J. Physiol. (1985), **364**, *pp.* 93–104
With 4 text-figures
Printed in Great Britain

DIFFERENTIATION OF VASODILATOR AND SUDOMOTOR RESPONSES IN THE CAT PAW PAD TO PREGANGLIONIC SYMPATHETIC STIMULATION

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(*Received 22 October 1984*)

SUMMARY

1. We monitored sweat secretion (using skin potential) and blood flow (using skin temperature) in the hind-paw skin of chloralose-anaesthetized cats pre-treated with guanethidine, and studied the responses to electrical stimulation of the ipsilateral lumbar sympathetic trunk.

2. Stimulation caused sweat secretion and an increase in skin blood flow which was almost entirely restricted to the paw pads and was completely ipsilateral. Stimulation of the tibial nerve trunk produced similar effects, except that the increase in blood flow was more prolonged.

3. The vasodilator effect of sympathetic trunk stimulation was not affected by chronic deafferentation of the paw.

4. Atropine methonitrate (0·5–1 mg/kg I.V.) abolished the sudomotor response to sympathetic stimulation, but did not attenuate the blood flow response.

5. Hexamethonium (1–2 mg/kg I.V.) abolished the vasodilator response to sympathetic stimulation, but did not affect the sudomotor response. Larger doses of hexamethonium (10–20 mg/kg) abolished both responses.

6. The data suggest that the lumbar post-ganglionic neurones mediating vasodilatation in the skin of the cat paw pad are distinct from those that mediate sudomotor secretion.

INTRODUCTION

In dogs or cats that have been pre-treated with noradrenergic neurone-blocking agents in order to abolish the effects of vasoconstrictor nerve activation, electrical stimulation of the sympathetic supply to the paw pads produces a local increase in blood flow (Brody & Shaffer, 1970; Rolewicz & Zimmerman, 1972; Bell & Lang, 1979).

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These workers interpreted the response as being due to activation of a population of specific vasodilator neurones. An alternative explanation, however, is that it represents functional hyperaemia in the skin of the paw secondary to sweat gland activation. Although the vasodilatation is not attenuated by atropine-like drugs, which completely abolish sudomotor secretion (Takahashi, 1964; Jänig & Kümmel, 1977), there is some evidence that exocrine gland activation may be associated with localized hyperaemia that is not dependent on muscarinic receptors, but may involve the release of a kinin (Fox & Hilton, 1958) or a peptide such as vasoactive intestinal polypeptide (VIP) (Lundberg, 1981).

In order to resolve whether vasodilatation elicited in the cat paw by activation of non-noradrenergic sympathetic neurones is independent of sweat gland activation, we have monitored simultaneously eccrine secretion and blood flow responses to stimulation of the sympathetic nerve supply in the hind paw of anaesthetized cats. The animals were pre-treated with the noradrenergic neurone-blocker guanethidine, and measurements were made before and after administration of muscarinic and nicotinic cholinergic antagonists. The results indicate that the populations of post-ganglionic neurones that mediate vasodilatation in the paw are separate from those that mediate sweat secretion. Some preliminary data have been reported to the Australian Physiological and Pharmacological Society (Bell, Jänig, Kümmel & Xu, 1982).

METHODS

Nineteen adult cats of either sex (body mass 2·3–4·3 kg) were pre-treated with guanethidine sulphate (Ismelin, Ciba-Geigy) 5 mg/kg s.c. 24 and 6 h before, or 48, 24 and 6 h before experimentation. An additional two animals that had not received guanethidine pre-treatment were also used. All animals were anaesthetized with α-chloralose (60 mg/kg I.P.) following induction with ketamine hydrochloride (Ketanest, Parke-Davis; 15 mg/kg I.P.). Additional supplements of chloralose were given in doses of 10–30 mg I.V. as required. The criteria for maintenance of adequate depth of anaesthesia were the persistence of miotic pupils and the absence of heart rate changes during mild noxious stimuli. Tracheostomy and urethral catheterization were performed, and one carotid artery and jugular vein were cannulated.

The animal was placed on its right side with the hind limbs extended, and one or both hind paws were immobilized in plantar flexion by surrounding them with a shallow pool of paraffin wax. During the course of the experiment, positive pressure ventilation was employed so as to maintain an end-tidal P_{CO_2} of approximately 4%, and immobilized with pancuronium (Organon) administered at approximately 0·2 mg/h. Body temperature was maintained at 37–38 °C using an oesophageal thermistor coupled to a thermostatically controlled heating blanket. Room temperature was 20–22 °C.

Peripheral nerve stimulation

The lumbar sympathetic trunks were exposed via a left retroperitoneal flank incision, and platinum hook stimulating electrodes were placed on one or both trunks between the third and fourth lumbar ganglia, after cutting the trunks rostral to the site of stimulation. In all guanethidine-treated animals, platinum electrodes were also placed on the intact posterior tibial nerve trunks at the ankle. In seven of these experiments, the fifth, sixth and seventh lumbar dorsal roots on both sides were exposed via a dorsal laminectomy, cut close to the spinal cord and placed on similar platinum electrodes. In the two experiments in which the animals were not pre-treated with guanethidine, only lumbar sympathetic trunks and dorsal roots were prepared for stimulation. Stimulating pulses at supramaximal voltage were delivered using an optically coupled square-wave stimulator. The sympathetic trunk was stimulated at 10–15 V in one of two ways: either with 15 s

periods of 1 Hz trains, each consisting of three 0·2 ms pulses delivered at 10 Hz, or with continuous 10 s trains of 0·2 ms pulses at 5 Hz. Stimulation of the tibial trunk or the dorsal roots employed 10 s trains of 0·5 ms pulses at a frequency of 1 or 5 Hz and 30–60 V.

Assessment of blood flow changes

In most experiments the skin blood flow changes in the hairless skin of the central paw pad and in the hairy skin about 1 cm proximal to this pad were monitored, using thermistor beads mounted in thin Perspex tubes which were positioned on the skin surface. In the other experiments thermistors mounted in the tips of 24 gauge hypodermic needles (Yellow Springs Instruments 524) were inserted subdermally in the same areas of the paw. The results obtained were similar for both methods, and will be reported together.

Assessment of sudomotor activity

It is well documented that sudomotor secretion is associated with a transient negative shift in the potential difference across the skin of the secretory area, together with a reduction in transcutaneous impedance (Wang, 1964). The 'electrodermal' or 'galvanic' skin responses have been shown to be proportional in magnitude to the amount of secretory activity (Lloyd, 1960; Morimoto, Imai & Watari, 1974), and the skin potential response to sudomotor nerve stimulation has been shown to be similar in magnitude and time course to the potential change recorded with a micro-electrode from the lumen of a single sweat gland (Shaver, Brusilow & Cooke, 1962). Causal association of the transcutaneous potential shift with sweat production is confirmed by the fact that both are abolished by administration of atropine (Jänig & Kümmel, 1977). In the present series of experiments, we required an index of secretory activation but were not concerned with quantitative changes in the amount of sweating. For this purpose, the monitoring of skin potential rather than of sweat exudation afforded two advantages. First, it provided an instantaneous monitor of secretory activity in response to short periods of sudomotor nerve stimulation, whereas exudation of sweat onto the skin surface is delayed and requires relatively prolonged stimulation, presumably reflecting the time taken to fill the sweat ducts (Lloyd, 1960; Morimoto *et al.* 1974). Secondly, it provided a reproducible index of secretion regardless of the interval between successive stimulation periods. By contrast, the amount of sweat exudation is reproducible only when stimulation periods are closely spaced and separated by precise intervals, probably because of progressive reabsorption from the ducts in the absence of stimulation (Lloyd, 1960; Morimoto *et al.* 1974). For the recording of skin potential, silver–silver chloride electrodes were positioned on the central pads of both hind paws, as described by Jänig & Kümmel (1977). An indifferent silver–silver chloride electrode was inserted subcutaneously about 2 cm away. The potentials were amplified with a direct-coupled pre-amplifier having an input impedance of 10 MΩ and an upper frequency limit of about 100 Hz.

Data collection

Carotid arterial blood pressure, heart rate as derived from a lead I electrocardiogram, skin temperatures and skin potential were recorded continuously on magnetic tape (SE 7000, EMI), and analysed with a MINC RT 11 and a PDP 11/60 computer.

Deafferentation

In two cats, the left hind limb was deafferented 21 days before experimentation, under sodium pentobarbitone anaesthesia, by cutting the fifth, sixth and seventh lumbar and the first sacral spinal nerves on the left side, just distal to the dorsal root ganglia. This procedure did not interfere with the sympathetic supply to the hind limb.

RESULTS

The mean blood pressure of all nineteen cats pre-treated with guanethidine was between 65 and 125 mmHg. The average resting blood pressure ($\pm$S.E. of mean) was $92 \pm 4{\cdot}1$ mmHg, and the heart rate was 169 ± 4 beats/min. The surface temperature of the hind-paw pads varied in different individuals from 26·7 to 34·2 °C (mean $32{\cdot}5 \pm 0{\cdot}34$).

Responses to sympathetic trunk stimulation

In all guanethidine-treated cats, stimulation of the lumbar sympathetic trunk produced a large (20–50 mV) negative shift in skin potential, which was maintained only during the period of stimulation (Fig. 1). This response was similar in characteristics to those previously reported to be correlated with sudomotor neurone discharge both by ourselves (Jänig & Kümmel, 1977) and by other workers (Shaver *et al.* 1962; Wang, 1964; Morimoto *et al.* 1974). In some animals, the negative shift

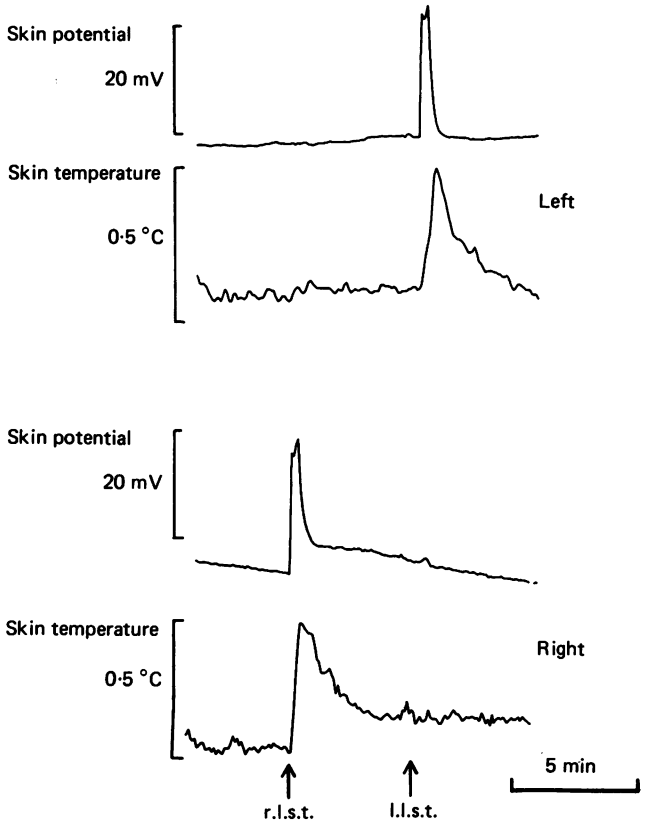

Fig. 1. Ipsilateral changes of skin potential (negative upwards) and skin temperature on the pads of left and right hind paws in response to electrical stimulation of right (r.l.s.t.) and left (l.l.s.t.) lumbar sympathetic trunks (0·2 ms, 15 V, 3 pulses at 10 Hz every second for 15 s). Cat was pre-treated with guanethidine (5 mg/kg s.c. 24 and 6 h before experiment).

was followed by a slow reversal of skin potential, which persisted for several minutes (see Fig. 4). The relationship of this late slow response to the secretory process is uncertain (see Shaver *et al.* 1962; Lang, 1968; Jänig & Kümmel, 1977), and all results described in this paper refer only to the fast, negative response.

Sympathetic stimulation in guanethidine-treated animals also produced an increase in pad skin temperature which began during the stimulation period, reached a peak after 20–30 s and decayed over 2–5 min (Fig. 1). The mean half-decay time for all

nineteen animals was 2·4 ± 0·3 min. The amplitude of this temperature increase ranged in different animals from 0·2 to 1·8 °C, with a mean value of 0·7 ± 0·10 °C. The amplitude of the temperature response was not correlated with the pre-stimulation skin temperature. The temperature of the hairy paw skin adjacent to the pads also increased following stimulation, but only by 0·1 °C or less (Fig. 3). Both skin potential and temperature responses were restricted to the ipsilateral limb (Fig. 1). Sympathetic stimulation was not usually accompanied by any appreciable change in arterial blood pressure. In isolated cases there was initially a small pressor response to stimulation, which was attributed to reflex activation of the adrenal medulla. This was abolished by repositioning of the stimulating electrodes so as to avoid current spread to the cut central end of the sympathetic trunk.

In the two cats that had not been pre-treated with guanethidine, sympathetic stimulation produced a fall in pad skin temperature of about 1 °C.

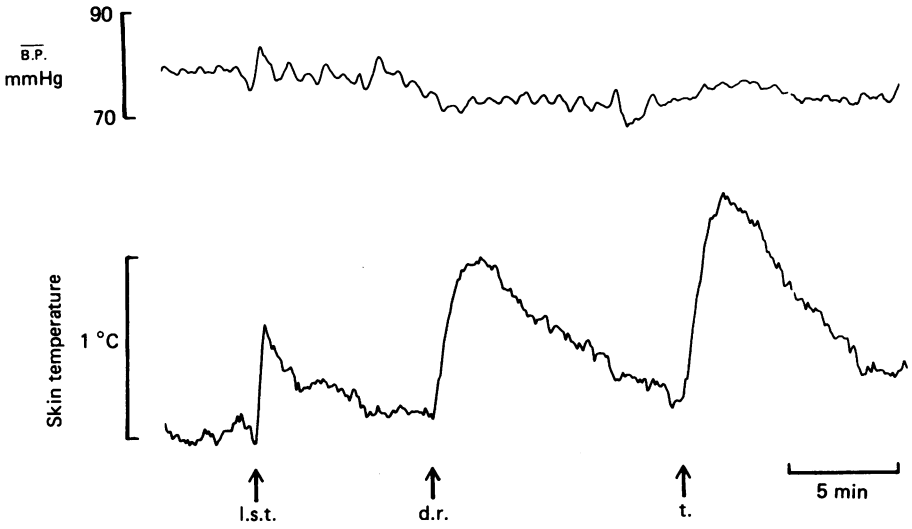

Fig. 2. Comparison between the increases in skin temperature of one pad of the left paw in response to stimulation of the left lumbar sympathetic trunk (l.s.t., 0·2 ms, 15 V, 3 pulses at 10 Hz every second for 15 s), left sixth and seventh lumbar dorsal roots (d.r., 0·5 ms, 40 V, 15 pulses at 1 Hz) and left tibial nerve (t., 0·5 ms, 40 V, 15 pulses at 1 Hz). The upper trace shows mean systemic arterial blood pressure. Cat was pre-treated with guanethidine (5 mg/kg s.c. 24 and 6 h before experiment).

Responses to tibial nerve and dorsal root stimulation

Stimulation of either the tibial nerve (nineteen experiments) or one or several of the dorsal roots of the fifth, sixth and seventh spinal nerves (seven experiments) produced increases in paw skin temperature that were usually greater in amplitude than those elicited by sympathetic stimulation. The amplitudes recorded ranged between 0·2 and 3·4 °C (mean for all responses 1·3 ± 0·17). In some animals, time courses of responses to tibial and to dorsal root stimulation were similar to those to sympathetic trunk stimulation. However, in the majority of cases, responses to either type of peripheral nerve stimulation were longer in duration than were the

corresponding responses elicited from the sympathetic trunk (Fig. 2; cf. Fig. 4). For all nineteen animals, the mean half-decay time for the tibial response was 4·9±0·3 min. Temperature increases occurred in both the hairless skin of the pads and in the adjacent hairy skin but, as was the case with sympathetic stimulation, the hairy skin response was considerably smaller in amplitude (Fig. 3).

In each of the two animals in which chronic deafferentation of one hind limb had been performed, the temperature response to tibial nerve stimulation was similar both in amplitude and in time course to that elicited by sympathetic trunk stimulation (Fig. 3). Dorsal root stimulation in the two cats that were not pre-treated with guanethidine also caused an increase in pad temperature.

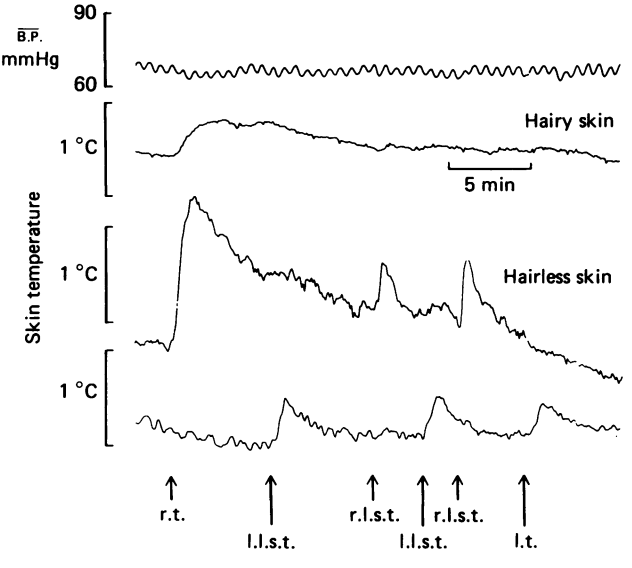

Fig. 3. Increases in skin temperatures of right and left paws in response to stimulation of each lumbar sympathetic trunk (r.l.s.t., l.l.s.t.) and each tibial nerve (r.t. and l.t.), in a cat from which the left fifth lumbar to first sacral dorsal root ganglia had been removed 21 days before. Traces, from above, are mean arterial blood pressure and temperatures of right paw hairy skin, right paw pad and left paw pad. Stimulus parameters were as in Figs. 1 and 2. Cat was pre-treated with guanethidine (5 mg/kg s.c. 24 and 6 h before experiment). Note the differences in amplitude of responses to sympathetic stimulation between hairy and adjacent hairless skin, and the differences in responses to tibial stimulation on control and deafferented sides.

Effects of acetylcholine antagonists on responses to nerve stimulation

In each of eight experiments performed on animals pre-treated with guanethidine, systemic administration of the muscarinic receptor antagonist atropine methonitrate (0·5–1·0 mg/kg) completely abolished the skin potential response to either sympathetic trunk or tibial nerve stimulation. By contrast, the increases in skin temperature were unaffected by atropine treatment (Fig. 4).

The ganglion blocking agent hexamethonium at a dose of 10 mg/kg I.V. abolished both skin potential and skin temperature responses to sympathetic stimulation, without attenuating the equivalent responses to tibial nerve stimulation (seven

experiments). This effect of hexamethonium persisted for at least 1 h. Lower doses of hexamethonium (1–2 mg/kg) had no effect on the amplitude of skin potential responses to sympathetic stimulation. However, these doses completely abolished the skin temperature responses to sympathetic stimulation without affecting those to stimulation of the dorsal roots (six experiments) or of the tibial nerve (twelve experiments) (Fig. 4). The selective effect on preganglionically evoked temperature responses wore off over about 20 min, and could be repeated by administration of a further similar dose of hexamethonium.

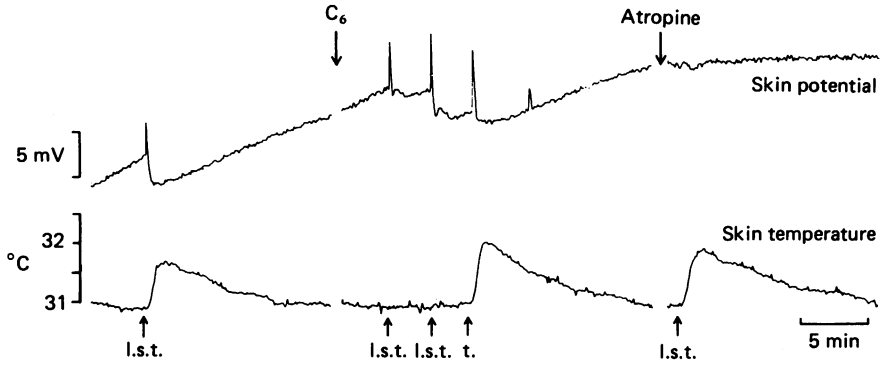

Fig. 4. Effects of hexamethonium and atropine on responses of skin potential (upper trace, negative upwards) and skin temperature of one pad of the left paw to stimulation of the left lumbar sympathetic trunk (l.s.t., 0·2 ms, 10 V, 5 Hz for 10 s) and left tibial nerve (t., 0·5 ms, 30 V, 5 Hz for 10 s). Cat was pre-treated with guanethidine (5 mg/kg s.c. 24 and 6 h before experiment). Hexamethonium (C_6) 2 mg/kg I.V. selectively abolished skin temperature responses to trunk stimulation, while atropine 0·5 mg/kg I.V. selectively abolished sudomotor responses. After hexamethonium treatment, sufficient time was allowed for recovery of temperature responses to sympathetic stimulation before administration of atropine.

DISCUSSION

It is well documented that active vasodilator responses to sympathetic nerve stimulation in the limb vasculature of cats and dogs can be elicited when concomitant vasoconstriction has been prevented by administration of a noradrenergic neurone-blocking agent. Several different components of this vasodilatation can be distinguished (Bell, 1983). One of them is restricted to the resistance vessels of skeletal muscle, and is abolished by peripheral administration of antimuscarinic drugs, implying that it is mediated by cholinergic nerves (Folkow & Uvnäs, 1948). This population has been implicated in the hyperaemia of skeletal muscle that may precede arousal-oriented movements (Abrahams, Hilton & Zbrożyna, 1964; Ellison & Zanchetti, 1973). A second type of response is resistant to antimuscarinic agents but is attenuated by histamine H_1-receptor antagonists (Beck, 1965; Lang, Bell, Conway & Padanyi, 1976). The nerves responsible for this response appear to supply vessels of both limb skin and muscle (Zimmerman, 1968; Brody & Shaffer, 1970; Lang *et al.* 1976). Finally, there is a response restricted to the vessels of the paw, and especially to the pads, which is resistant to blockade by either antimuscarinic or

antihistamine agents (Zimmerman, 1968; Brody & Shaffer, 1970; Bell & Lang, 1979). In the dog, pharmacological, biochemical and histochemical data indicate that the post-ganglionic neurotransmitter involved is dopamine (see Bell, 1982, 1984*a*). However, analysis of the physiological significance of this population of nerves is difficult because sudomotor nerves also supply the paw pads, and the activation of these fibres is known to be associated with local hyperaemia (Roddie, Shepherd & Whelan, 1957; Love & Shanks, 1962). The possibility therefore exists that at least part of the pad dilatation is secondary to sweat gland activation. Clarification of this point was the principal aim of the present investigation.

We observed that electrical stimulation of the lumbar sympathetic trunk in the guanethidine-treated cat produced sweat secretion, as shown by the transient negative shift in skin potential, and an increase in skin temperature of the paw pad. As the skin temperature fell following nerve stimulation in animals that had not received guanethidine, so that the vasoconstrictor supply to the paw was intact, it may be concluded that the increased temperature reflected a local increase in blood flow. As both sudomotor and blood flow responses could be abolished totally by doses of hexamethonium which did not affect equivalent responses elicited by stimulation of the tibial nerve trunk, the fibre populations activated by sympathetic trunk stimulation above the fourth lumbar ganglion appear to be purely preganglionic. This is confirmed further by the fact that horseradish peroxidase applied to the medial plantar nerve of the cat labels post-ganglionic cell bodies only in the fourth lumbar ganglia and below (McLachlan & Jänig, 1983). We also found that the vasodilator response was insensitive to large doses of atropine, and was almost entirely restricted to hairless skin of the paw pads. In these characteristics, therefore, it was similar to the dilator responses described previously in the literature as occurring in the vasculature of the paw (Zimmerman, 1968; Brody & Shaffer, 1970; Bell & Lang, 1979).

Resistance of the vasodilator response to atropine is not in itself evidence against the dilation being secondary to sudomotor nerve activation. Some data exist suggesting that the local hyperaemia normally associated with exocrine glandular activation may be less sensitive than is the secretory process itself to antimuscarinic drugs, and this has been attributed to liberation of other vasodilator substances such as kinins or VIP from the axon terminals (Fox & Hilton, 1958; Lundberg, Änggård, Fahrenkrug, Hökfelt & Mutt, 1980). Our experiments have demonstrated that doses of hexamethonium insufficient to produce detectable failure of ganglionic transmission to sudomotor neurones, completely abolished vasodilator responses to preganglionic stimulation. Atropine-resistant vasodilatation and VIP overflow in exocrine glands during cholinergic nerve activation is pronounced only with intensities of preganglionic stimulation greater than those necessary for maximal secretion (Fox & Hilton, 1958; Lundberg, 1981; Andersson, Bloom, Edwards & Järhult, 1982). It is possible, therefore, that partial blockade of transmission to sudomotor neurones could reduce the frequency of post-ganglionic firing to a level below that necessary to sustain dilatation, without appreciable inhibition of secretory activity. However, two lines of evidence argue against this interpretation as an explanation for our findings. First, in cat salivary gland the frequencies of preganglionic stimulation that are required to elicit either atropine-resistant dilatation or VIP overflow are considerably higher

than those which we employed (Andersson *et al.* 1982). Secondly, salivary secretion and salivary gland vasodilatation evoked by preganglionic stimulation are both sensitive to the low doses of hexamethonium that we found to be selective for dilator responses (Wien & Mason, 1951; Andersson *et al.* 1982).

A more likely interpretation of our findings is that paw pad dilation and sudomotor secretion are mediated through separate populations of post-ganglionic neurones that have different sensitivities to hexamethonium. It is known that autonomic ganglion cells can be classified into two types on the basis of their response to preganglionic activation. Some cells always respond to a single presynaptic impulse with a suprathreshold synaptic potential which initiates an action potential (Blackman, Crowcroft, Devine, Holman & Yonemura, 1969). Others respond only with a subthreshold synaptic potential, and require the summation of several inputs for action potential production (Blackman & Purves, 1969). These two types of ganglionic synapses have been designated as 'strong' and 'weak' respectively (see Hirst & McLachlan, 1984). In the case of 'strong' synapses, many more quanta of acetylcholine are released from the preganglionic terminals than is the case with 'weak' synapses (Hirst & McLachlan, 1984), so that 'weak' synapses are more susceptible to the local presence of receptor-blocking agents such as hexamethonium. Our results are therefore compatible with the view that the ganglionic neurones supplying the sudomotor innervation to the cat's paw receive inputs that are relatively 'strong', while those that provide dilator innervation to the pad vessels receive inputs that are relatively 'weak'. The existence of these two types of sympathetic neurones in the outflow to the hind limb is supported by recent work in one of our laboratories, which has shown that vasoconstrictor neurones supplying hind-limb skin and muscle exhibit widely different sensitivities to hexamethonium during preganglionic activation (Bell, 1984*b*).

Although our results indicate that the dilator fibre population is distinct from the mediating eccrine sweat secretion, it could be activated physiologically in parallel with the sudomotor population, and so might participate in the local hyperaemia necessary for effective sweat production. On the other hand, vasodilator nerves are known to supply the digital vasculature in a variety of avian species, where sweat glands are absent (Johansen & Millard, 1974; Bell & Rome, 1984), so similar neural populations might be expected to exist in mammals.

The digital localization of the dilator response suggests that any physiological role is likely to be a thermoregulatory one. There is evidence that, in the dog, hypothalamic and spinal cord warming may evoke an active neural vasodilatation of the paw pads (Schönung, Wagner & Simon, 1972; Peter & Riedel, 1982). In the cat, we have been unable to elicit paw pad vasodilatation by hypothalamic warming (W. Grewe, W. Jänig, H. Kümmel & S. Varma, unpublished observations), although we have some evidence consistent with such a response to spinal cord warming (Gregor, Jänig & Riedel, 1976; Jänig & Kümmel, 1981). Alternatively, digital vasodilator nerves could be involved in the protective increases of digital blood flow that are seen in cold-acclimatized animals, including man, during local exposure of the extremities to cold (Hampton, 1969; Henshaw, Underwood & Casey, 1972; Johansen & Millard, 1974; Bell, 1983).

Vasodilatation in the paw pad was elicited in our study not only by activation of

sympathetic efferents but also by retrograde activation of sensory fibres. Available evidence indicates that the only sensory neurones involved in cutaneous dorsal root dilatation are the non-myelinated nociceptive population (Gasser, 1950; Lembeck, 1983), and the phenomenon appears to be mediated by a peptide such as substance P (Lembeck, 1983; Kenins, Hurley & Bell, 1984). The vessels that participate in dorsal root vasodilatation have been assumed to be arterioles or venules. It is therefore of some interest that we observed dorsal root responses to be considerably greater in magnitude in the hairless skin of the pads than in the adjacent hairy skin. To some extent this difference might be due to different densities of nociceptive innervation of the two skin areas (see McLachlan & Jänig, 1983), but differences in vascular responsiveness may also be involved. The most striking characteristic of the microcirculation in paw pads that distinguishes it from that in hairy skin is the predominance of arteriovenous shunts (Folkow & Sivertsson, 1964; Baker, 1972). Our results are therefore compatible with the view that dorsal root dilatation may influence shunt vessel behaviour as well as that of precapillary and post-capillary resistance vessels.

This work was supported by the Deutsche Forschungsgemeinschaft (W.J.) and the Deutscher Akademischer Austausschdienst (H.X.). We gratefully acknowledge provision of travel funds from the Deutscher Akademischer Austausschdienst (C.B. and H.X.) and the University of Melbourne (C.B.). Dr E. M. McLachlan made helpful comments on the manuscript.

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