cardiac fibres have been attributed to modifications of SR Ca^{2+} uptake[17]. Glucagon has been reported to stimulate myocardial adenyl cyclase activity in broken cell preparations[8] and to increase tissue levels of cyclic AMP in intact heart cells[10] and it is possible that glucagon's relaxation of K^+-induced contracture occurs as a consequence of a cyclic AMP stimulated increase in SR Ca^{2+} uptake. This, in turn, would increase the quantity of Ca^{2+} available for release to the contractile elements upon subsequent depolarization and account for the augmentation of force.

Catecholamines and dibutyryl cyclic AMP increase the slow inward Ca^{2+} current in heart[3]. The resultant elevation in $[Ca_i^{2+}]$ reduces the electrochemical gradient for Ca^{2+} into the cell and/or effects a more rapid activation of K^+ repolarizing currents[18,19]; as a result the action potential shortens. Membrane potential modulates myocardial force[20] and catecholamine (cyclic AMP)-induced earlier repolarization might accelerate the initiation of relaxation and shorten the twitch. This would be independent of the enhancement of SR Ca^{2+} uptake by cyclic AMP. The lack of a significant effect of glucagon on twitch duration probably reflects its modest actions on Ca^{2+} influx[21], repolarization[4] and presumably triggered relaxation or alternatively, as Marcus et al.[9] suggest, glucagon does not shorten time to peak isometric force because of its limited inotropic potency.

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Prostaglandin E_2 increases mechanically evoked potentials in the peripheral nerve

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Summary. Subdermal injections of PGE_2 (5 µg) in the rat foot lead to increases in the potentials evoked in sensory nerve branches by the mechanical stimulation of the skin. This sensitization of both A and C fibres complements the previously described hyperalgesic effects of prostaglandins of the E series.

In addition to the well known potentiating effects of prostaglandins of the E series (PGE_1 and PGE_2) on the action of pain-producing substances[1,2], their direct intradermal injection or subdermal infusion cause erythema, oedema and, in some cases, long-lasting hyperalgesia[3,4]. The purpose of this research was to study the effects of algesic doses of PGE_2 on the electrical activity of a sensory nerve. To that end we injected 5 µg PGE_2 in the subdermal space of the rat foot and recorded the potential evoked in a branch of a sensory nerve by the innocuous stimulation of the skin. Additionally, the activity of single sensory units with A fibres was also studied.

Material and methods. Male Wistar rats (250–320 g) were anaesthetized (1.25 mg/kg urethane i.p.) and had their left leg tied down securely and the saphenous nerve exposed within a paraffin pool formed by the flaps of the incision. A platinum electrode was positioned under a branch of the nerve and another hooked onto nearby moist skin. The nerve was ligated proximally and records were made of its activity as the appropriate receptive area of the skin was stimulated mechanically.

Stimulation consisted of the electronically-controlled contact of a metal stylus with the skin at a distance of 40–52 mm from the point of recording (tip diameter of stylus: 0.5 mm; force adjustable to a maximum of 2.5 g). Contact time was set at between 10 and 500 msec in cycles of up to 32 deliveries and at rates of 0.2–1 delivery per sec. This stimualtion was designed to activate skin mechanoreceptors with A and C fibres but not high threshold 'mechanical' or 'polymodal' nociceptors[5]. Both the onset and the withdrawal of the stimulus evoked nerve potentials. Single units, responding to the mere bending of hairs, were isolated in specially dissected few fibre preparations. After calculations of conduction velocity these were assigned as rapidly adapting hair follicle receptors[6]. In all cases recordings took place both before and at various intervals after the injection of PGE_2 into the interdigital subdermal space of the foot.

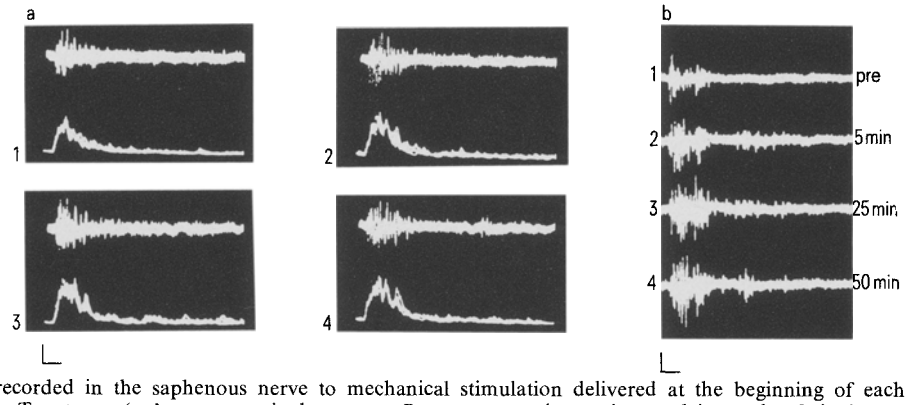

Fig. 1. Responses recorded in the saphenous nerve to mechanical stimulation delivered at the beginning of each sweep. *a* Stimulus duration, 200 msec. Top trace: 'on' response, single sweeps. Bottom trace: 4 superimposed integrals of single sweeps (time constant: 2 msec) at 3-sec intervals. 1) prior to PGE_2 injection; 2) 15 min after injection; 3) 40 min; 4) 60 min. Calibration: time; 10 msec; amplitude: nerve response, 50 μV; integral: 10 μV. *b* Stimulus duration 10 msec. Single sweeps. 1) prior to PGE_2 injection; 2) 5 min after injection; 3) 25 min; 4) 50 min. The 2 groups of multi-fibre activity on the left are the fast-fibre response to the stimulus 'on' and 'off'. Later firing is due to slowly-conducting fibres. Calibration: time, 10 msec; amplitude 50 μV.

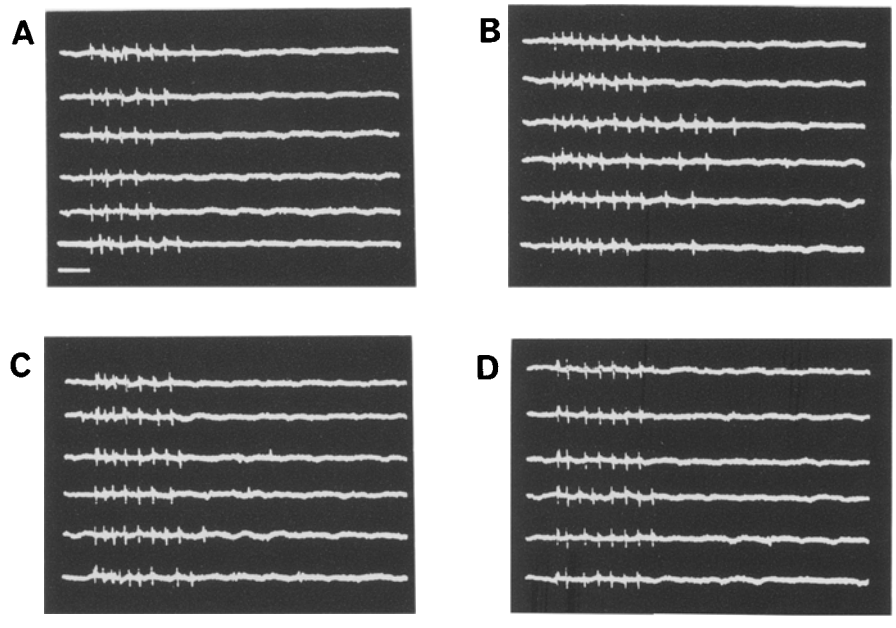

Fig. 2. Responses of a unit isolated in a 'few-fibre' preparation to an electronically controlled mechanical stimulus effecting the bending of a hair. *A* Prior to injection. *B-D*: following 5 μg PGE_2 injected 14 mm away; *B* 2 min; *C* 10 min; *D* 20 min. Stimulus duration: 100 msec starting at the beginning of each sweep. In all cases traces represent a series of 6 stimulus deliveries at 1/sec starting from the bottom. Time calibration (in A): 10 msec.

In 35 experiments injections were made with a microsyringe of 5 μg PGE_2 obtained from a stock solution of 10 mg PGE_2 crystals in 1 ml ethanol (stored at −20 °C) and dissolved in 10 μl saline. Control injections of the appropriate amount of ethanol in saline were given to 5 further animals. Following pilot experiments in which it was noticed that oedematous conditions led to the abatement of the evoked response (see below) only those preparations were used in which the area of mechanical stimulation was within the erythematous zone produced by the PGE_2 but did not itself become oedematous. The dose of PGE_2 chosen parallels the total amount infused in the human arm with algesic consequences[2].

Evoked electrical events in the nerve were amplified, intergrated electronically or averaged (Neurolog equipment, Digitimer Ltd., U.K.) and subsequently stored on tape. A spike trigger circuit was employed as a discrinimator of unit action potentials.

Results. Following PGE_2 injection, a degree of erythema developed within 5–15 min and was often accompanied by slight oedema. These persisted for at least 1 h and often for more than 3 h. During an initial period of 3–20 min the evoked response remained largely unaltered or attenuated slightly. Subsequently, however, progressive substantial increases were recorded in 29 preparations (figure 1, A, B). Control preparations yielded only small variations in the evoked response. Increases in both amplitude and duration of the early part of the response (due to A-fibre activity) were particularly prominent. Characteristically, it was the withdrawal rather than the application of the mechanical stimulus that yielded the highest responses, hinting to a similarity with the clinically observed phenomenon of 'rebound tenderness'[7].

Significant increases were also obtained on the part of the evoked response in which slow multi-unit contributions were recorded (unmyelinated (C) fibres conducting at 0.4–1.5 m/sec; figure 1, B). The averaged records of these responses, however, provided an underestimate of their significance due to their lower amplitude and considerable spread over time. Superimposition of electronically integrated single sweeps on the screen of a storage oscilloscope allowed for improved determination of changes in this part of the evoked response.

In 6 experiments the post-injection evoked response was curtailed for long periods of time (over 40 min) but returned to pre-injection values or higher at a later stage.

This correlated with the observation that, initially, the area under stimulation became considerably oedematous; response enhancement was therefore demonstrated satisfactorily only in the erythematous surround of the oedema.

Recording were also made of the activity of 11 single units isolated in 'few-fibre' preparations. When electrical stimulation at A-fibre levels was applied to the nerve distal to the sites of recording, it resulted in their activation. In addition, the slight bending of a hair by the stimulating stylus was sufficient stimulus for their maximal firing; these units were therefore assigned as hair-follicle units with myelinated fibres[6]. After PGE_2 injection 8 such units yielded higher numbers of impulses per stimulus delivery (figure 2); 2 units showed fewer impulses and the activity of a further unit remained unaltered.

Discussion. The present experiments have shown that the subdermal injection of PGE_2 leads to increased sensory input as judged by the multi-fibre activity in a peripheral nerve evoked by a standard tactile stimulus. Prostaglandins of the E series are thought to be released in the skin following the kind of noxious stimulation that gives rise to inflammation[8]; inflammation pain as well as PGE-induced hyperalgesia can be explained as the outcome of receptor sensitization by PGEs[1,9]. Nociceptors possess small myelinated or unmyelinated fibres. Handwerker[9] has demonstrated the sensitizing effects of PGE_2 on unmyelinated nociceptor fibres; we have demonstrated the sensitization of myelinated as well as unmyelinated fibres, some of which subserve tactile sensation whilst others are implicated in nociception. Such sensitization may well be a contributing factor to the inadequately understood hyper-aesthesic properties of the area of secondary hyperalgesia (tenderness) surrounding the focus of an inflammatory lesion[10].

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Lesions in the substantia nigra of rats induce thermoregulatory deficit in the cold[1]

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Summary. Rats with either electrolytic or chemical (6-hydroxydopamine) lesions in the substantia nigra displayed decreased metabolism and hypothermia when they were exposed to cold (8 °C T_a), although they showed no deficiency in thermoregulation at both moderate (22 °C) and hot (30 °C) environmental temperatures.

It is well known that the nigrostriatal dopamine (DA) pathways are one of the 3 main types of DA pathway in the brain[2-4]. The nigrostriatal DA fibres originate from cell bodies in the substantia nigra (SN). These fibres ascend through the lateral and mid-hypothalamus, and fan out to innervate the neostriatum. In addition, it is now well established that in Parkinson's disease, there is a characteristic pattern of both cell loss in the substantia nigra and DA decrease in the striatal nuclei[5,6]. Further, it has been suggested that patients with Parkinson's syndrome show a thermoregulatory deficit[7]. We have, therefore, investigated the effects of both electrolytic and chemical (6-hydroxydopamine, a depletor of catecholaminergic nerve fibres) lesions to the SN on the metabolic, respiratory and vasomotor activities as well as body temperature responses of rats at various ambient temperatures (T_a), in order to determine the nature of the contribution that the nigrostriatal DA pathways might make to thermoregulatory control.

Materials and methods. Adult male Sprague-Dawley rats weighing between 250 and 300 g were used in all experiments. The animals were housed individually in wire-mesh cages in a room maintained at 25 ± 2.0 °C. The animals were given free access to tap water and granular feed. In preparation for the SN lesions, the animals (under the general anesthesia of sodium pentobarbital, 6 mg/100 g, i.p.) were placed in a Kopf stereotaxic instrument and prepared with bilateral electrolytic destruction of the SN (pars compacta) on the animal's left and right sides, according to the atlas of König and Klippel[8]. The following coordinates and current parameters were used: AP, −2.4, L, −1.6, and H, −2.6; 2 mA for 10 sec, anodal current. The electrode used to produce lesions was stainless steel insulated with teflon except for 0.5 mm at the tip. In preparation for chemical lesions, using the same stereotaxic techniques, an aliquot containing 1 µl of 6-hydroxydopamine (6-OH-DA, Sigma, 50 µg) was slowly infused via a 27-gauge stainless steel cannula (with the outer diameter of 0.45 mm) into the SN pars compacta. 2-3 weeks after the operation the animals were tested for thermoregulatory activity in a small partitional calorimeter. Metabolic rate (M) was calculated from the animal's oxygen consumption. Metabolic rate was calculated in W assuming an RQ = 0.83 so that 1 l of oxygen consumed per h was equivalent to a heat production of 5.6 W[9,10]. Respiratory evaporative heat loss (E_{res}) was calculated by measuring the increase in water vapor content in the helmet effluent air over that of the ambient air. Evaporative heat loss expressed as W was calculated from evaporative water loss assuming the latent heat of vaporisation of water to be 0.7 W/h/g of water[9,10]. Rectal (T_r), foot skin (T_f), tail skin (T_t) and back skin (T_{bsk}) temperatures were measured using copper-constantan thermocouples. Measurements were obtained every min as a d.c. potential with a Hewlett-Packard digital voltmeter (DVM 3455) interfaced online to a CPU Hewlett-Packard 9825 computer which calculated temperatures, M and E_{res} and relayed them on an online Hewlett-Packard 9871