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THE EFFECT OF ADRENALINE ON NERVE ACTION POTENTIALS

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It has been shown by Bülbring & Burn [1939] that in the perfused hind-leg of the dog, when the vascular tone is low, adrenaline can increase the muscular contraction by restoring the responsiveness of the preparation to stimulation of the motor roots. We have now investigated the effect of adrenaline on excitation and conduction in the sciatic nerve trunk of the cat with its natural circulation.

Method

Cats were used either anaesthetized with chloralose or decerebrated or spinal. The most constant preparation proved to be the spinal, eviscerated and adrenalectomized cat, although the phenomenon to be described was without exception obtainable in both the other preparations. The sciatic nerve was exposed in the gluteal region and divided above the point of entry of its blood supply from the gluteal vessels; the blood supply was thus carefully preserved. Below this a short stretch of nerve was freed for the application of Sherrington glass-shielded electrodes. The leg was held by bone drills through the femur, and the tendo Achillis was fixed to an isometric lever. The posterior tibial nerve was isolated in the lower half of the leg and arranged for leading off the action potentials with silver wires and thread loops. The femoral, the lateral cutaneous nerve of the thigh, and the external peroneal and hamstring branches of the sciatic nerve were cut. For repetitive discharge a neon stimulator was used and with high frequencies of stimulation a rotating commutator was put across the output to permit stimulation for 1/15th sec., three times per sec. A Keith Lucas pendulum and coreless induction coils were used for single shocks. To minimize the effect of changes in nerve resistance a resistance of 50,000 Ω was connected in series with the

electrodes. The recording apparatus consisted of a push-pull input stage [Toennies, 1938] with three further stages of R.C. coupled amplification and a cathode-ray oscillograph. Most of the work was done with a fixed plate camera and a linear time base. For the moving paper camera used in the later experiments we are deeply indebted to Dr E. H. J. Schuster.

All preparations were left for 1 hr. before recording. The thresholds could be relied on to stay steady for 3–4 hr. The intra-arterial injections of adrenaline were made through a cannula in the iliac artery of the opposite side pointing towards the aorta.

RESULTS

As Gasser & Grundfest [1939] have stated, the sciatic nerve action potential in the cat usually shows fused α and β spikes, which can be referred to as the $\alpha\beta$ spike, and a δ spike. Under various conditions of stimulation and with long conduction distances the α and β spikes may be separated (Fig. 3).

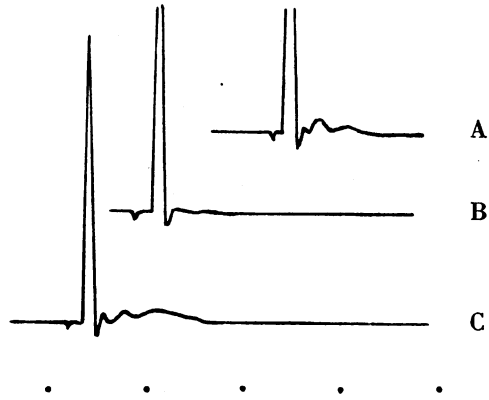

Fig. 1. Decerebrated cat. Action potentials set up by maximal stimuli 20 per sec. A, before; B, 50 sec. after 25μg. adrenaline; C, 2 min. later. Time: 1 d.v. = 10msec.; 0·66 mV. = 1 cm.

The spike potentials from α fibres produced by maximal stimuli at any frequency up to 450 per sec. were completely unaffected by injection of any dose of adrenaline from 5 to 25μg. The δ spikes produced by maximal stimulation once per sec. or less were also unaffected by adrenaline. At frequencies of 5–20 per sec. the δ spike height fell rapidly at first to a steady level. Injection of adrenaline further reduced or abolished the δ spikes within 45 sec., and they recovered within 2–3 min. (Fig. 1). The maximal diminution coincided with the maximal rise in blood pressure

and passed off together with it. This effect of adrenaline on the δ spikes could be reproduced by occlusion of the aorta for 1 min. after which recovery occurred within 1 min. (Fig. 2). In our experiments fatigue of δ fibres occurred so rapidly with maximal stimuli at rates above 20 per sec., even when the blood supply to the nerve was undisturbed, that no observations on the effect of adrenaline during higher rates of stimulation were made.

With submaximal stimulation at frequencies from 1 to 250 per sec. intra-arterial injection of adrenaline in doses from 5 to 25 μg. increased the αβ spike by an average of 100 % (Fig. 3). The amount of increase was not directly related to the dose of adrenaline, the requirement of which

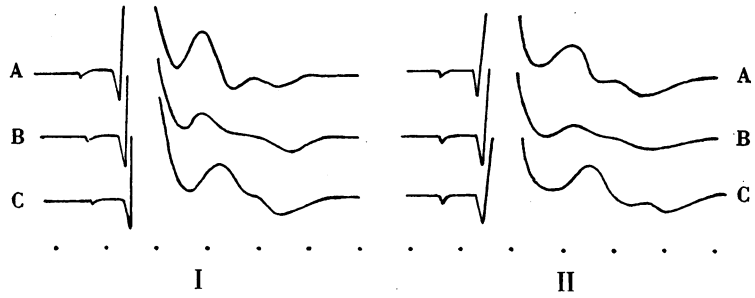

Fig. 2. Decerebrated cat. Action potentials set up by maximal stimuli 5 per sec. I: A, before; B, 70 sec. after 25 μg. adrenaline, showing reduction of δ spike; C, recovery of δ spike. II: A, before; B, during occlusion of aorta for 65 sec.; C, 1 min. after release of aortic clamp. Time: 1 d.v. = 2 msec.; 1·0 mV. = 1 cm.

varied in different cats; in some cats the effect could be readily demonstrated with 5 μg. adrenaline only, in others 25 μg. would produce the effect. However, within the same animal, the same dose of adrenaline injected intravenously or into the artery of the opposite leg produced only about half the effect seen with adrenaline injected into the same leg; although the rise in blood pressure and consequently the improvement in the general circulation was the same or greater. The increase of the αβ spike began after 1–1½ min.; it reached its maximum usually at 2 min., i.e. when the effect on the blood pressure was passing off, and disappeared after 3–5 min. This effect of adrenaline on αβ spikes could not be reproduced by clamping the aorta for 1 min., which had no effect on the threshold at frequencies up to 200 per sec. The adrenaline effect could, however, be prolonged when the aorta was clamped 10 sec. after the injection of adrenaline. In one experiment the increase of the αβ response which previously had disappeared in 3½ min., now persisted until the

aortic clamp was removed after 4 min., when it disappeared within ½ min.

The lowering in threshold by adrenaline was also evident in δ fibres with submaximal stimuli at rates up to 40 per sec. In one experiment with maximal stimuli at 1 per sec. αβ and δ spikes were quite unaffected by 25μg. adrenaline; at a rate of 20 per sec. the δ spikes were abolished 1 min. after the injection of 25μg. adrenaline and had returned to normal

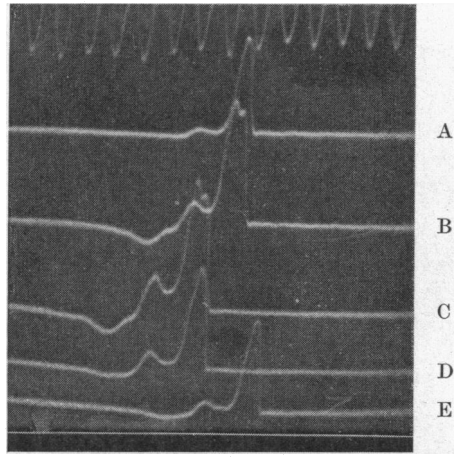

Fig. 3.

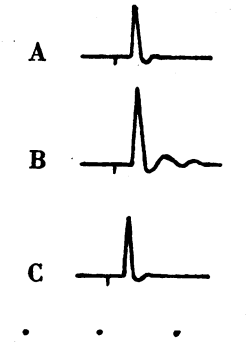

Fig. 4.

Fig. 3. Spinal cat, eviscerated, adrenalectomized. Action potentials set up by stimuli 25% of maximal at 1 per sec. A, before; B, 40 sec. after 5μg. adrenaline; C, after 1½ min.; D, after 2½ min.; E, after 3½ min. Time: 1 d.v. = 2 msec.; 0·4 mV. = 1 cm. Read from right to left.

Fig. 4. Same experiment as Fig. 1. Action potentials set up by submaximal stimuli 36 per sec. A, before; B, 3 min. after 20μg. adrenaline; C, 5 min after. Time: 1 d.v. = 10 msec.; 0·7 mV. = 1 cm.

after 3 min. (Fig. 1); the αβ spikes remained unchanged. Immediately afterwards with stimuli 20% of maximal at 36 per sec. both αβ and δ spikes increased in amplitude after the injection of 20μg. adrenaline, reaching their greatest height after 3 min. and falling again in 5 min. (Fig. 4).

Other methods were tried of raising the blood pressure. Intravenous injection of 20 c.c. normal saline caused a rise of blood pressure to the same extent as did 20μg. adrenaline, but had no effect on the height of response of the nerve to submaximal stimuli, though it increased the muscle tension. No effect was observed with ephedrine in doses of 1 and

2 mg. In one experiment 0·5 unit pituitary (posterior lobe) extract caused an increase of 80 % in height of nerve response which lasted for over 30 min., in fact as long as the rise in blood pressure and the increase in muscle tension persisted. In another experiment 7·5 mg. ergotoxine abolished the increase in α spike height with submaximal stimuli produced by adrenaline, and reversed the effect on δ spikes due to maximal stimuli.

While we have never failed to obtain with adrenaline an increase in the height of response of $\alpha\beta$ fibres to submaximal stimuli with the nerve in the best possible condition, the effect was much greater when there was evidence of fatigue. In nerves in good condition the effect varied from 30 to 115 %; but at the end of an experiment on a spinal animal, when the blood pressure had fallen to 30 mm. Hg, increases of response from 10μV. to 1 mV. have been seen. This was present with stimuli at 1 per sec. In early experiments, where the nerve had been incompletely guarded from fatigue, increases of 300 % in height of response were frequently observed. A small increase in the power of β fibres to respond to stimuli at 250 per sec. was seen in a fatigued nerve after adrenaline.

When muscle tension and nerve action potentials were recorded, a striking absence of parallelism between the effect of adrenaline on muscle and nerve was observed. For instance, when no effect on the response in nerve could be seen with maximal single shocks at 1 per sec., 100 % increase of muscle tension could be observed when the muscle was fatigued. On the other hand, with maximal interrupted tetani of high frequency, 25μg. adrenaline in the same experiment completely abolished the muscle tension for 1 min. after the injection, again without any change in the $\alpha\beta$ spike potential. When with a maximal tetanus of 20 per sec. complete abolition of the δ spikes occurred within 1 min. after the injection of adrenaline, the muscle tension rose at the same time by 160 %. And when with submaximal stimulation there was an increase in muscle tension it always began earlier and outlasted the increase in the nerve response; sometimes a transient decrease of muscle tension was observed while the nerve action potential was growing. A further investigation of the effect of adrenaline on the nerve muscle junction is called for.

Discussion

It appeared from the experiments of Bülbring & Burn [1939] that adrenaline had probably an effect on excitation of the motor roots in the isolated perfused hind limb of the dog. We have now obtained an increase in the spike height of the normal sciatic nerve in cats, which must be

chiefly due to a change of threshold. The effect of fluctuation in the inter-electrode resistance has been minimized by the use of a resistance of 50,000 Ω in series with the stimulating circuit and the electrodes. An effect of the magnitude of that described could not be due to any decrease in inter-electrode tissue fluid possible within physiological conditions.

The possibility remains that adrenaline produced an increase in the K/Ca ratio in the nerve which was responsible for the shift in threshold. We have at no time seen repetitive discharge at the height of the adrenaline effect. Its onset is also very rapid compared with the effect of changes in *p*H and calcium-ion concentration described by Lehmann [1937*a*, *b*].

The nerve was isolated with great care, with minimal disturbance of its blood supply, and stimulation was avoided as far as possible before making observations. Therefore, we believe that, although the effect described may reach a much greater height in fatigued nerve, adrenaline can produce a lowering of threshold in healthy nerve. There was some evidence that adrenaline increased the rate of recovery of excitability of nerve, possibly by accelerating processes concerned with supernormality [Graham & Lorente de Nó, 1938]. This could be more easily studied if the phenomenon were reproducible *in vitro*.

In decerebrate preparations with intact suprarenals, fluctuations of threshold were frequently observed which could be attributed to the discharge of adrenaline from the suprarenal glands. It is possible that this has been one of the difficulties in the study of the excitability of mammalian nerves *in situ*.

The depression of δ spikes can be reproduced by occluding the blood supply, and it is synchronous with the greatest vasoconstriction in the blood vessels of the perfused nerve (Bülbring, unpublished observations). It is therefore to be attributed to anoxaemia, to which δ fibres are almost as susceptible as B fibres [Grundfest, 1939].

Summary

1. The effect of adrenaline has been studied on the excitability of the cat's sciatic nerve *in situ*.

2. In healthy nerve intra-arterial injection of 5–25 μg. adrenaline increases the height of the action potential produced by submaximal stimuli. This effect is due to a lowering of threshold; it lags behind and outlasts the vascular action of adrenaline.

3. The effect of adrenaline is much larger when the nerve shows fatigue.

4. The same doses of adrenaline reduce or abolish the δ spike in the action potential produced by maximal stimuli; this effect is attributed to the reduction of blood flow caused by adrenaline.

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