NOTES ON THE PHYSIOLOGY OF THE CARDIAC NERVES OF THE OPOSSUM (DIDELPHYS VIRGINIANA).

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The knowledge of the physiology of the cardiac nerves has been derived from the study of such a very limited number of species that it is desirable to extend the study to other forms. So far as we are aware, no one has investigated the innervation of the heart of a marsupial; hence the following observations upon the opossum may be not without interest.

1. METHODS OF EXPERIMENTING.

As the opossum does not seem to have been used hitherto for physiological experiments, we shall record our observations in some detail.

It may be said that, in general, the opossum is a very favorable subject for physiological experiments; it is of convenient size, the blood-vessels are comparatively large and tough, the blood pressure is moderately high, and anæsthetics are remarkably well borne. In some of these respects the opossum offers marked advantages over the rabbit; on the other hand the large amount of fat which, as is well known, this animal tends to accumulate often makes operations very difficult.

In our experiments the blood pressure and the heart rate were recorded by the mercury manometer in the usual manner.

Anaesthetics.—We have used the following anæsthetics: ether, chloral hydrate (in doses of 1 grm.), morphia sulphate (in doses of .03-.04 grm.) and morphia sulphate and chloral hydrate combined in the proportion of .75 grm. of the latter to .01 grm. of the

former. The morphia and chloral were injected hypodermically. The above mentioned combination of morphia and chloral is probably the best anæsthetic for experiments upon the circulation; animals anæsthetized by it have a good blood pressure; the heart beat is strong and regular, and the vagi are in a condition of moderate tonicity, which seems to be their normal condition.

Normal blood pressure.—The blood pressure was determined only in animals anæsthetized by some of the above drugs; in such animals the arterial pressure, as determined by a cannula in one of the carotid arteries, varied from about 120 to 135 mm. of mercury. Curare affected the blood pressure but little.

Rate of the heart-beat.—The heart rate as determined in anæsthetized animals varied from 144 to 218 beats per minute, being lowest in animals under the influence of morphia alone and highest in etherized animals. When chloral was used, either alone or in combination with morphia, the rate of the beat was between the above mentioned figures. Determinations of the heart rate of the normal animal by means of the stethoscope were not very satisfactory; apparently, however, it was somewhat less than the above—about 120 per minute. Hence the anæsthetic or the operation necessary for the insertion of the cannula had increased the rate of the heart, most probably by diminishing the tonic activity of the vagi.

2. THE VAGUS.

Section of the vagi.—Section of the vagi was followed by results varying in the different experiments according to the degree to which the vagus centres were in activity, and this again varied with the anæsthetic employed. In animals under the influence of chloral or morphia an increase in the heart rate and a rise of blood pressure usually followed section of these nerves; in etherized animals there was little or no effect. Occasionally there was a rise of blood pressure although the heart rate was not affected. Such a rise of blood pressure without any change in the heart rate is not an infrequent occurrence in other animals; the most probable explanation of such cases is that there are fibres in the vagus which on being stimulated

are able to weaken the heart-beat, and that at times they are in a state of tonic activity or have been stimulated in some manner.*

Stimulation of the vagus.—The effects upon the heart of stimulating the peripheral end of the vagus of the opossum are essentially similar to those observed in other mammals; they differ markedly, however, in certain respects.

It seems to us that stimulation of the opossum's vagus is, as a rule, more efficient than is the case with the mammals ordinarily used in the laboratory. For instance, we have never failed to obtain a standstill of the heart by stimulating the vagus with induced currents of moderate intensity (secondary coil of an ordinary Du Bois-Reymond coil 9 to 12 cm. from the primary). As is well known, failure to obtain this result is frequently met with in cats† and occasionally in dogs.

Escape of the heart from stimulation of the vagus.—The heart when brought to a standstill by stimulation of the vagus soon commences to beat again and quickly reaches a "constant level," as described by Hough‡ for the cat and dog. The time required for this escape to occur and the manner of its occurrence and its extent varied greatly. The most usual mode of escape seemed to be that in which the heart, after remaining at a standstill for a short time, suddenly began to beat at a rate which it maintained as long as the stimulation continued. Sometimes this rate was remarkably slow, as is shown in the following experiment:

Feb. 9. Female opossum, etherized. Heart rate 38½ in 10 seconds; blood pressure 102 mm. Hg. Stimulation of the peripheral end of the left vagus with an induced current of moderate intensity caused complete standstill of the heart for 90 seconds. The heart then began to beat at the rate of 5 in 10 seconds, and continued to beat at this rate as long as the stimulation continued (15 minutes), and for some time afterwards. The blood-pressure curve in this experiment is very interesting; with the first three beats of the heart the pressure rose to 64 mm. Hg, or to considerably more than one-half the normal pressure. It fell to 48 mm.

* Cf. Howell, *Journal of Physiology*, xvi (1894), 304.

† This is true of the guinea pig also, as one of us (D. W. H.) has observed.

‡ Hough, *Journal of Physiology*, xviii (1895), 177.

and then rose to 54, at which height it remained during the remainder of the stimulation.

In the above experiment a heart rate of 5 in 10 seconds maintained a blood pressure one-half as great as did a rate of 38½, or nearly eight times as rapid. We shall give later similar instances of the independence of the heart rate and blood pressure.

When the heart was merely slowed by stimulation of the vagus, but not brought to a standstill, a slight escape usually occurred, as was described by Hough for the cat. For example, in one experiment it escaped from 7½ to 10½ beats in 10 seconds, the rate before stimulation having been 26 in 10 seconds. In another case it escaped from 14 to 15 beats in 10 seconds, the vagus having been stimulated when the heart was beating at the rate of 32½ beats in 10 seconds.

After-effect of vagus stimulation.—Perhaps the most marked peculiarity of the effect of stimulating the vagus of the opossum is the fact that the effect upon the heart continues for some time after the stimulation ceases. In the mammals ordinarily used for laboratory purposes and also in the guinea-pig, as one of us (D. W. H.) has observed, the heart after being stopped or slowed by stimulation of the vagus very quickly returns to its normal rate when the stimulation is discontinued; in the dog, in fact, both the heart rate and the blood pressure usually rise considerably above their previous level. In the opossum, however, the return of the heart to the normal rate after stimulation of the vagus is almost always much slower, and we have never observed a secondary acceleration of the heart or a rise of blood pressure. The curve shown in Fig. 1, p. 715, is a good illustration of what usually occurs.

The after-effect varies with the strength of the stimulus, being much more pronounced with a strong than with a weak current. A point of interest is that of two currents of unequal strength, but each of sufficient strength to cause total inhibition, the stronger one causes a longer after-effect. A similar relation between the after-effect upon the heart and the strength of the stimulus is seen when the accelerator nerves are stimulated; of two stimuli, each causing a maximum acceleration, the stronger one causes the longer after-effect.

This after-effect of vagus stimulation is observed when stimuli of very brief duration are employed, so that it can scarcely be attributed to the effect upon the heart of an imperfect supply of blood; besides, as was shown above, the blood pressure usually rises very quickly and sometimes goes above the previous level, although the heart is greatly slowed. Moreover, a local injury to the nerve at the point stimulated, acting as a continuous stimulus, cannot be considered the cause, for cutting off this part of the nerve does not cause the after-effect to disappear. In fact, the long-continued effect upon the heart of vagus stimulation seems to be due to some change in the heart, just as does the long after-effect observed when the accelerators are stimulated.

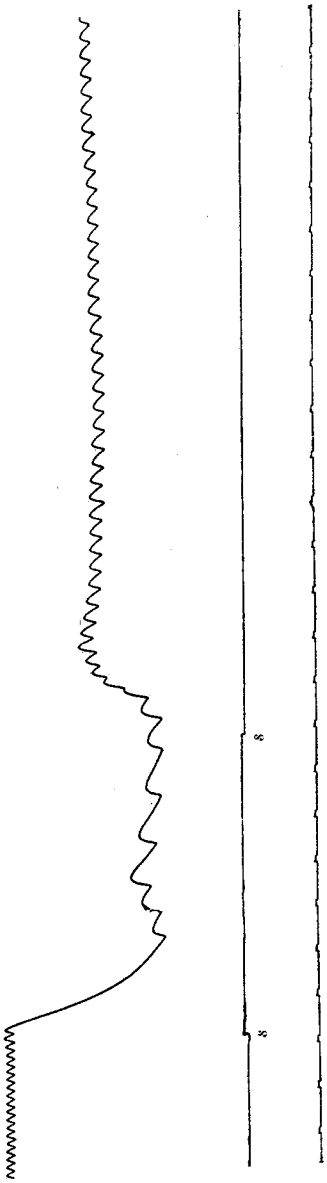

FIG. 1.

Stimulation of the peripheral end of the right vagus (*-s*); secondary coil 6 cm. from the primary. The pen used to mark the stimulation also wrote the base line. The time is in intervals of 2 seconds. The heart rate before stimulation was 28 in 10 seconds; in the course of one minute after the stimulation had ceased this rate returned. Curve to be read from left to right.

Effect upon the blood pressure of stimulating the peripheral end of the vagus.— One of the most constantly observed peculiarities of the effect of stimulation of the peripheral end of the vagus is the lack of correspondence between the effect upon the heart rate and the blood pressure. The heart may be greatly slowed and yet the blood pressure remain at the previous level or even rise above it.

Thus in one case the heart rate was slowed from 31 to 23 beats in 10 seconds, or 26 per cent, while the blood pressure rose from 127 to 143 mm. Hg. The same thing is even more strikingly shown in Fig. 2.

In this experiment the heart had been completely inhibited by a strong stimulation of the vagus; on weakening the current slightly the heart began to beat at the rate of $16\frac{1}{2}$ beats in 10 seconds and the blood pressure rose above its previous level, when the heart had been beating at the rate of $37\frac{1}{2}$ in 10 seconds.

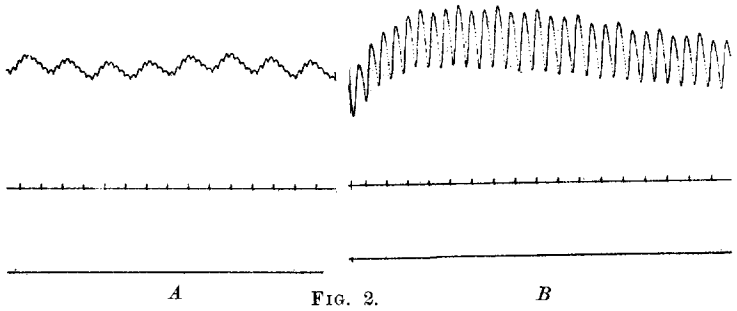

FIG. 2.

Stimulation of the peripheral end of the right vagus. *A* shows the heart rate ($37\frac{1}{2}$ beats in 10 seconds) and blood pressure before stimulation. The heart was stopped for several seconds by stimulation of the vagus; the stimulating current was made weaker, the heart began to beat at the rate shown in *B*, and the blood pressure rose and remained at this higher level notwithstanding the slower heart rate. The pleural cavities had been opened and artificial respiration maintained. Time in seconds. Curves to be read from left to right.

That the rise of blood pressure or absence of a fall in these cases is not due to a stimulation of vaso-constrictor nerves, but is due to a direct action upon the heart, is shown by the fact that when atropin is given in sufficient quantity to paralyze the vagus endings, stimulation of the vagus no longer affects the blood pressure. The simplest explanation of this phenomenon appears to us to be that with the slower rate and consequent better filling of the heart the total volume of blood ejected was increased to such an extent that the arterial pressure rose.

These are certainly striking examples of how widely the heart rate

may vary with but slight changes in the blood pressure. A similar phenomenon is frequently observed when the accelerator nerves are stimulated; the heart rate may be greatly accelerated, although the blood pressure is but slightly affected.

3. THE DEPRESSOR NERVE.

We have found a depressor nerve in every opossum but one in which we have looked for it.

Anatomy.—The depressor in the opossum is very similar both anatomically and physiologically to that of the rabbit. It varies somewhat in its origin, but is usually formed by two roots, one from the superior laryngeal nerve and the other from the ganglion of the trunk of the vagus. Sometimes one of these roots seems to be absent; the nerve then arising by a single root.

Stimulation of the depressor.—When the central end of one of the depressor nerves is stimulated with the ordinary faradic current, the blood pressure slowly falls until it reaches a certain level, at which it remains as long as the stimulation continues. After the cessation of stimulation the blood pressure slowly returns to its former height; the return seems to occur more quickly after stimulating with a weak than with a strong current, although the fall of pressure was the same (*i. e.* maximal) in both cases. In all cases a longer time was required for the return than for the fall of pressure.

The maximum effect upon the blood pressure may occur after the stimulation has ceased if this is of brief duration. Thus in one experiment the stimulation continued 20 seconds; before the stimulation the blood pressure was 70 mm.; at the end of the first 10 seconds of stimulation it was 56 mm.; at the end of 20 seconds, 44 mm., and 10 seconds after the cessation of stimulation it was 40 mm., from which height it slowly returned to the normal.

Stimulation of the depressor causes a slight reflex slowing of the heart in case the vagi are intact. If the stimulation is continued for some time the heart rate, as well as the blood pressure, remains at a constant level, differing in this respect from the effect in the rabbit, in which animal the effect upon the heart usually disappears very

soon after the stimulation begins. After the stimulation the heart rate seems to return to the normal sooner than does the blood pressure.

The effect upon the respiration of stimulating the depressor nerve varied in the different experiments; in some, respiration seemed to be not at all affected, while in others it was slowed or completely inhibited for a short time. Sometimes, in the same animal, one depressor affected the respiration while the other did not. The effect upon the blood pressure, however, was always the same, whatever the effect upon the respiration.

Comparison of the effect of stimulating the depressor and the central end of the vagus.—Stimulation of the central end of the vagus was usually followed by a fall of blood pressure. This was true whether the other vagus was cut or intact. The fall of blood pressure in these cases, however, differed as a rule from that following stimulation of the central end of the depressor; in the case of the vagus the blood pressure almost always returned to or rose above its previous level during the stimulation, provided that this was somewhat prolonged, whereas with the depressor the blood pressure remained at a uniform low level throughout. A similar difference has been described by Bayliss* in the effects of stimulating the central end of the vagus and of the depressor in the rabbit.

The respiration was inhibited by stimulation of the central end of the vagus, and it seemed possible that the rise of blood pressure during long-continued stimulation of the vagus described above might be due to stimulation of the vaso-constrictor centre by beginning asphyxia. That this explanation will not hold, however, is shown by the fact that sometimes the blood pressure does not rise after the previous fall during the stimulation of one vagus while it does when the other vagus is stimulated, although the respiration was inhibited in both cases.

Sometimes the effect upon the blood pressure of stimulating the central end of one vagus differed from that resulting from stimulation of the central end of the other and both differed from the typical depressor effect. There is nothing to indicate that in these cases the

* Bayliss, *Journal of Physiology*, xiv (1893), 316.

condition of the vaso-motor centre had changed in the intervals between these stimulations; hence the simplest explanation of these various results is that these different nerves contain fibres having different physiological functions, and the effect upon the blood pressure is determined by the nature and number of the fibres stimulated.*

We may suppose, for example, that some of these nerves contain fibres which cause a fall of blood pressure by inhibiting the vaso-constrictor centre, while others excite the vaso-dilator centre.

4. THE ACCELERATOR NERVES.

On the whole our experiments on the accelerator nerves have not been entirely satisfactory; this has been due, in part, to the fact that these nerves are usually surrounded by fat, which makes their preparation very difficult.

Anatomy.—The anatomy of these nerves in the opossum seems to be very similar to that in the other mammals thus far investigated; apparently, however, there are greater individual variations in the opossum. The first three or four thoracic ganglia of the sympathetic chain are usually united to form one large ganglion, the "stellate ganglion"; occasionally, however, these ganglia are united to form two smaller instead of one large ganglion. The stellate ganglion or the ganglion having the same position as the stellate ganglion is united with the inferior cervical ganglion of the sympathetic by two nerve trunks which form a well marked *annulus of Vieussens*, although at times there is but one nerve connecting the ganglia. The *rami communicantes* passing from the lower cervical and upper thoracic spinal nerves form a plexus from which a variable number of branches pass to the stellate ganglion. Frequently two or three small branches pass from each of the spinal nerves in this region to the plexus. The number of branches passing from the plexus to the stellate ganglion is usually four or five. One or two *rami communicantes* join the sympathetic nerve between the stellate ganglion and the first separate thoracic ganglion. Stimulation of the various *rami communicantes*

* Bayliss, *op. cit.*, p. 317; Howell, *op. cit.*, p. 310; Hunt, *Journal of Physiology*, xviii (1895), 402.

between the last cervical and 3rd dorsal nerves inclusive has caused acceleration of the heart, as has also stimulation of the sympathetic below the entrance of the 3rd *ramus communicans*. From the stellate ganglion the accelerator fibres, as shown by stimulation, pass in part to the inferior cervical ganglion through the nerve or nerves (*annulus of Vieussens*) connecting these ganglia, and in part directly towards the heart from the stellate ganglion or in small branches given off from the annulus. In a few animals a comparatively large nerve, evidently corresponding to the "*nervus accelerans*" of the cat, passed from the stellate ganglion directly towards the heart; stimulation of this nerve caused marked acceleration.

Stimulation of the accelerator nerves.—In most respects the effect of stimulating these nerves is the same as in other mammals—an increase in the heart rate, with or without a rise of blood pressure. Perhaps the most interesting point which we have observed is the tendency of the ventricle to beat irregularly when they are stimulated. Very frequently the first effect of the stimulation was to cause a slowing of the rate of the ventricle; this was followed, either during or after the stimulation, by a more rapid but often irregular rate. Judging from what we have seen with great ease in the experiment upon the calf described in the following paper and from less satisfactory observations upon the opossum's heart, we are confident that the slowing and irregularity of the ventricle were due to the ventricle's failing to respond to all the beats of the auricles. Sometimes the ventricular beat followed each auricular beat and at other times only every second or third beat. This irregularity of the ventricle was most marked when strong stimuli were applied to the accelerators; still it occurred also when weak stimuli were applied so that the total effect upon the heart was slight. As a rule after this slow or irregular rate had continued for a variable length of time, it was suddenly replaced by a uniform rapid rate. In other cases the first effect of stimulation was a slight acceleration which soon gave way to the slow or irregular rate as the stimulation continued; after the stimulation the rapid regular rate appeared again. In some cases the acceleration was very considerable, *e. g.* in one experiment there was an increase from 23 to 41½ beats in ten seconds, or an acceleration

of about 80 per cent resulting from the stimulation of the above-mentioned branch of the stellate ganglion ("*nervus accelerans*").

The effect upon blood pressure of stimulating these nerves was variable. As a rule the blood pressure was but little affected even when the acceleration was considerable, resembling in this respect the result so frequently obtained in the dog and cat. Thus in the experiment mentioned above in which there was an acceleration of 80 per cent, there was no change in the blood pressure.

In other respects the effect of stimulating the accelerator nerves in the opossum is similar to that observed in other mammals. Thus a moderately strong stimulus is required for an effect to be produced, and the difference between the strength of a minimal and a maximal stimulus is not great. The latent period is long and there is a long after-effect. Sometimes during the after-effect there is a sudden slowing of the heart rate, although it remains above the normal; from this new rate there is a gradual return to the normal. For example, in one case the rate before stimulation was 23 beats in 10 seconds, soon after stimulation it was 38; it then suddenly changed to 27, from which rate it slowly dropped to 24. We know of no explanation of this peculiarity.

The following figures from one of our experiments are interesting as bearing upon the relation of the inhibiting to the accelerator nerves: First the accelerator nerves were stimulated alone and the heart rate increased from 32 to $38\frac{1}{2}$ beats in 10 seconds (*i. e.* there was an acceleration of 20 per cent). The vagus was now stimulated for some time; the heart rate fell from 33 to $13\frac{1}{2}$ in 10 seconds; during the stimulation of the vagus the accelerators were stimulated again with the same strength of current as before; the rate increased to 20 (*i. e.* there was an acceleration of 48.1 per cent, or a greater acceleration relatively than when the accelerators were stimulated alone).

Obviously the effect in this case of stimulating the two nerves simultaneously was the resultant of the effects of stimulating the nerves separately. This result agrees entirely with what one of us* has found to be the case in experiments upon dogs and cats.

* Hunt, *Journal of Experimental Medicine*, ii (1897), 151.