5 msec duration at intensities of 0·5–15 V and frequencies of 0·5–20 Hz for periods of 15–20 sec.

In many experiments the sciatic nerve was exposed, the peroneal branch sectioned and a Perspex cuff bearing a pair of platinum electrodes was applied to the tibial branch. Muscle contraction was elicited by square wave pulses of 0·1 msec duration applied at intensities of 1–8 V and frequencies of 1–10 Hz. On several occasions nerve activity was recorded from the sciatic nerve on the same side as the dorsal roots whilst they were stimulated. In these experiments the peroneal branch of the sciatic nerve was sectioned a few centimetres beyond its origin and filaments which were dissected free from it were arranged over bipolar silver-wire recording electrodes, the whole site being incorporated into a paraffin pool. Nerve activity was displayed on an oscilloscope (Tetronix 565) photographed by an oscilloscope camera and processed by a signal averager (Ortec).

## RESULTS

The sole response observed on antidromic stimulation of the dorsal roots was an increase in the venous outflow of the gastrocnemius muscle with no change in systemic arterial pressure (Fig. 1). Maximum effects on blood flow were produced by stimulation with pulses of 0·3–0·5 msec duration and intensities of 8–10 V. When

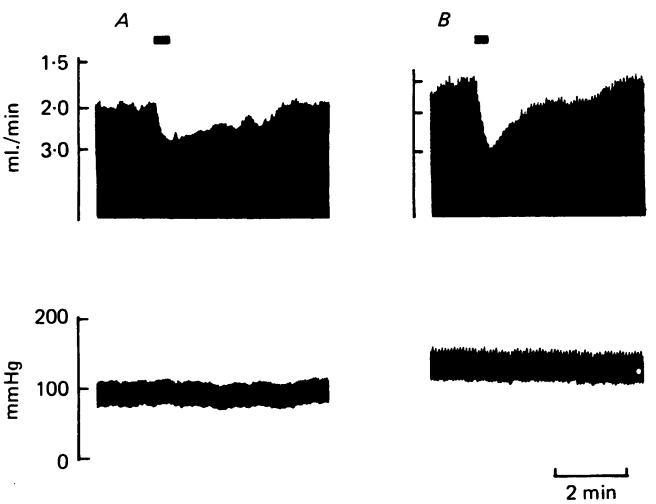


Fig. 1. Examples taken from two different cats of muscle vasodilatation produced by stimulation of peripheral end of dorsal root $L_7$ with pulses of 10 V intensity and 0·3 msec duration at a frequency of 10 Hz for 20 sec. Upper traces: venous outflow from gastrocnemius muscle. Lower traces: arterial blood pressure. (The bars above the flow records indicate the period of stimulation.)

the pulse width and intensity were supramaximal, the magnitude of the dilatation was graded according to the stimulus frequency, the threshold being 3–4 Hz and the response reaching a maximum at 10–12 Hz. When all stimulus parameters were supramaximal, the largest dilatations were produced by stimulation of $L_7$ and led to flow increases of 50–60 %. Stimulation of $L_6$ or $S_1$ alone increased flow by no more than 10–15 %, but the response could be augmented up to an 85 % increase from the resting level of flow when all three roots were stimulated simultaneously. When studying possible mediators of this dilator response, described later, $L_7$ was stimu-

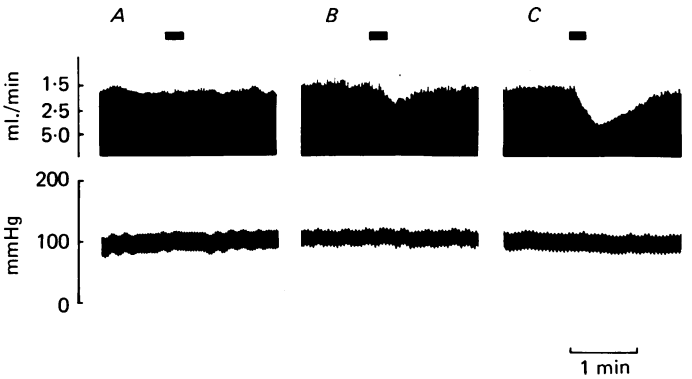


Fig. 2. Effect of varying pulse duration on the response to stimulation of peripheral end of dorsal root $L_7$. Cat, chloralose. Traces as in Fig. 1. Changes in muscle blood flow produced by stimulation with 20 sec trains of rectangular pulses of intensity 10 V, frequency 10 Hz and durations (*A*) 0·1 msec, (*B*) 0·15 msec and (*C*) 0·3 msec.

lated alone: analysis was only carried out on dilator responses of at least 50 % over resting flow (range 50–60 %, mean 53 %, see Table 1).

The relationship between the magnitude of the muscle vasodilatation and the pulse width is illustrated in Fig. 2. The fact that relatively long pulses of high intensity were necessary to elicit the dilatation indicated that activity in the small diameter afferent fibres was particularly important for the response, as would have been expected from the early work of Hinsey & Gasser (1930) on antidromic vasodilatation in skin. Electroneurogram recordings supported this conclusion. When the stimulus pulses were short and intensities low, the spike discharge recorded in the peroneal nerve was of fairly short latency, indicating excitation of fast-conducting, myelinated fibres. When pulses were of at least 0·15 msec duration and about 6 V in

TABLE 1. Effects of different substances on the response to stimulation of peripheral end of cut dorsal root $L_7$. Responses are given as percentage increases from resting flow. In each experiment, these were averaged from three responses before, and three responses after, administering each agent; the ranges given are the ranges of these averages

| | Test substance | | | |
|---|---|---|---|---|
| | Gallamine 4 mg/kg I.V. | Atropine 0·1–1 mg/kg I.V. | Indomethacin 0·05–0·2 mg/kg I.A. or 0·5–2 mg/kg I.P. | Acetylsalicylic acid 20–25 mg/kg I.P. or I.V. |
| No. of expts. | 4 | 5 | 12 | 5 |
| Control | | | | |
| Range | 52–56 | 52–60 | 50–60 | 50–58 |
| Mean | 55 | 57 | 57 | 56 |
| After drug | | | | |
| Range | 50–55 | 54–60 | 0–30 | 18–35 |
| Mean | 52 | 58 | 10 | 23 |

intensity, a long latency discharge appeared which reached a maximum with pulses of 0·3 msec duration and about 8 V intensity, exactly those values which were most effective in eliciting the dilator response. The conduction velocity calculated for the late wave of activity was approximately 1·25 m/sec, indicating discharge in poorly myelinated or unmyelinated fibres.

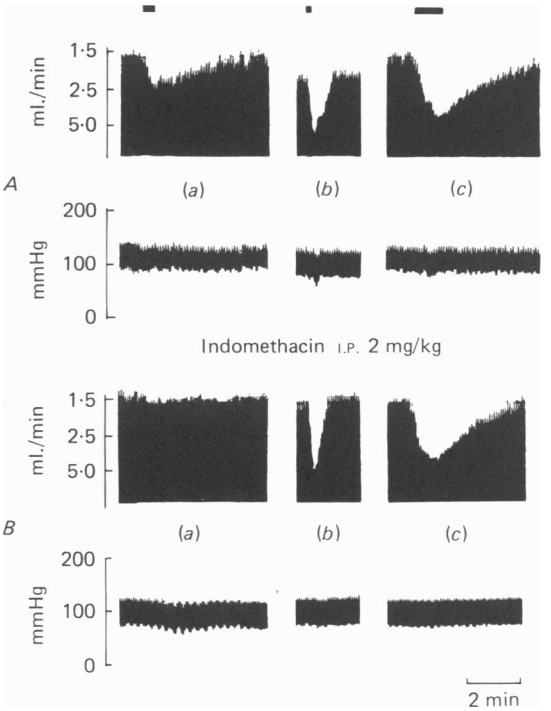


Fig. 3. Cat, chloralose. Traces as in Fig. 1. *A*, records showing responses to (*a*) stimulation of peripheral end of dorsal root $L_7$ with pulses of intensity 10 V and duration 0·3 msec at 10 Hz, (*b*) close arterial injection of ACh (1 $\mu$g), and (*c*) stimulation of sciatic nerve with pulses of 8 V, duration 0·1 msec at a frequency of 2 Hz. *B*, responses to same stimuli as in *A*, 30 min after indomethacin 2 mg/kg I.P. Horizontal bars show timing of each stimulus for records in *A* and *B*.

The conduction time for the late C wave from the site of stimulation to the gastrocnemius muscle was 125–135 msec, but the dilator response did not begin until 10–15 sec after the onset of stimulation and was thus of relatively long latency. The peak flow was reached 10–15 sec later, after which blood flow slowly returned to control level over the next 3–4 min, usually uninterruptedly, as shown in Fig. 1*A*, but sometimes after a plateau, as illustrated in Fig. 1*B*. Thus the response was slow to develop and long outlasted the 15–20 sec stimulation period.

The dilatations were not associated with overt muscle contractions and they were comparable in every respect after the animal had been paralysed with gallamine (Flaxedil, 4 mg/kg I.V.), as shown in Table 1. There was no change in the response in experiments in which the ventral roots were cut and pulled well away from the

stimulating electrode, or when the cord was transected at $L_5$, i.e. between the most caudal outflow of the preganglionic sympathetic neurones and the level of dorsal root stimulation. Atropine in doses of 0·1–1 mg/kg I.V., which was sufficient to abolish vasodilator responses to close arterial injection of acetylcholine (ACh, 1 $\mu$g), did not affect the dorsal root dilatation (Table 1), neither did guanethidine (two experiments) in doses which are known to block effects of adrenergic nerve stimulation in the cat (4 mg/kg, I.V.).

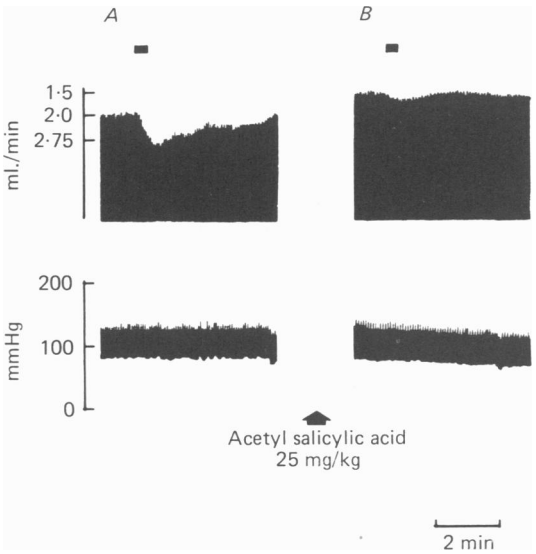


Fig. 4. Cat, chloralose. Traces as in Fig. 1. Recordings showing responses to stimulation of peripheral end of dorsal root $L_7$ with pulses of intensity 10 V, duration 0·3 msec at a frequency of 10 Hz (*A*) before and (*B*) 20 min after acetylsalicylic acid (25 mg/kg I.P.).

The long latency and prolonged nature of the response suggested the mediator to be a substance which was newly synthesized within the muscle and which was broken down or diffused away very slowly. Prostaglandins can be synthesized by many tissues and several members of the group have vasodilator properties, so it seemed reasonable to test the possibility that prostaglandins might be responsible for this dilatation. For this purpose, indomethacin, a powerful inhibitor of prostaglandin synthesis, was injected intravenously into the general circulation in a few preliminary experiments in doses of 0·5–2 mg/kg. When administered in this way, indomethacin substantially reduced the antidromic dilatation, but it so often produced a significant fall in systemic blood pressure that this was rejected as a method for analysing the cause of the local response. It was subsequently found that when given intraperitoneally (0·5–2 mg/kg) or close arterially (0·05–0·2 mg/kg) indomethacin had no effect on arterial blood pressure and that some 30 min after administration by either route the dilatation was reduced (by at least 70%) or abolished (Fig. 3 and Table 1). Ordinarily, the response would be obtained on repeated stimulation at intervals of 10–15 min for up to 3 hr. This made it possible to test how long the effect of indomethacin persisted. It was found not to be long-lasting; for recovery

could be almost complete 1 hr after giving the drug. During the period when the dorsal root dilatation was reduced, the increase in muscle blood flow produced by a close arterial injection of ACh was not changed (Fig. 3) and there was no impairment of the functional hyperaemia produced by submaximal twitch contractions of the muscle for periods of up to 20 sec or by tetanic contractions for up to 10 sec.

The dorsal root dilatation was also reduced by acetylsalicylic acid (20–25 mg/kg, I.V. or I.P.) another inhibitor of prostaglandin synthesis (Fig. 4). This drug was less effective, however, as the dilatation was not reduced more than 70 % and was never abolished (Table 1). Again there was no antagonism of the response to ACh or of the dilatation induced by muscle contraction.

## DISCUSSION

These experiments have established that stimulation of dorsal roots towards the periphery can readily evoke a vasodilatation in the skeletal muscle of the hind limbs. This supports the early reports of Bayliss (1901) and the direct observations of Krogh, Harrop & Rehberg (1922) on frog muscles, and must outweigh the negative results obtained, using different methods of stimulation, by Celander & Folkow (1953*a*). The response is to be attributed entirely to stimulation of dorsal root afferent fibres, and not, even in part, to the activation of sympathetic or somatic efferent fibres. First, it was not affected by pharmacological antagonists of the autonomic transmitters, noradrenaline or ACh, neither was it changed by transection of the spinal cord at $L_6$, a procedure which would have disconnected the site of stimulation from the preganglionic sympathetic outflow. Secondly, it was never accompanied by visible muscle contraction, could be elicited in an animal paralysed with gallamine and still occurred when the ventral roots had been cut and pulled well away from the site of stimulation. The stimulus therefore cannot have produced the dilatation by activating sympathetic efferents or by exciting ventral roots to produce muscle contraction and its associated functional hyperaemia.

The dilatation we have described must be due to antidromic stimulation of afferent fibres, and this conclusion is firmly supported by anatomical evidence. Although it is well documented that there are afferent fibres in ventral roots, it has been accepted for many years, largely on the basis of the careful studies of Hinsey (1934) on the lumbo-sacral enlargement of cats that the dorsal roots contain *only* afferent fibres. Coggeshall and his co-workers (Coggeshall, Coulter & Willis, 1974; Langford & Coggeshall, 1979), with the added benefit of modern histochemical and histological techniques, have provided convincing evidence for both of these points. Their most recent electronmicroscopical study of the dorsal roots $L_6$–$S_1$ of the rat (Langford & Coggeshall, 1979) has shown conclusively that they contain no efferents, either somatic or sympathetic.

The neurogram recordings and the stimulus parameters which had to be used to elicit the dilatation seen in the present experiments indicate that the response depends on activation of the small myelinated or unmyelinated fibres. These findings are very similar to those made by Hinsey & Gasser (1930) in their experiments on antidromic vasodilatation in cutaneous vasculature. They are also compatible with the results of Celander & Folkow (1953*b*), who showed that dorsal root vasodilatation

only appeared in the paw when electrical stimuli of long pulse width were given to the dorsal roots or when noxious stimuli which are known to excite small afferent fibres were applied to the paw itself. None of these results indicate whether the vasodilation depends entirely on activity in the smaller fibres or whether it requires the larger and smaller fibres to be excited simultaneously.

The latency of the dilatation in the muscle was 10–15 sec and the maximum response was attained some 10–15 sec later. This is reminiscent of the long latency of the antidromic vasodilator response in the skin and, as has been noted before (Lewis & Grant, 1924), suggests the action of a vasodilator substance which is newly synthesized on afferent stimulation rather than one already present and available for release. Various substances have been suggested as possible mediators of the cutaneous response. Acetylcholine (Wybauw, 1936) and histamine (Lewis, 1927; Krogh, 1922) have both been proposed, but subsequent investigations have not supported them (Holton & Perry, 1951; Ungar & Parrot, 1939). Antidromic stimulation of sensory nerve fibres of the skin of the rabbit ear was shown long ago to liberate ATP (Holton, 1959), but the amounts released were some $10^5$ times less than those required to reproduce the vasodilator effect of stimulation, and ATP has not been found to be released on activation of other sensory nerve fibres (Burnstock, 1972). Even Holton (1959) believed that the ATP was released in association with some other transmitter. In 1953, Lembeck postulated that substance P was responsible for antidromic vasodilatation but there is still no direct evidence of this. It is present in particularly large amounts in dorsal roots (Lembeck, 1953; Lembeck & Gamse, 1977), in smaller myelinated and unmyelinated sensory fibres (Hokfelt, Kellerth, Nilsson & Pernow, 1975) and is vasodilator (Gaddum & Schild, 1934); but there is no evidence that it is released at the periphery during stimulation of sensory nerve fibres (Lembeck, Gamse & Juan, 1977).

The present experiments showed the dilatation to be greatly reduced or abolished by inhibitors of prostaglandin synthesis. Indomethacin was far more effective as an inhibitor than aspirin, which is consistent with other results on the relative potencies of these agents as prostaglandin synthetase inhibitors. The full effect of indomethacin lasted only 20–30 min, a property which has been noted by other workers (Bowery & Lewis, 1973) and, furthermore, the drugs did not interfere with other vasodilator responses. Thus it seems likely that the action of indomethacin and aspirin on the dorsal root response was due specifically to inhibition of prostaglandin synthesis rather than to a non-specific action, for example on the sensitivity of the vascular smooth muscle. These experiments therefore provide reasonable evidence to suggest that the antidromic vasodilatation in skeletal muscle is mediated at least partly by locally synthesized prostaglandins.

In previous work a good case has already emerged for the involvement of prostaglandins in the response of the eye to dorsal root activation. Ambache (1955, 1956), investigating the effects (vasodilatation, increased intra-ocular pressure and meiosis) produced by stimulation of the pure sensory, trigeminal nerve isolated a substance released during stimulation which when injected produced the same pattern of response. After further investigation (Ambache, 1957, 1959) the substance was identified as an unstable fatty acid hydroperoxide, a member of the group of substances from which prostaglandins may be synthesized. More recently, Ängaard &

Samuelsson (1964) isolated a substance present in sheep irides and in the sensory nerve which seemed to be identical with the prostaglandins, while Waitzman & King (1967) established that $PGE_1$ and $PGE_2$ injected into the eye produced the antidromic response.

Experiments on the cutaneous antidromic response have also yielded results which suggest that prostaglandins are involved. When given as an injection into human skin, prostaglandins produce the flare and wheal which are characteristic of the triple response and, when given by slow infusion, they increase the sensitivity to painful stimulants, such as bradykinin (Ferreira, 1972). Hyperalgesia has long been known to accompany the antidromic response and it lasts as long as the flare (Lewis, 1927); so too does the heightened sensitivity produced by the action of prostaglandins. There are also indications that the substance released during dorsal root stimulation may raise the excitability of the afferent nerve terminals to the extent of evoking action potentials in the afferent nerve fibres. This was suggested by experiments on human subjects in which antidromic stimulation of cut dorsal roots with the roots on either side intact resulted in the sensation of pain (Foerster, 1927) and is supported by work on frog skin which showed that antidromic stimulation of an afferent fibre from one area of skin often evoked 'spontaneous' action potentials in afferents with overlapping or adjacent terminal fields (Habgood, 1950). Prostaglandins have this property also. When injected into human skin in concentrations comparable to those reached locally they produce a feeling of warmth (Ferreira, 1972) and when injected subcutaneously or intramuscularly in higher concentrations they produce the sensation of pain (Collier, Karim, Robinson & Somers, 1972; Karim, 1971).

Prostaglandins have not, as yet, been assayed in the venous effluent from skeletal muscle during dorsal root stimulation. However, Herbacynska-Cedro, Staszowska-Barczak & Janczewska (1973) detected prostaglandins in the venous effluent of skeletal muscle after 5–10 min tetanic contraction, and Kilbom & Wennmalm (1976) found that indomethacin substantially reduced the reactive hyperaemia produced in the human forearm by 5 min arterial occlusion. On the other hand, we have shown that the vasodilator response to a brief tetanus is not modified by indomethacin. Since prolonged periods of tetanic contraction or muscle ischaemia stimulate the small myelinated and unmyelinated afferent fibres (Hník, Hudlická, Kučera & Payne, 1969; Iggo, 1961; Kumazawa & Mizumura, 1978), it seems reasonable, in the light of the present experiments, to propose that prostaglandins were synthesized and released in skeletal muscle in the course of the studies mentioned above because the small afferent fibres were subject to continuous activation.

An old idea which has enjoyed much support is that of dilatation due to a local axon reflex in sensory neurones, as described by Lewis (1927). He envisaged orthodromic activity from sensory terminals in the skin being reflected antidromically down collateral branches serving arterioles. There is anatomical evidence demonstrating the existence of afferent fibres with this pattern of branching (Hinsey, 1928; Stacey, 1969) but there is no physiological evidence that this so-called axon reflex occurs. Indeed, considering all the evidence afresh it seems more reasonable to propose that it is simply activity in smaller myelinated and unmyelinated fibres which is essential for dorsal root dilatation and that the direction of the impulse traffic is immaterial.

Marshalling the evidence from a variety of experiments on several different tissues it appears that prostaglandins fulfil many of the criteria necessary for the mediator of dorsal root dilatation and its accompanying effects. There is, however, no reason to suggest either that prostaglandins are released from the afferent nerve terminals, or that they are the only substances involved. In the light of Holton's suggestion (1959), mentioned already, that rather minute amounts of ATP are released together with some other substance, it may be significant that ATP and ADP have been found to be potent and rapid stimulators of prostaglandin synthesis in a number of perfused organs and tissues (Needleman, Minkes & Douglas, 1974). Since prostaglandins can be synthesized by many tissues including nerves, connective tissue, mast cells and blood vessel walls, it is still an open question whether some other agent is released from the afferent fibres which in turn triggers the synthesis of prostaglandins.

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