THE ACTION OF NICOTIN ON THE CILIARY GANGLION AND ON THE ENDINGS OF THE THIRD CRANIAL NERVE.

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THE ciliary ganglion in mammals receives nerve-fibres from the 3rd nerve, from the 5th nerve, and commonly also from the cervical sympathetic[1]. It has in consequence been considered as a group of cells placed, according to the predilection of the particular observer, on the course of either the 3rd or on the 5th or on the ciliary branch of the cervical sympathetic nerve.

Since nicotin readily paralyses nerve-cells of the sympathetic type it seemed to us worth while to determine its action upon the ciliary ganglion. In doing so we have noticed also its effect upon the various functions of the 3rd nerve.

Our experiments have been made chiefly upon rabbits and cats, one or two only having been made upon dogs; the animals were in all cases under the influence of anæsthetics; for rabbits, chloral and the alcohol, chloroform, ether mixture were used; for cats, chloroform, the a.c.e. mixture and usually morphia; for dogs, morphia and the a.c.e. mixture.

Laying bare the 3rd nerve in the skull presents no particular difficulty. We removed a variable amount of the anterior part of the brain on one or on both sides, and usually tied and cut the 3rd nerve as close to the brain as possible. In the cat, the bleeding, especially from the bones of the skull, is much more profuse than in the rabbit. In some cases the 3rd nerve rapidly loses its irritability, probably in consequence of the great enfeeblement of the circulation of blood in the head, which is not infrequently caused by the operation. As the

[1] An excellent account of the anatomical connections of the ciliary ganglion in a considerable number of animals, has recently been given by Jegorow (*Archives Slaves de Biologie*, T. II. 1886, T. III. 1887). We have dissected the ciliary ganglion in the rabbit, cat, and dog and have nothing to add to Jegorow's account.

irritability diminishes, one or other of the normal actions of the 3rd nerve may disappear before the rest. The piece of nerve between the brain and the skull is short, so that there is considerable risk of escape of current, unless care be taken; in the rabbit and cat, such an escape of current is readily appreciated by the contraction of the masseter muscle.

Stimulation of the 3rd nerve in the skull causes, as is well known, the following effects.

(1) Contraction of the pupil.
(2) Contraction of the ciliary muscle.
(3) Contraction of the superior, inferior, internal straight muscles of the eye, and of the inferior oblique muscle.
(4) Contraction of the levator palpebræ, and consequent elevation of the upper eyelid.

In some mammals stimulation of the 3rd nerve causes also a protrusion of the nictitating membrane, but this protrusion has been taken to be a passive one, due to the movement of the eye, for it can be produced, to a certain extent at any rate, by pressing on the eye. According to H. Müller[1] the protrusion of the nictitating membrane in the dog and goat, is brought about by the retractor bulbi muscle, which is supplied by the 6th nerve. He does not say how the retractor produces this effect.

It will be convenient to give at once such points in the behaviour of the nictitating membrane as we have noticed. In the rabbit and cat, stimulation of the 4th nerve causes no movement of the nictitating membrane. Stimulation of the 6th nerve causes great protrusion of the membrane, and the degree and time of protrusion appear to be to some extent independent of the degree and time of retraction of the globe of the eye. In the cat, after section of the 3rd nerve in the skull, we have, by sponging the nictitating membrane, obtained effects like those produced by stimulating the 6th nerve; these effects were apparently reflex for they ceased on cutting the 6th nerve. In the rabbit after a small dose of nicotin has been given, stimulation of the 3rd nerve will sometimes cause protrusion of the nictitating membrane without causing any movement of the eye. It is possible that in these cases there was an escape of current to the 6th nerve in the cavernous sinus, but if there had been an escape of current to the 6th, we should have expected that the 5th nerve also lying alongside it, would have been stimulated, and there was no sign of this. In any case, since the eye was not withdrawn in the orbit, the experiment shows that the nictitating membrane may be protruded independently of a contraction of the retractor bulbi. In our experiments on

[1] H. Müller. *Würzburger naturw. Zeitschrift.* Bd. II. p. 59, 1861.

the effect of injecting nicotin, the paralysis of the protruding movement of the nictitating membrane took place at very nearly the same time as the paralysis of the elevating movement of the upper eyelid. Strong stimulation of the 3rd nerve causes movement of the nictitating membrane after the contents of the eye are removed, but not after the eye itself has been removed; stimulation of the sympathetic readily causes retraction of the nictitating membrane even after the removal of the eye.

If, after observing the effects of stimulating the 3rd nerve, about 10 milligrams of nicotin are injected into a vein of a rabbit or cat, and the 3rd nerve is stimulated, no effect of any kind follows. All the functions of the nerve are for a time annulled. Similarly, stimulation of the 4th and 6th nerves causes no movement of the eye.

Since no nerve-cells lie in the course of the nerve-fibres running to the external muscles of the eye, or to the elevator of the eyelid, it is obvious from what we know of the action of nicotin, that the absence of contraction in those muscles when their nerves are stimulated in the skull, can only be due to a paralysis of the nerve-endings in the muscle. We have taken the inferior rectus as the type of all of these muscles; after injection of nicotin, stimulation of the branch of the 3rd nerve, which supplies the inferior rectus, close to its point of entrance into the muscle is without effect; stimulation of the muscle direct causes contraction at once.

A dose, then, of about ten milligrams of nicotin, is sufficient to paralyse the nerve-endings of the extrinsic muscles of the eye. But this amount of nicotin is not sufficient in the rabbit and rarely in the cat to paralyse the nerve-endings of the other muscles of the body; muscular contraction can still be produced by stimulating the 5th, the 7th or any spinal nerve.

The most convenient way of stimulating the 5th nerve is by placing the electrodes just medially of the cavernous sinus, a little to one side and in front of the exit of the 3rd nerve, the contraction of the masseter can easily be felt.

We find that the nerve-endings in the striated orbital muscles are also paralysed by curari more readily than the nerve-endings in the other skeletal striated muscles of the body. After 0·5 c.c. of a 1 p.c. solution of curari has been injected into a vein of a cat, stimulation of the 3rd nerve no longer causes movement of the eye, or of the upper eyelid, or of the nictitating membrane, though stimulation of 5th nerve still causes contraction of the masseter muscle. In order to produce a temporary paralysis of the nerve-endings in the masseter, about 1 c.c. of the curari solution is required. The minimal

amount will of course vary, according to the preparation of curari used. Curari in large amount paralyses the cells of the ciliary ganglion.

The other effects of the 3rd nerve cease, not because of a paralysis of motor nerve-endings, but because of the paralysing action of nicotin upon the nerve-cells of the ciliary ganglion. For stimulation of the short ciliary nerves still causes contraction of the sphincter iridis and of the ciliary muscle even after 100 mgrs. of nicotin have been injected (cp. Exp. I). The short ciliaries lie on the optic nerve at its entrance into the eye, and we have usually stimulated them at this spot without separating them from the optic. After section of the cervical sympathetic or after extirpation of the eye, stimulation of the optic nerve with the short ciliaries still causes a ready contraction of the pupil. We have in one or two cases in the cat isolated the short ciliaries and stimulated them separately as in the following experiment:—

EXPERIMENT I.

Cat. Chloroform. Trachea connected with a bottle of a. c. e. mixture. The ciliary ganglion was exposed by the method given by Jegorow[1], the 3rd nerve and the short ciliaries isolated for a short distance on either side of the ganglion. Stimulation of the 3rd nerve caused prompt constriction of the pupil.

1.20. 5 c.c. of a 1 p.c. solution of nicotin (= 50 mgrs.) injected into the jugular vein.

1.28. Stimulate 3rd nerve centrally of ganglion—no effect.

Stimulate ciliary ganglion—constriction of pupil, but less[2] than before injection.

Stimulate short ciliaries—prompt constriction of pupil.

1.34. Repeat stimulation—same result.

1.37. 5 c.c. of a 1 p.c. solution of nicotin injected into the jugular.

1.39. Repeat stimulations—same result.

Cut off the cornea, and cut through the iris; there was profuse bleeding, showing that the circulation had not been interrupted by the operation.

Dissect out 3rd nerve, ganglion and short ciliaries on the opposite side.

Pass a needle through the edge of the cornea so that its point rests on the anterior surface of the lens.

Stimulate 3rd nerve centrally of ganglion—no effect.

Stimulate short ciliaries—movement of needle showing protrusion of lens and contraction of the ciliary muscle.

[1] Jegorow. *Arch. f. Anat. u. Physiol.* (Physiol. Abth.) p. 149, 1886.

[2] The diminished effect of stimulating the ciliary ganglion was probably due to the presence of small accessory ganglia on the short ciliaries.

In the cat we have made one experiment in a modified form, applying nicotin locally to the nerve-cells. The ciliary ganglion was exposed, a portion of the 3rd nerve running to the ganglion and of each of the main short ciliary nerves passing from it were isolated and stimulated. Warm 1 p. c. nicotin was then brushed over the ganglion and the nerves in connection with it so far as they were visible. The result of this application of nicotin was to completely abolish the action on the pupil of the part of the 3rd nerve lying centrally of the ganglion. The nerve-fibres had not been injured by the nicotin, for the short ciliary nerves—to which nicotin had been also applied—produced on stimulation a prompt contraction of the pupil. Furthermore some of the short ciliaries and the 3rd nerve itself just centrally of the ciliary ganglion gave rise on stimulation to a reflex twitch of the muscles of the face, that is the afferent 5th fibres coursing with the third nerve were uninjured.

We regard it then as proved that the fibres of the 3rd nerve which run to the sphincter muscle of the iris and those which run to the ciliary muscle are connected with nerve-cells in the ciliary ganglion.

It has been shown by Langley and Dickinson[1] that the cervical sympathetic is not connected with nerve-cells (of the sympathetic type) peripherally of the superior cervical ganglion; and consequently that the nerve-cells of the ciliary ganglion are not on the course of sympathetic nerve-fibres.

There remain the fibres of the 5th nerve which run to the ciliary ganglion. Some of these are certainly afferent, some, it is possible, may be afferent visceral fibres. Either kind might conceivably be connected with nerve-cells in the ciliary ganglion. There is no entirely satisfactory evidence whether they are or are not so connected. We have already mentioned that local application of nicotin in moderate amount to the ciliary ganglion does not prevent the short ciliary nerves from causing a reflex movement. This fact might be taken as showing that the

[1] *Proc. Roy. Soc.* Vol. XLVI. p. 423, 1889, and this *Journal*, Vol. XI. p. 265, 1890.

The superior cervical ganglion in the rabbit is sometimes much elongated and has an upper and a lower swelling, from the upper swelling fibres proceed to the internal carotid, from the lower swelling fibres proceed to the external carotid. In one case in which this separation of the ganglion into two parts was very marked, we found, after injection of nicotin, that stimulation of the lower ganglionic swelling had no distinct effect on the pupil, whilst dilation of the pupil was readily obtained by stimulating the upper swelling. And it appears not unlikely that in the ordinary single ganglion there may be a considerable separation of cells into groups according to the destination of the fibres proceeding from them.

afferent fibres concerned are not connected with nerve-cells in the ciliary ganglion, (for if they were, the cells should be paralysed by the nicotin and the centripetal impulses blocked,) and hence that very probably no afferent fibres of the 5th are connected with nerve-cells in the ciliary ganglion. But this conclusion is at present not justified, for it is doubtful whether nicotin does stop the passage of afferent impulses through a spinal ganglion; certain it is, that a dose of nicotin considerably greater than sufficient to stop the passage of efferent nervous impulses through sympathetic nerve-cells still leaves a free way through the spinal ganglia to afferent nervous impulses[1]. As regards the possibly existing efferent visceral fibres of the 5th nerve, we have made no experiments.

The question of the connection of the ciliary ganglion with the 5th nerve is, then, only touched by our observations in so far as we have shown that the great majority of the nerve-cells must be connected with fibres of the 3rd nerve.

Many observers consider the ciliary ganglion to be homologous with a spinal ganglion, and this view is held even by some of those who take it as belonging to the 3rd nerve. From a physiological stand-point a spinal ganglion is a ganglion connected with afferent fibres, and a sympathetic ganglion is one connected with efferent fibres. Each may perhaps contain a few elements characteristic of the other, but this has not been proved. From this stand-point and limiting attention to what is actually proved about the ciliary ganglion, there can be no hesitation in considering it as homologous with a sympathetic ganglion, although its nerve-cells have no connection with the cervical sympathetic.

Order of paralysis by nicotin of the different functions of the third nerve.

We have said above that it takes about 10 milligrams of nicotin to paralyse all the functions of the 3rd nerve; the exact amount required depends in part of course upon the weight of the animal, but independently of this the minimal amount appears to be sometimes a little less and sometimes a little more than 10 milligrams.

The various functions are not paralysed with equal ease; differences are brought out either by noting the minimal amount of nicotin

[1] It is conceivable that nicotin paralyses the nerve-cells of a spinal ganglion, but that in consequence of the mode of connection of the cells with the nerve-fibres, impulses can still travel from the periphery to the central nervous system.

required to paralyse each function, or by paralysing all and noting the time taken for each function to recover.

In the rabbit we find the order of ease of paralysis is:—

1. Sphincter of iris.
2. Extrinsic muscles of the eye.
3. Elevator of the eyelid[1].

The action of the 3rd nerve (centrally of the ciliary ganglion) on the pupil is much more easily paralysed than its action on the extrinsic muscles of the eye. The minimal dose of nicotin is 5½ to 6 milligrams. The paralysis in this case is, however, but brief, it passes off in about a quarter of an hour. The nerve-cells of the fibres to the ciliary muscle are apparently paralysed at the same time as those of nerve-fibres to the sphincter iridis, but we have not made accurate observations with regard to this.

The other actions of the 3rd nerve require very nearly the same amount of nicotin to annul them, viz. about 10 milligrams, but we have found the raising of the eyelid[2] to return a little earlier than the movements of the eye; sometimes also after a dose of 9 or 10 milligrams stimulation of the 3rd nerve will still cause elevation of the eye[2], but will not cause contraction of the extrinsic muscles of the eye. As we have said, these actions cease in consequence of a paralysis of motor nerve-endings.

When 10 milligrams of nicotin have been given, the normal effect on the iris of stimulating the 3rd nerve in the skull does not return for three-quarters of an hour to an hour, but a trifling effect may be visible much earlier; it is difficult to determine exactly when the 3rd nerve is beginning to recover its function, for there appears to be a first stage of recovery in which the contraction of the pupil on stimulating the 3rd nerve is so slow as to escape observation, and to be marked only by the somewhat smaller size of the pupil at the end of the stimulation.

The pupillo-dilator nerve-cells of the superior cervical ganglion are paralysed less readily by nicotin than the pupillo-constrictor nerve-cells of the ciliary ganglion, but they are paralysed a trifle more readily than the motor nerve-endings in the 3rd nerve in the extrinsic muscles of the eye. The following experiment will serve to show some of these points:—

[1] When the third nerve is stimulated with increasing strength of currents, starting with minimal, the elevation of the eyelid is first obtained, then the contraction of the extrinsic muscles of the eye, and lastly the contraction of the sphincter iridis. We have tried this on the dog only.

[2] And protrusion of the nictitating membrane, cf. above p. 461.

EXPERIMENT II.

Rabbit. Sept. 30, 1891. Chloral injected per rectum. Tracheotomy, tube connected with a bottle of a. c. e. mixture. Cervical sympathetic tied and cut. Third nerve in skull tied and cut, the anterior part of the brain being removed. A weak interrupted current was used throughout for the nerve stimulation.

Stimulate sympathetic – pupil readily dilates.

Stimulate III nerve – pupil readily contracts; there is also elevation of the upper eyelid, protrusion of the nictitating membrane, turning of the eyeball inwards with a rotatory movement.

4.0. Inject into a vein 5 *mgrs. of nicotin*, in a 1 p.c. solution.
Stimulation of the cervical sympathetic and of the 3rd nerve still has the normal effects, but less readily.

4.10. Inject into a vein 5 *mgrs. of nicotin.*

4.15. Stimulate III nerve – elevation of upper eyelid, protrusion of nictitating membrane, both less than normal; these effects were also produced by subsequent stimulations and need not be mentioned again.
– slight movement of eyeball.
– no effect on pupil.

Stimulate sympathetic – no effect on pupil.

Stimulate V nerve – prompt contraction of masseter muscle.

4.26. Stimulate sympathetic – pupil dilates; this was caused also by subsequent stimulations and need not be mentioned again.

4.33. Stimulate III nerve – movement and rotation of eyeball.
– no effect on pupil.

4.38. Stimulate III nerve – movements of eyeball prompter and freer.
– no certain effect on pupil.

4.43. Stimulate III nerve – pupil is a trifle smaller at the end of the period of stimulation, but no movement actually observed.

4.53. Stimulate III nerve – slight contraction of pupil during stimulation.

5.3. Stimulate III nerve – good contraction of pupil.

Summary.

The fibres of the 3rd nerve which run to the iris and to the ciliary muscle are connected with nerve-cells in the ciliary ganglion.

A small dose of nicotin (about 6 mgrs.) paralyses for a time the

nerve-cells of the ciliary ganglia, so that impulses passing to them down the 3rd nerve are blocked.

A large dose of nicotin (100 mgrs.) does not paralyse the endings of the short ciliary nerves in the iris and the ciliary muscle.

In the rabbit, the order of ease of paralysis with nicotin of the nerve-cells and nerve-endings which we have investigated is:

1. Nerve-cells of the ciliary ganglion on the course of the nerve-fibres to the sphincter iridis and (probably) ciliary muscle.
2. Nerve-cells of the superior cervical ganglion on the course of the nerve-fibres which cause dilation of the pupil.
3. Nerve-endings of the 3rd, 4th and 6th nerves in the extrinsic muscles of the eye. The nerve-endings of the 3rd nerve in the elevator of the eyelid and the nerve-endings in the muscle causing protrusion of the nictitating membrane are paralysed a little less readily than those in the extrinsic muscles of the eye.
4. Nerve-endings in muscles supplied by the 5th and 7th nerves. About the same time as these, all the nerve-endings in the skeletal muscles of the body are paralysed.