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THE MECHANISM OF THE VASOMOTOR REFLEXES PRODUCED BY STIMULATING MAMMALIAN SENSORY NERVES

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It has often been suggested that afferent impulses, in response to a nocuous stimulus, have a part in initiating the changes in blood pressure which may follow severe injury. The idea gets an added interest from some recent suggestions that these impulses are carried in at least two types of fibre, the delta fibre and the unmyelinated C fibre [Zotterman, 1939], and it calls for a close analysis of the reflex changes in blood pressure produced by various kinds of electrical stimulation of an afferent nerve.

It is known that stimulation of the central end of the cut sciatic nerve in the cat can have either a pressor or a depressor effect. Weak stimulation [Hunt, 1895], or stimulation at low frequencies [Gruber, 1917], gives a depressor reflex; if either the strength or frequency is increased, the reflex may become pressor. Two views are held about this reversal, produced by increasing either strength or frequency of stimulation; they are reviewed by Ranson [1921], who believed that the pressor reflex was related to a greater central summation of impulses. Hunt [1895], on the other hand, had suggested that the pressor and depressor reflexes were served by different types of afferent fibre, the pressor fibre having a higher threshold.

This question is reopened here. Clark, Hughes & Gasser [1935] found that there is still a vasomotor reflex if all the fibres in the sensory nerve except the unmyelinated C fibres have been inactivated by asphyxiating the nerve. Their experiment has been repeated here under controlled conditions, to find the nature of this vasomotor reflex; and dissociation of fibres has also been produced here by cocaine, which affects the smallest fibres first [Gasser, 1935], and by cooling, which produces a sensory dissociation that is not closely related to fibre diameter [Bickford, 1939].

Methods

Cats were used for the experiments. Thirty out of thirty-six were anaesthetized with nembutal, given intraperitoneally in the dose of 35 mg./kg. body weight. Deep anaesthesia was maintained by giving 10–20 mg. intravenously at intervals. Three animals were anaesthetized with urethane,

given by stomach tube in the dose of 2 g./kg. body weight: the stomach tube was passed under ethyl chloride anaesthesia. Three other animals were decerebrated under ether, and were subsequently given 10 mg./kg. of curare intravenously, and then ventilated artificially. In the anaesthetized animals, care was taken to maintain a deep and as far as possible a constant level, so as to prevent any visible reflex movements during stimulation or any vigorous respiratory reflexes, since either of these would give rise to uncontrolled secondary changes in the blood pressure.

The nerve usually chosen for stimulation was the medial popliteal, and its extension, the posterior tibial. The nerve was dissected out from the middle of the thigh down to the ankle, without cutting the arteries supplying it, and all its muscular branches in this region were cut. The nerve itself was usually cut through at the ankle. The electrodes were of platinum, housed in perspex holders of the Sherrington type.

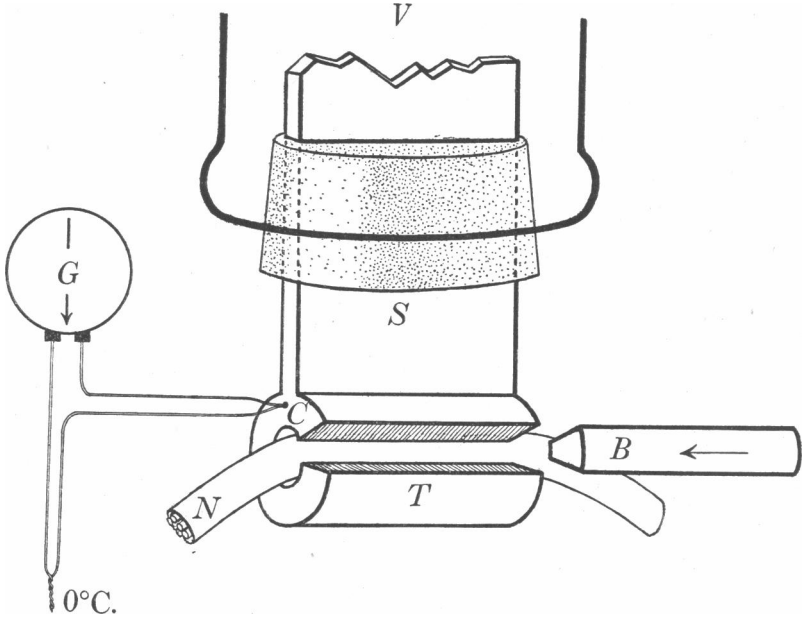

Fig. 1. Diagram of the apparatus used for cooling or freezing nerves. For description see text.

Stimulation was provided by condenser discharges. Stimuli with time constants of either 1 or 0·1 msec. were used; the former were provided by a neon tube stimulator of conventional design, and the latter by a hard valve circuit. These instruments were calibrated for strength, frequency, and duration of stimulus on a cathode-ray oscilloscope. The time constant (RC) of a condenser discharge in sec. was calculated from the stimulator circuit: it is the product of the capacity of the discharging condenser in μF. and the resistance through which it discharges in MΩ.

Asphyxia of a nerve was produced either by a sphygmomanometer cuff tied round the limb and inflated to 40 mm. above arterial blood pressure, or by tying the arteries supplying blood to the limb. It was found that a number of arteries must be tied if the blood supply is to be cut off completely; otherwise a collateral circulation is soon established. Permanent ligatures were tied round the last two pairs of lumbar arteries, both internal iliac arteries, the caudal artery, and both inferior epigastric arteries. A loose loop of silk was then passed round the external iliac artery of the side to be asphyxiated later on, and this was brought out of the abdominal incision through a short flanged ebonite tube, round which the skin and muscles were stitched up. When it was necessary to asphyxiate the limb, the artery was lifted up by this loop, and was occluded with a rubber-padded clip passed down the tube. The efficiency of this method was tested by injecting

1% trypan blue into the jugular vein with the arterial ligatures in position, and if there was no colouring of the limb in question after 15 min., it was considered that its blood supply had been cut off.

Nerves were *cooled* with the apparatus shown in Fig. 1. The cooling element itself is a copper tube (*T*), with a longitudinal slot cut in it, through which the nerve (*N*) is inserted. The tube is $\frac{3}{4}$ in. long, and its wall is about three-quarters of the thickness of the nerve it contains. A block of copper (*B*) slides into the slot, and completes the encirclement of the nerve. Both this block and the tube are silver-plated. The tube is soldered to a vertical copper strip (*S*) $\frac{1}{8}$ in. thick, which passes up through a rubber bung into a vacuum flask (*V*), containing either ice or an ice and salt mixture. The temperature of the tube *T* is measured from a thermocouple soldered into it (*C*), and lying as close to the nerve as possible. Another thermocouple is kept at 0° C. A range of temperatures down to −6° C. can be obtained.

Results

Stimulation of normal nerves

Relation of the reflex to the strength of stimulation. Fig. 2 illustrates an experiment in which the central end of the posterior tibial nerve was stimulated with shocks of time constant 1 msec. and frequency 3 per sec. The nerve was stimulated for periods of 20 sec., starting with a strength of 4 V., and increasing in subsequent stimulations up to 28 V. The results are typical of all the experiments in the series. There is a fall of blood pressure with weak stimuli of 4, 6, and 12 V., a fall followed by a rise with an intermediate stimulus of 22 V., and a rise with the strongest stimulus of 28 V.

The accompanying record of respiration shows a slight decrease in amplitude when the blood pressure fell, and an increase when the blood pressure rose.

Relation to the duration of the stimulus. When a stimulus was used with the shorter time constant of 0·1 msec., it was found impossible to produce any pressor reflexes, even with strong stimuli (60–80 V.), provided that the frequency of stimulation was less than 100 per sec. This is illustrated by Fig. 3, which contrasts the depressor reflex, obtained at 60 V. with a short-lasting stimulus, with the large pressor reflex obtained at 25 V. with a longer stimulus. The stimulus frequency was kept constant at 10 per sec.

Relation to the frequency of stimulation. If the strength of stimulation is such that depressor reflexes are obtained with a low stimulus frequency, pressor reflexes can often be obtained by increasing the frequency of stimulation alone (Fig. 4). This reversal usually happens when the frequency is raised above 100 per sec., and it was found even with a stimulus of short time constant (0·1 msec.), though the reflex rise in blood pressure was then never more than 20 mm. of mercury.

All the reflex effects described so far have been found consistently in animals anaesthetized with nembutal or urethane, and in curarized decerebrated animals. The type of reflex response was not affected by cutting both vagi and cauterizing the tissues round the carotid sinus, although both pressor and depressor reflexes were larger after this had been done.

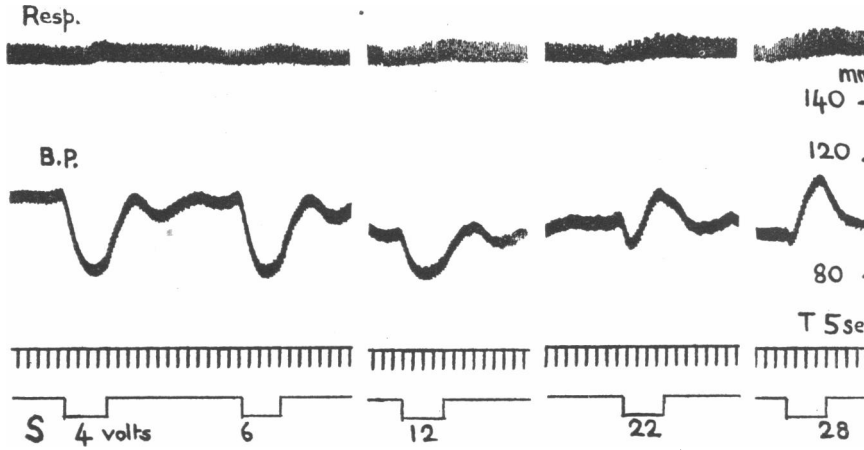

Fig. 2. Records of the vasomotor (*B.P.*) and respiratory (*Resp.*) reflexes produced by stimuli of various strengths applied to the central end of the posterior tibial nerve. Weak stimulation gave a depressor reflex and strong stimulation a pressor reflex. Respiration recorded by Gaddum's method. Anaesthetic, urethane. Frequency of stimulation, 3 per sec. Time constant, 1 msec.

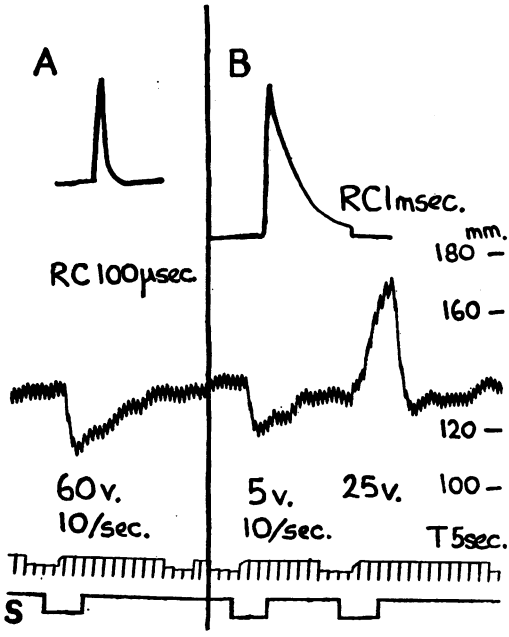

Fig. 3. Records of the reflex changes in blood pressure produced by stimulating the central end of the posterior tibial nerve. In *A* a strong stimulus of short time constant (0·1 msec.) gave a depressor reflex. In *B* the time constant was 1 msec. and a pressor reflex was obtained with the weaker stimulus of 25 V. Anaesthetic, nembutal. Frequency of stimulation 10 per sec. The tracings inset above show the configuration of the appropriate stimuli: they were taken from cathode-ray oscilloscope records.

In the remaining experiments described below, a stimulus with a time constant of 1 msec. has been used, and the frequency has usually been kept constant throughout each experiment. Pressor and depressor reflexes have been produced by strong and weak stimulation respectively, and the nerve has been altered, proximal to the stimulated point, by cocainizing, asphyxiating,

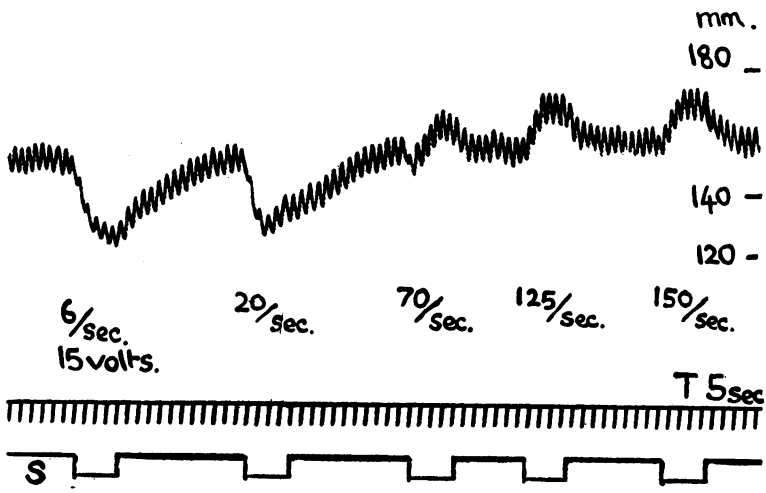

Fig. 4. Records of the reflex changes in blood pressure produced by stimulating the central end of the posterior tibial nerve at a fixed strength of stimulus but with a variable frequency. Anaesthetic, nembutal. Strength of stimulus, 15 V. Time constant, 1 msec.

or cooling. Possible errors caused by the spread of electrical stimulus across the block have been eliminated by placing the distal electrodes at least 1 in. beyond the block, and, in most experiments, by using a control pair of electrodes proximal to the block.

The effect of cocaine

Two pairs of electrodes were used, one applied to the posterior tibial nerve at the ankle, and the other to the same nerve above the knee. Before applying cocaine, control stimulation was carried out at each pair of electrodes with weak and strong stimuli. 0·5 c.c. of 1% cocaine hydrochloride was then slowly infiltrated under the nerve sheath between the pairs of electrodes, through a very fine hypodermic needle. After this the nerve was stimulated at each pair of electrodes every minute, and the vasomotor reflexes obtained by stimulation proximal and distal to the narcotized portion were compared.

Five minutes after applying the cocaine, no pressor reflex could be obtained by stimulating distally (Fig. 5), and a depressor reflex was the response

to the strongest stimulation (30 V.). The reflexes obtained by stimulating proximally were unchanged. After 15 min. the nerve was usually completely blocked by the cocaine, and reflexes were only obtained by stimulating proximally.

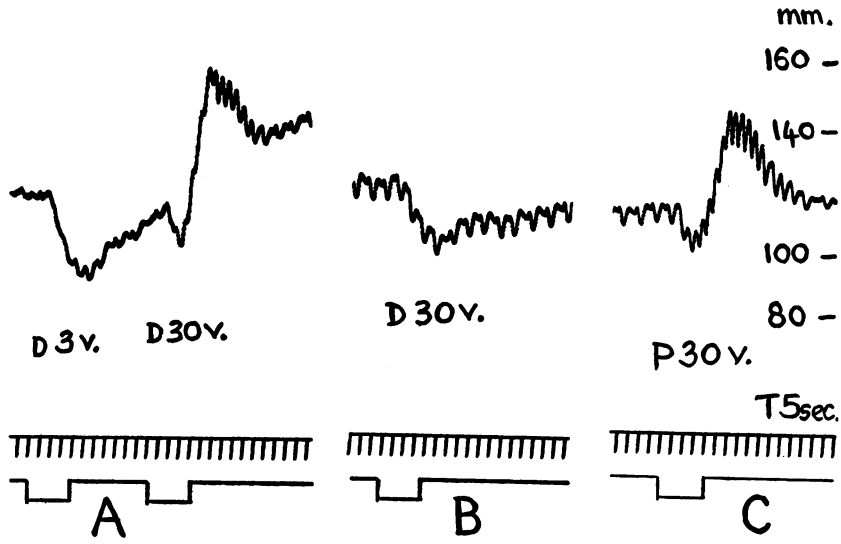

Fig. 5. Records showing the effect on the vasomotor reflexes of applying cocaine to the nerve proximal to the stimulated point. A. Depressor and pressor reflexes obtained with weak and strong stimuli before applying cocaine. B. Depressor reflex obtained by strong stimulation distally, 5 min. after applying 0·5 c.c. 1% cocaine. C. Pressor reflex obtained by strong stimulation proximal to the cocainized point. Anaesthetic, nembutal. Frequency of stimulation, 2 per sec. Time constant, 1 msec.

The effect of asphyxia

Electrodes were applied to the posterior tibial nerve of each leg. It was confirmed before starting the experiment that the vasomotor reflexes obtained by stimulating each nerve were similar for the same strengths of stimulus. One leg was then asphyxiated, either with a sphygmomanometer cuff or by tying the arteries supplying it.

There was no change in the reflexes from the asphyxiated side for 30–40 min., but after this the depressor reflex obtained with weak stimulation became smaller, and finally disappeared after 50–60 min. At this stage of asphyxia it was still possible to obtain pressor reflexes with strong stimulation (30 V.), and often small pressor reflexes were seen with the weaker stimuli, which had given only depressor reflexes before asphyxia. The pressor reflex response to strong stimulation (30 V.) of the asphyxiated nerve was usually slightly larger than that obtained when the same stimulus was applied to the normal nerve of the other leg.

When the blood supply was restored, the depressor reflex appeared again, and after 10 min. there was no difference between the reflexes obtained by stimulating the two nerves (Fig. 6).

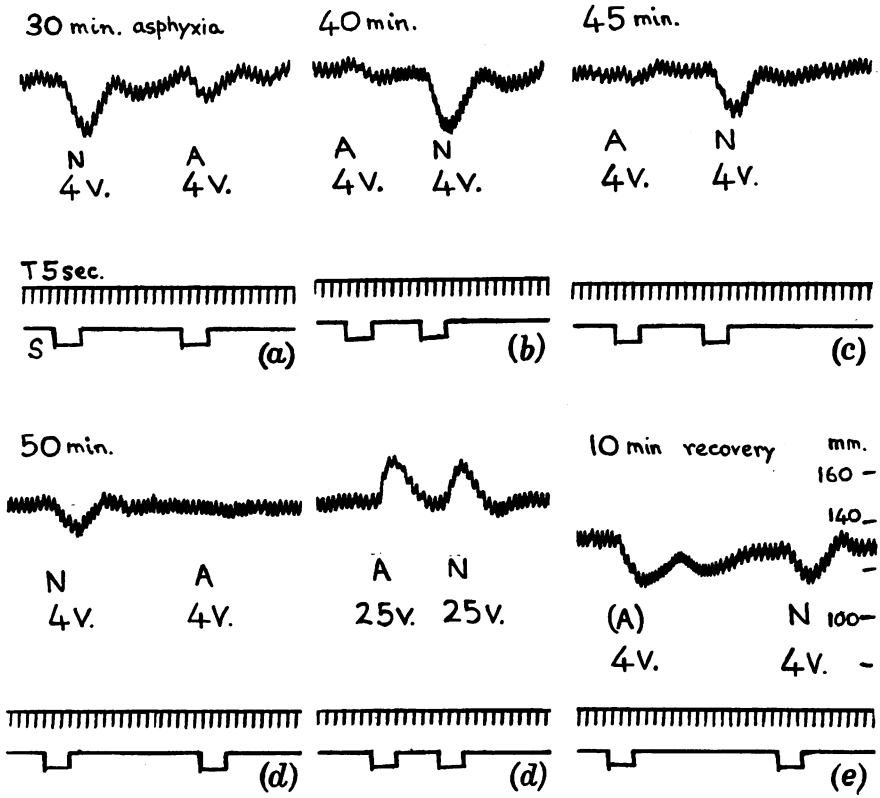

Fig. 6. Records of the vasomotor reflexes produced by stimulating the posterior tibial nerves. One nerve (*A*) had been asphyxiated by tying the arteries supplying the appropriate limb; the other nerve (*N*) was normal. (*a*) Weak stimulation of each nerve (4 V.) 30 min. after occlusion of the blood supply. (*b*) Similar stimulation after 40 min. (*c*) Similar stimulation after 45 min. (*d*) Weak (4 V.) and strong (25 V.) stimulation of each nerve after 50 min. (*e*) Weak (4 V.) stimulation of each nerve 10 min. after removing the arterial clip and restoring the blood supply. The depressor reflex from the asphyxiated nerve is abolished after 50 min., though the pressor reflex remains at the end of this time. The depressor reflex appears again after restoring the blood supply. Anaesthetic, nembutal. Frequency of stimulation, 3 per sec. Time constant, 1 msec.

Asphyxia, therefore, in contrast to cocaine, abolishes the depressor reflex first, but the pressor reflex remains, and is often rather larger than before.

The effect of cooling and freezing

Cooling. The nerve was cooled to various temperatures between 4 and 10° C. with the apparatus which has been described (Fig. 1). It was stimulated distal

to the cooled point, after 10 min. had been allowed for the nerve to reach an even temperature. After stimulation, the cooling element was removed, and stimulation was repeated after 5–15 min., when the nerve had returned to body temperature.

When the nerve was cooled to temperatures between 5 and 7° C., the depressor reflex obtained with weak stimulation at 2 per sec. was smaller than normal, and the pressor reflex with strong stimulation was sometimes unaltered and sometimes slightly larger than normal.

When the nerve was cooled to 4° C., no depressor reflex could be obtained at all, and the pressor reflex was rather smaller than normal (Fig. 7). When the

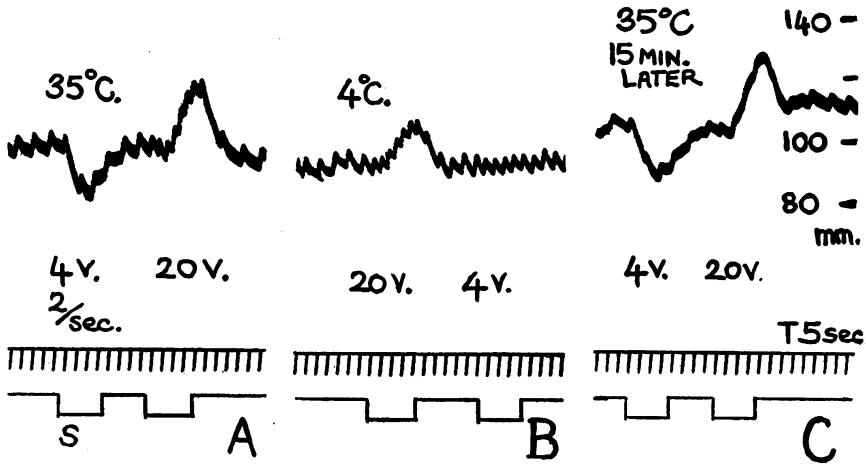

Fig. 7. Records showing the effect on the vasomotor reflexes of cooling the nerve to 4° C. proximal to the stimulated point. A. Depressor and pressor reflexes obtained with weak and strong stimuli before cooling. B. Depressor reflex abolished but pressor reflex still present after cooling to 4° C. C. Depressor and pressor reflexes obtained as before, 15 min. after removing the cooling element. Anaesthetic, nembutal. Frequency of stimulation, 2 per sec. Time constant, 1 msec.

cooling element was removed, both pressor and depressor reflexes reappeared within a few minutes.

Cooling the nerve to temperatures below 4° C. abolished both pressor and depressor reflexes.

Freezing. Two pairs of electrodes were applied to the nerve, and the cooling element between them. The nerve was cooled to −3 or −4° C. with an ice and salt mixture, and kept at that temperature for 5–7 min. By the end of that time it was frozen hard, and it was removed from the cooling tube with a camel-hair brush moistened with warm Ringer-Locke solution.

Stimulation at each pair of electrodes was then carried out every 5 min. There was usually no vasomotor reflex response to stimulation at the distal pair of electrodes for about 10 min. A pressor reflex then appeared on strong

stimulation, and as stimulation was repeated this gradually became larger, until after an hour or more the strongest stimulation (30 V.) gave a much larger

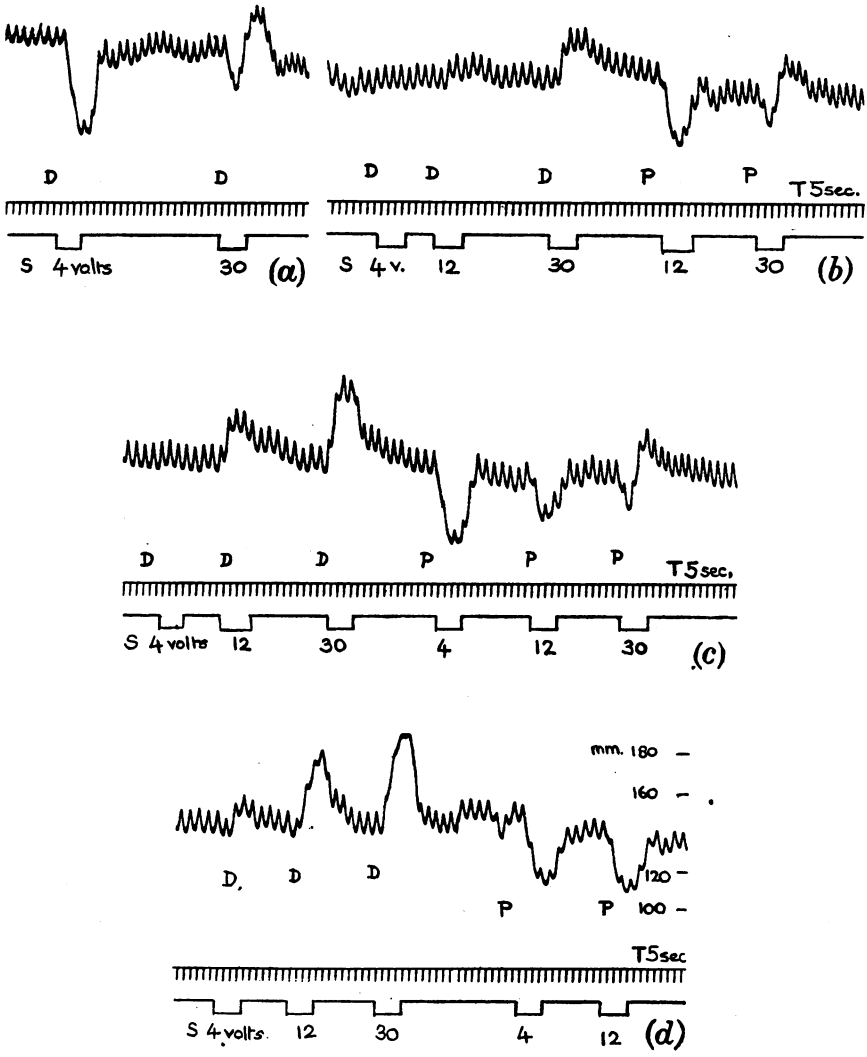

Fig. 8. Records showing the effects on the vasomotor reflexes of freezing the nerve (7 min. at −4° C.). Two pairs of electrodes were used, proximal (*P*) and distal (*D*) to the point frozen. (*a*) Depressor and pressor reflexes obtained with weak and strong stimulation before freezing. (*b*) Stimulation at distal and proximal electrodes 20 min. after freezing. (*c*) Stimulation after 40 min. (*d*) Stimulation after 80 min. The pressor reflex returns after freezing; it is larger than before and can be obtained with weaker stimuli. The depressor reflex does not return. Anaesthetic nembutal. Frequency of stimulation, 6 per sec. Time constant, 1 msec.

pressor reflex than could be obtained by stimulating at the proximal pair of electrodes. At this stage, a weak stimulus (4 V.) also gave a small pressor

reflex, though the same weak stimulus at the proximal electrodes gave a large depressor reflex (Fig. 8).

It was usually impossible to obtain depressor reflexes by stimulating distal to the portion of nerve which had been frozen, at any time during the rest of the experiment, but sometimes there was a partial recovery after 2 hr. or more, and then a small depressor reflex was obtained again.

The effect of cooling or freezing the sensory nerve resembles that of asphyxia in that the depressor reflex is the first to be abolished by cooling, and the last to return after freezing.

Discussion

These experiments confirm the previous observations that the type of vasomotor reflex obtained by stimulating the central end of a cut sensory nerve depends on both the strength of stimulation [Hunt, 1895], and the stimulus frequency [Gruber, 1917]. They also emphasize the importance of a sufficiently long shock-duration in obtaining pressor reflexes. Ashkenaz [1939] claimed that it was not possible to produce a reversal from a depressor to a pressor reflex merely by increasing the strength of stimulation; but his results suggest that he used shocks of too short a duration (see Fig. 3).

The experiments also throw some light on the question originally discussed by Ranson & Billingsley [1916], who suggested that any influence which reduced the number of impulses in an afferent nerve would tend to abolish the pressor reflex, and that it would then be easier to obtain a depressor reflex. They believed, therefore, that the appearance of a pressor reflex was the result of increased central summation. The results described above show that nerves blocked by cocaine fulfil this prediction, but that the opposite is true of blocks produced by asphyxia or cold. There can be no doubt that each of these three blocking agents reduces the number of nervous impulses passing centrally; the abolition of the depressor reflex and the persistence of the pressor reflex after asphyxia or cooling cannot therefore be explained on the assumption that the pressor reflex is simply the expression of increased central summation.

These results, on the other hand, support the classical idea that sensory nerves contain pressor and depressor afferent fibres of different sizes, the pressor fibres having a higher threshold to stimulation, and being the more resistant to asphyxia or cooling, while the depressor fibres have the lower threshold, and are more resistant to cocaine. If two types of afferent peripheral fibre do exist, it is not unreasonable that the pressor reflex is larger than normal when the depressor antagonist has been inactivated by asphyxia, cooling, or freezing.

No attempt has been made here to identify the precise types of fibre responsible for the pressor and depressor reflexes by means of their action potentials, but some tentative conclusions can be made about them. Clark *et al.* [1935] found from the action potential that the only fibres resisting asphyxia

for 45 min. were unmyelinated C fibres, and it has been shown here that the only vasomotor reflex persisting after the sensory nerve had been asphyxiated for this time was a pressor reflex. It is probable, therefore, that many of the pressor afferent fibres belong to the C group. This means that they have a higher threshold than the depressor fibres, and a longer excitation-time (Fig. 3).

The depressor afferent fibres, on this supposition, must belong mainly to the A group, being those which are the most resistant to narcosis with cocaine, and the least resistant to asphyxia. It is impossible, without the electrical evidence of the action potential, to tell to which subdivision of the A group these fibres belong.

The effect of cooling and freezing the sensory nerve, in these experiments, has been similar to that of asphyxiating it, and although the effects of cold on the different types of fibre are not accurately known, it is significant that human 'second pain', which is probably mediated by unmyelinated C fibres [Lewis & Pochin, 1938], is the last sensation except warmth to be lost when a cutaneous nerve is cooled [Bickford, 1939]. Some further experiments are in progress on the effects of cold on the different fibres of a peripheral nerve.

There is one discrepancy between the results given here and those described by Hunt [1895]. Hunt found that cooling a sensory nerve first abolished the pressor reflex obtained by stimulating the nerve, and that the depressor reflex persisted longer. The entirely opposite result described here may depend on the fact that a stimulus of 2 per sec. frequency was used, while Hunt used a repetitive stimulus from an inductorium, with presumably a higher frequency. The use of a higher frequency of stimulation, when the nerve is at a low temperature, must bring in the complication of Wedensky inhibition, and it is probable that the smallest fibres, by virtue of their long refractory period, are more susceptible to this inhibition than larger fibres. In confirmation of this idea, it has occasionally been observed here that when a nerve was cooled to about 6° C., a reversal from a pressor to a depressor reflex was produced by increasing the frequency of stimulation from 2 to 20 per sec. This effect was only seen when the nerve was at a low temperature at the time of stimulation: it did not occur in nerves partially blocked by freezing, which had returned to body temperature before stimulation.

The reversal from a depressor to a pressor reflex, which occurred when the frequency of stimulation was raised above 100 per sec. (Fig. 4), and which Gruber [1917] was the first to observe, may depend on an increase in central summation of the kind which Ranson & Billingsley [1916] had proposed, and which has recently been discussed by Ashkenaz [1939]. It is a phenomenon of a different kind from the reversal produced by increasing the strength of stimulation; the latter is more likely to depend on the higher threshold of the pressor fibre.

It remains to discuss the possible importance of these principles in the clinical question of the vasomotor reactions after severe injury. C fibres, on the evidence of experiments on human beings [Lewis & Pochin, 1938] and on animals [Zotterman, 1939], carry slowly conducted impulses associated with 'second pain'. These fibres adapt slowly, and their discharge, in response to a single cutaneous stimulus in the cat, is apt to be prolonged. Most of the pressor afferent fibres probably belong to this group. On the evidence of these same authors, the fibres carrying impulses of the accurately localized 'first pain' belong to the A group, and are probably delta fibres. This group probably contains depressor rather than pressor afferents; and it may be that afferent impulses in these fibres, which adapt more rapidly, can play a part in the reaction to injury which is known as primary shock, and from which recovery is often spontaneous. But if any nervous discharge has to do with the more serious condition of secondary traumatic shock, a question which remains very controversial, it is more likely to be a discharge in slowly adapting fibres, possibly in those of the C group, which appears to have given a pressor reflex under the experimental conditions described in this paper.

Summary

1. Electrical stimulation has been applied to the central end of the cut posterior tibial and other mixed nerves in cats, which were either deeply anaesthetized with nembutal or urethane, or else decerebrated. Stimulation at low frequencies causes a reflex rise in blood pressure with strong stimuli, and a fall with weak stimuli. This agrees with the results obtained by Hunt [1895].

Only depressor reflexes can be produced, however, even with very strong stimulation, when the time constant of the stimulus is as short as 0·1 msec.

2. When cocaine, an agent which inactivates the smallest fibres first [Gasser, 1935], is applied to the nerve proximal to the point stimulated, the pressor reflex is abolished before the depressor reflex.

3. When the nerve is blocked by cold or asphyxia, the depressor reflex is abolished first, and the persisting pressor reflex often becomes larger than before. Asphyxia, in contrast to cocaine, affects the largest fibres first [Clark *et al.* 1935]: the effect of cold on fibres of different sizes is not so clearly known.

4. On this evidence, it is suggested that the pressor and depressor reflexes have separate afferent fibres in sensory nerves, the pressor fibres possibly belonging to the C group, and having a higher threshold to stimulation.

5. If the strength of stimulation is kept constant, a reversal from a depressor to a pressor reflex can be produced by increasing the frequency of stimulation alone, as Gruber [1917] originally found. It is suggested that this type of reversal depends on central summation of impulses.

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