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THE ACTION OF DRUGS IN MUSCULAR FATIGUE*

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Evidence that the sympathetic system plays a part in muscular contraction was first found by Orbeli in 1923. He stimulated the motor roots in the frog repeatedly and recorded the contraction of the gastrocnemius. As the stimulation proceeded the height of the contraction diminished, and he then stimulated the sympathetic fibres in addition; in the majority of the experiments he observed an increase in the height of the contraction. Several workers have since confirmed Orbeli's observations in the frog, but few clear results have been obtained in warm-blooded animals. The relation of the sympathetic supply to the motor innervation has been studied in the sea-gull and the pigeon, but without general agreement on the significance of the results. In 1930 Miss Baetjer made observations in the cat in which she showed quite clearly that the effect described by Orbeli could be obtained in that species. Her results were of two kinds: in some experiments stimulation of the sympathetic led to an augmentation of the muscle contraction, and in others it diminished the muscle contraction; this diminution she attributed to the diminution of blood-flow through the muscle caused by vasoconstriction. The augmentation of contraction by sympathetic stimulation was observed when the muscle was fatigued; the evidence indicated that it was accompanied by a diminution of blood-flow and occurred in spite of it; Miss Baetjer's paper did not, however, establish this.

The observations which Dr. Edith Bülbring and I have made arose out of an attempt to discover the function of vasodilator fibres in the sympathetic supply of the muscles of the dog. We were led to study the effect of sympathetic stimulation in the contracting muscles. The experiments performed have been of different kinds. Those which offer least ambiguity in interpretation were experiments in which defibrinated blood was pumped through the hind leg of a dog, the pressure in the arterial cannula being recorded by a manometer; the outflow from the vein was measured by Gaddum's outflow recorder. Since the skin was removed from the leg the tissue perfused was almost entirely muscle. The spinal cord was exposed and the last three lumbar and first two sacral roots were separated from the cord; the dorsal roots were cut away as far as the ganglion, and the motor roots thus prepared for stimulation. The sympathetic chain was also prepared for stimulation. By fixing a steel rod through the lower end of the femur and connecting

the tendo Achillis to a tension lever the tension developed by the gastrocnemius muscle during an isometric contraction was recorded.

Changes of Blood-flow in Muscle Contraction

The preparation has made it possible to investigate afresh the changes of blood-flow during muscle contraction. With a normal degree of vascular tone and a contraction exceeding five seconds in duration there is a large fall of arterial resistance and a corresponding increase in venous outflow during the contraction, whether this is a tetanus or whether it occurs in response to interrupted stimulation. For those of us who are accustomed to thinking of blood-pressure changes as brought about mainly by nervous impulses, particularly impulses passing along sympathetic fibres, the extent of the vasodilatation caused by muscular contraction is very surprising. If the muscle is stimulated by way of the motor roots in the anaesthetized animal there is no fall in the general blood pressure despite the vasodilatation; this must mean that a large volume of blood is deviated from the skin or intestines to the muscles in order that the fall may be prevented. The redistribution of blood is accomplished by the sympathetic system, and in animals from which this system has been removed exercise is followed by a conspicuous fall in blood pressure. Thus we see that exercise not only involves increased formation of energy in the body but provides a valuable gymnastic exercise for the blood vessels.

When a record has been kept of the tension developed by the perfused gastrocnemius we have observed an initial contraction corresponding in some experiments to as much as 18 kg.; this tension then declined, and was maintained at a level which depended on the blood-flow through the muscle. When the stroke of the pump was increased so that more blood was driven through, the venous outflow rising from 100 to 140 c.cm. per minute, the tension rose by 0.75 kg., and fell again when the original blood-flow was restored. Thus, as might be expected, the tension varies in proportion to the blood-flow.

The Orbeli Phenomenon

When, during the course of a tetanus produced by stimulation of the motor roots, the sympathetic chain was also stimulated, after a short latent period the tension in the gastrocnemius rose and was maintained at a higher level until the sympathetic stimulation stopped. As a result of the tetanus the inflow of blood was greater and the outflow from the vein was also greater, but during the

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stimulation of the sympathetic chain the flow of blood through the muscle was reduced below the original level. Thus the rise in tension occurred in spite of a reduction in the blood-flow. By experiments of this kind it was possible to confirm Baetjer's results showing that the phenomenon described by Orbeli could be observed in mammals, and to demonstrate in addition that it occurred even when the blood-flow was diminished. That the smaller blood-flow was a hindrance to the rise of tension is evident from the presence of a second rise of tension as the vasoconstriction passed off. Evidently the first rise was the resultant of two effects, both produced by the stimulation, the one raising the tension and the other diminishing it by reducing the blood-flow.

Similar effects were obtained by the injection of adrenaline. When doses of adrenaline corresponding to 7 γ and 20 γ were injected into the arterial cannula during a tetanus there was a diminished blood-flow, but nevertheless an increase of muscle tension of 1 kg. and 2 kg. respectively. When larger doses—for example, 100 γ —were injected the vasoconstriction was then so great that the tension was reduced.

In other experiments the motor roots were given stimuli repeated at a rate of 110 per minute. When some degree of fatigue was evident from the gradual diminution of the tension developed at each contraction the sympathetic chain was stimulated for thirty seconds, with the result that the tension was increased by about 1 kg. When, later, 20 γ of adrenaline was injected there was a rise of tension of about 2 kg.

The Action of Cocaine

Some interesting observations have been made with cocaine. It has long been known that the Peruvian Indians are accustomed to perform feats of endurance by the aid of coca leaves, which they chew. Since the identification of cocaine as the active principle there has been some confusion about the action of cocaine in muscular contraction, and it remains till now undecided whether the effect exerted in the Indians was an action on the central nervous system or whether it was a peripheral action on the muscle itself. Recently Macgregor, in my laboratory, has investigated the action of cocaine on the muscle of the cat, and has shown that when stimuli are applied to the sciatic nerve the intra-arterial injection of cocaine causes a diminution in the tension developed. Dr. Bülbring and I have found, however, that when a rapid rate of stimulation is maintained the initial drop in tension after the injection of cocaine is followed by a striking and prolonged rise in tension to twice the initial value. We made experiments in cats in which the brain was destroyed and also carried out perfusion experiments in which the inflow of blood was determined by the stroke of the pump and the arterial resistance. The injection of 2 mg. of cocaine hydrochloride into the blood going to the leg, after causing an initial drop in tension which passed off in thirty seconds, then produced a rise in tension from 4 to 5 kg. This increased tension persisted for several minutes. The injection of cocaine was practically without effect on the blood-flow through the muscles of the leg; there was a very slight diminution.

These observations seem to us to provide a demonstration of the basis of the action of cocaine in increasing endurance and lessening fatigue, and suggest that it is unnecessary to postulate an action on the central nervous system as playing any part. We think this action of cocaine can be regarded as a further evidence that it is a sympathomimetic substance.

The Action of Ephedrine

It has been known for some time that ephedrine has an action on skeletal muscle inasmuch as it has a beneficial effect in myasthenia gravis. The discovery was apparently made by a lady who suffered both from this disease and from asthma, and who found that in taking ephedrine for asthma the myasthenia gravis improved as well. When ephedrine is injected into a cat in which the brain has been destroyed, in which the tension of the gastrocnemius is recorded, and in which the sciatic nerve is repeatedly stimulated so that fatigue has been produced, a large and prolonged rise of tension is observed. Now the injection of the ephedrine was also attended by a rise of blood pressure due both to increased cardiac output and to vasoconstriction; it can scarcely be doubted that there was an increased blood-flow through the muscle, and that the increased tension was in part at least due to this effect. In the period from fifteen to sixty minutes after the injection there was no appreciable change in the blood pressure, yet the muscle tension increased from 4.5 to 4.8 kg., so that vascular changes did not account for the whole effect. This was proved by experiments in which the muscles were perfused by means of a pump and in which the only vascular effect produced by the ephedrine was a very slight diminution of blood-flow through the muscle. When the sciatic nerve was continuously stimulated 110 times a minute until fatigue lessened the tension developed in the gastrocnemius, the injection of 1 mg. ephedrine hydrochloride then produced a rise in tension similar to that produced by 1 γ adrenaline, but lasting very much longer; the tension was increased by about 60 per cent.

Now Gaddum has put forward the view that many of the actions of ephedrine are to be explained by supposing that it diminishes the rate of removal of adrenaline. We were therefore concerned to discover what effect ephedrine exerted in the contracting muscle on the response to adrenaline. We found that whereas 4 γ adrenaline raised the tension from 4.5 to 5.5 kg., after the injection of 2 mg. ephedrine it caused a rise from 4.5 to 7 kg.

We think there can be little doubt that in these effects of ephedrine—both in the effect it exerts directly and also in the effect on the adrenaline response—we have the physiological basis of the use of ephedrine in myasthenia gravis.

Other Sympathomimetic Substances

In addition to ephedrine we have tested three other sympathomimetic substances—namely, dihydroxyphenylethylamine, sympatol (or synephrine), and tyramine—and have found all of them active in raising the tension. The first has the same ring-structure as adrenaline, but without the $-\text{OH}$ and the $-\text{CH}_3$ groups in the side-chain. Sympatol has the same side-chain as adrenaline, but only one $-\text{OH}$ group in the ring in the *para* position. Finally, tyramine has a ring like sympatol and a side-chain like dihydroxyphenylethylamine.

Actually tyramine (base) was found about twice as potent in its direct effect on muscle tension as ephedrine hydrochloride, which might suggest that it was a better agent for the treatment of myasthenia gravis; tyramine has, however, little or no augmentor action on the adrenaline response. It would be interesting to know how tyramine compares with ephedrine in treatment; for if tyramine is better, then clearly the direct action is the more important, whereas if ephedrine is better, then the augmentation of the adrenaline effect is the more important.

The action of racemic sympatol, or synephrine, was found much more like that of adrenaline in onset and duration, but 1,000 times weaker. In dihydroxyphenyl-ethylamine we met a much more potent substance, for in a series of experiments we found consistently that it was only one-hundred-fold weaker than adrenaline in raising muscle tension, and in action it was more prolonged. Since the pressor action of this substance is not greater than that of tyramine, it should be more suitable for use in treatment than any of the other sympathomimetic amines. It is unfortunately not easy to obtain; our own sample was given to us by the late Professor Barger. Table I contains a summary of the relations

TABLE I

Substance	Potency in Raising Tension compared with Adrenaline	Whether Action is Prolonged	Whether Effect of Adrenaline is Increased
Dihydroxyphenyl-ethylamine	100 times weaker	Yes	No
Racemic sympatol or synephrine	1,000 " "	No	No
Tyramine	1,000 " "	Yes	No
Ephedrine	2,000 " "	Yes	Yes

of the different substances; from this it is seen that ephedrine is the only substance which augments the action of adrenaline, and that sympatol, which has the same side-chain as adrenaline, is the only substance which has a brief action like that of adrenaline: the others exert a more prolonged action.

Histamine

Lastly I would like to mention that one or two observations indicate that histamine diminishes the muscle tension; this effect has not yet been fully investigated by us, but we have seen that it does not always occur. We believe that in those circumstances in which there is little fatigue when adrenaline fails to increase the tension, then histamine does not diminish it; on the other hand, when there is fatigue, so that adrenaline augments the tension, then an injection of histamine causes a fall of tension.

Effect of Adrenaline on Motor Roots

There has been for many years a controversy on the relation of the sympathetic nervous system to skeletal muscle. Boeke, the well-known Dutch histologist, believes that he has observed sympathetic fibres which end in striated muscle in places where the blood vessels are absent, and so he supposes that there is a direct sympathetic innervation of skeletal muscle fibres. On the basis of Orbeli's experiment in the frog and of similar observations in the cat and in the dog, we could suppose that the function of these fibres was to increase the force of muscular contraction in fatigue. The existence of such a mechanism would certainly be appropriate. When muscular work begins the sympathetic is engaged in redistributing the blood, so that the skin and intestines get less and the muscles more; when muscular work is severe the sympathetic system must at all costs maintain a high blood pressure in order to preserve a sufficient coronary flow; if necessary blood must be cut off from the skeletal muscles for this purpose. To compensate for this, however, we can suppose that the Orbeli mechanism comes into play by the aid of the fibres which Boeke thinks he has demonstrated.

We have seen, however, that the action of adrenaline injected into the blood stream is similar to that of

sympathetic stimulation, and since this adrenaline must diffuse from the blood into the muscle substance it is likely that the sympathetic fibres in the blood-vessel walls would anyhow exert a similar effect; for when they are stimulated and cause vasoconstriction they liberate a humoral transmitter similar to adrenaline that diffuses into the muscle substance. Thus a direct sympathetic innervation of muscle fibres need not exist in order to account for what is observed.

What kind of an action do adrenaline and the other sympathomimetic substances exert on the muscle whereby the tension in fatigue is augmented? Since it is exerted by adrenaline after giving ergotoxine, and by other substances when there is only the smallest change in the blood-flow, we do not see how the action can be due to a vascular effect. In attempting to put forward any positive suggestion we are obliged to describe some observations we have made on the transmission of impulses travelling along the motor nerves from the roots. Often in the course of our experiments we had observed that the response to stimulation of the roots became steadily less, and finally disappeared, and we looked upon this as the inevitable failure of vital function in the artificial conditions of a perfusion system. We have discovered, however, that the contractile response of the muscle can be restored by the addition of adrenaline to the perfusing blood.

For example, we performed experiments in which a stimulus lasting ten seconds was applied to the motor roots at intervals of two minutes. At the beginning of the experiment the initial tension developed was 10 kg., at a time when the perfusing pressure was 100 mm. The tone rapidly fell, and the tension which was developed during successive stimulations fell also to 1 kg. Adrenaline was slowly added to the reservoir collecting blood after reoxygenation, and the vascular tone rose; when a total of 100 γ was added to 600 c.cm. blood the tension developed in response to stimulation was restored to 10 kg. In each experiment it was possible to watch the diminution or disappearance of the response to motor-root stimulation and its restoration by the addition of adrenaline many times. To cause a disappearance of the response it was not necessary to apply a stimulus lasting ten seconds in order to fatigue the muscle; the response to single shocks also disappeared. The effect of the adrenaline on the muscular response always lagged far behind its effect on the vascular tone—for example, 100 γ adrenaline was added to the blood during ten minutes, and when the highest arterial pressure was reached of 90 mm., stimulation of the motor roots still produced no response. The arterial pressure then fell as the adrenaline was destroyed, and when it was only 40 mm. stimulation of the motor roots produced a tension of 12 kg.

We found this effect of adrenaline on the response to motor-root stimulation difficult to explain; it seemed as though by the action of adrenaline a store of some substance was created either in the muscle or in the blood, the presence of which was necessary for the response to motor-root stimulation. We therefore investigated the effect of adding different substances to the blood. We found that the steady addition of sodium lactate did not restore the response; nor did the addition of dextrose, of dextrose and insulin, or of extract of suprarenal cortex (eucortone). We found, however, that the disappearance of the response to stimulation of the motor roots was not accompanied by any change in the response to direct stimulation of the muscle itself. This made it appear that the failure of the response could have nothing to do

with conditions in the muscle or in the blood, but rather with conditions at the neuromuscular junction.

In the hope of excluding the effect of the vascular changes produced by adrenaline we gave ergotoxine first. We found that adrenaline then failed to restore the response. This led us to the provisional conclusion that the effect of adrenaline must be, in spite of all appearances, in some way or other vascular.

Adrenaline and the Orbeli Phenomenon

The first question to be discussed is whether the ability of adrenaline to restore the response of the motor roots to single shocks is related to the Orbeli phenomenon. Previously we imagined that the Orbeli phenomenon—that is to say, the increase of tension observed on stimulation of the sympathetic chain during a tetanus or during interrupted stimulation—was due to an effect on the metabolism of the muscle, whereby as a result of the action of the adrenaline-like humoral transmitter more energy was made available and the response to a constant stimulus became greater. If, however, the Orbeli phenomenon is related to the ability of adrenaline to restore the response of the muscle to single shocks, it is clear that it has nothing to do with the metabolism of the muscle, since the failure of the motor roots to cause contraction is not accompanied by any failure of the muscle to respond to direct stimulation. The failure of single shocks applied to the motor roots to cause contraction must be due to a failure of the nerve ending to transmit the impulse to the muscle, and somehow or other adrenaline must restore the transmission when it has failed. If the Orbeli phenomenon has the same explanation, then the rise of tension on stimulation of the sympathetic fibres is to be explained as due to improved transmission of the motor impulses at the nerve ending.

In one respect only do the observations hitherto made indicate that the two phenomena have a different explanation—namely, in respect of the action of ergotoxine. After giving ergotoxine, adrenaline is able to cause an increase in tension during the application of interrupted stimulation. Hitherto, however, after giving ergotoxine we have failed to observe a restoration of the response to stimulation of the motor roots when adrenaline is added to the circulating blood. This difference suggests at first sight that the two phenomena are unrelated. This may well be so, but we do not yet give up hope of finding an explanation which will harmonize the difference.

In conclusion we would like to call attention to the practical significance of the finding that, in a perfusion system, stimuli applied to the motor roots may cease to be transmitted to the muscle, and that the transmission can be restored by the addition of adrenaline to the blood. We have here evidence that the conditions of the circulation can modify the transmission of impulses to the skeletal muscles.

This evidence may be a clue to the muscular weakness which is found in Addison's disease or in shock, when the blood pressure becomes very low; there may be in both these conditions a partial failure of neuromuscular transmission, and the evidence indicates the great importance of maintaining the blood pressure in order to combat this failure. So far as Addison's disease is concerned the recent evidence of Secker fits in very well. He has shown that, in a cat from which the suprarenal glands have been removed, repeated stimulation of the cervical sympathetic chain results in a condition in which the nictitating membrane no longer responds to the stimu-

lation. Injection of cortical extract rapidly restores the response. Here is evidence that the body requires a certain concentration of the cortical hormone to enable some sympathetic nerves to function properly. If this is true of the vasoconstrictor fibres we have at once an explanation of the low blood pressure seen in Addison's disease. When the cortical hormone is deficient the sympathetic impulses cannot maintain the vascular tone. Our own evidence now carries the pathology still further. Because of the low blood pressure and poor circulation we can expect a deficient transmission of motor impulses at the neuromuscular junction, and in consequence great muscular weakness.

A similar sequence of events may occur in shock, where, as we know, there is a large fall in blood pressure with accompanying muscular weakness. Perhaps the observation that histamine can reduce muscle tension has a bearing on the explanation of shock; if so, the view that histamine is a cause of shock may be revived in a different form.

Summary

When the gastocnemius muscle of a dog is caused to contract by stimulation of the motor roots the tension developed during a tetanus or during interrupted stimulation lasting some minutes is augmented either by stimulation of the sympathetic chain or by injection of adrenaline.

Cocaine, which causes an initial drop in muscle tension during nerve stimulation, also causes a rise in tension afterwards; this is probably the basis of the action of cocaine in increasing endurance.

Ephedrine augments the tension developed by the muscle, and also augments the tension-raising power of adrenaline; this is probably the basis of the action of ephedrine in myasthenia gravis. Tyramine is twice as strong as ephedrine, and dihydroxyphenylethylamine is twenty times as strong as ephedrine. These substances should be tried in myasthenia gravis.

It has been demonstrated that when stimulation of the motor roots fails to evoke a muscular response the neuromuscular transmission can be restored by adrenaline. The evidence that circulatory conditions may affect neuromuscular transmission may explain the muscular weakness of Addison's disease.

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The following is the programme of the provincial meeting of the Tuberculosis Association to be held at Cambridge from March 30 to April 1: Thursday, March 30, 2.30 p.m., Professor Sebrechts (Bruges), "Apicolysis with Plombage by the Pectoral Muscles in the Surgical Treatment of Giant Cavities: The Technique and the Results at Bruges from 1926 to 1938"; 4.30 p.m., Problem cases presented by Drs. E. T. W. Starkie, T. W. Davies, and A. Brownlee. Friday, March 31, 9.45 a.m., Mr. N. R. Barrett, "Tuberculosis of the Thoracic Wall"; 11.15 a.m., Dr. F. R. G. Heaf, "How Far should the State Consider the Individual in Planning a Tuberculosis Scheme?"; 2.30 p.m., visits; 7 p.m., president's reception; 7.30 p.m., annual dinner. Saturday, April 1, 9.45 a.m., Dr. Brian Thompson and Mr. E. S. Evans, "Tuberculous Cervical Adenitis"; 11 a.m., Mr. R. Scott Stevenson, "Radiology of the Larynx"; 12 noon, annual general meeting. Further particulars can be obtained from the honorary secretary of the association, 26, Portland Place, W.1.