Brit. J. Pharmacol. (1952), 7, 665.

THE ACTION OF NICOTINE ON THE CILIARY GANGLION

BY

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(Received June 7, 1952)

The existing conception of the peripheral autonomic nervous system is that due to Gaskell (1916), who supposed that the ganglia of the cranio-sacral division lie within or close to the organ they innervate and have short fibres which represent the postganglionic effector element. The sympathetic ganglia, on the other hand, lie outside the organ they supply, and have long easily distinguishable postganglionic fibres. In general, Dale's classification of the two systems according to the humoral transmitter liberated at postganglionic nerve endings agrees with Gaskell's anatomical distinction, but certain exceptions of cholinergic fibres running within the sympathetic system are known. Evidence that there are adrenergic fibres running in the parasympathetic system has been put forward by Ambache (1951) and Ambache and Edwards (1951), who noted that in the isolated intestine, after the parasympathetic elements have been exposed to the action of botulinum toxin or atropine, nicotine produces an inhibition of movement instead of the contraction elicited before. This action of nicotine is abolished by hexamethonium or ephedrine, and the authors suggested that there are present in the intestine itself, within the parasympathetic plexus, ganglia having short adrenergic postganglionic fibres which inhibit intestinal movements. Kottegoda (unpublished observations), working in this laboratory, finds that nicotine exerts on isolated rabbit auricles an inhibitory action followed by a stimulant action. After atropine has been given to paralyse the cholinergic elements, nicotine has only a stimulant action, and this is abolished by hexamethonium. He suggests that ganglia having adrenergic postganglionic fibres are also present in heart muscle. These observations indicate, therefore, that preganglionic fibres within the parasympathetic system terminate in or near the organ not only at ganglion cells having cholinergic postganglionic fibres, but at others having adrenergic fibres.

Dale and Laidlaw (1912) found that nicotine produced a dilatation of the cat's pupil after the corresponding superior cervical ganglion had been removed and the suprarenal glands excluded from the circulation. They considered that this effect was not due to a direct action of nicotine on the iris muscle, because the phenomenon could not be demonstrated *in vitro*. Nor did they think the dilator effect could be produced by the liberation of an adrenaline-like substance from deposits of chromaffin tissue in the sympathetic system, since exclusion from the circulation of all but a small portion of the sympathetic system by ligating the aorta at the diaphragm did not reduce the effect.

There remains the possibility, therefore, that nicotine acts on the iris muscle indirectly through the ciliary ganglion. By analogy with the experiments on the isolated intestine and auricles cited above, it seems reasonable to suppose that the

ciliary ganglion may contain cells having adrenergic postganglionic fibres which are stimulated by nicotine to produce a dilatation of the pupil. The experiments described below were designed to test this hypothesis.

METHOD

In cats under chloralose anaesthesia the right ciliary ganglion was removed according to the technique of Shen and Cannon (1936). An incision about 3 cm. long was made extending from the auditory meatus towards the eye, and sufficient of the orbit was chipped away to open the sheath and make dissection behind the eye possible. The external rectus muscle was retracted dorsally, and the ciliary ganglion found by tracing centrally the branch of the third nerve supplying the inferior oblique muscle. After removal of the ciliary ganglion both superior cervical ganglia were removed, and the suprarenal glands were tied off. The right pupil will be referred to as the denervated pupil, and the left pupil with ciliary ganglion intact as the innervated pupil. The nictitating membranes were fastened back and the eyelids slit to expose the pupils as completely as possible. Pupil size was recorded photographically, a control picture being taken before each injection, and thereafter at 1 min. intervals starting 30 sec. after the injection. Drugs were injected into the femoral vein.

RESULTS

The resting diameter of the innervated pupil was a slit, and that of the denervated pupil 10–16 mm. (Fig. 1). In each of 17 cats 2 mg. nicotine base produced a

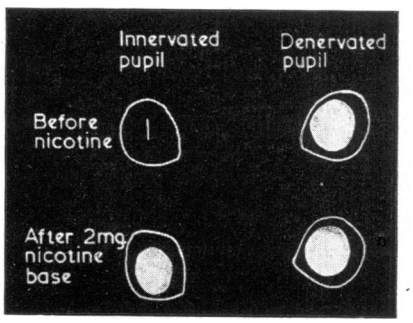

FIG. 1.—Drawings made from photographs showing the effect on the cat's pupil of intravenous nicotine. The innervated pupil has only the parasympathetic nerve supply intact.

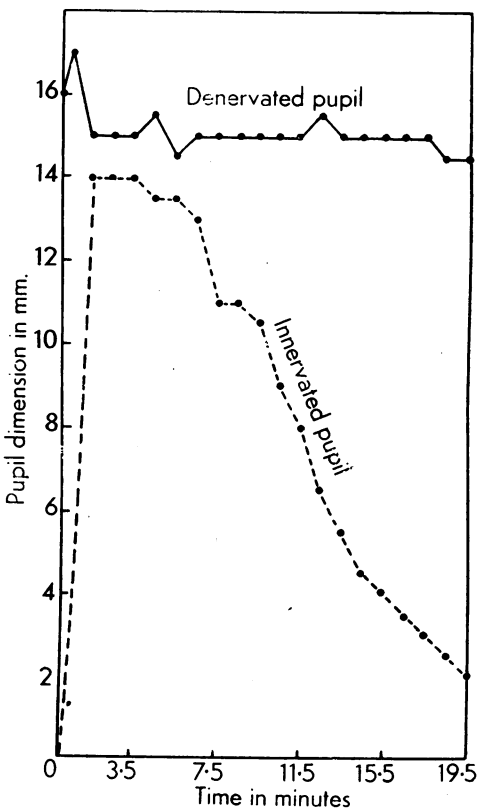

FIG. 2.—Graph showing the effect of nicotine (2 mg. base injected intravenously at zero time) on the denervated pupil and on the pupil having a parasympathetic nerve supply only, in a cat.

dilatation of the innervated pupil which disappeared slowly in about 20 min. (Figs. 1 and 2). In 5 cats there was a dilatation of 1–2 mm. in the denervated pupil which passed off in 2 min., but in the remaining 12 cats there was no effect on this pupil. Spontaneous fluctuations of about 0.5 mm. were often seen in the size of both pupils.

In 3 cats the innervated pupil was kept in shadow and was not therefore maximally constricted. Nicotine, in doses ranging from 0.1–2 mg. base, produced no trace of constriction, and above the threshold dose the only effect observed was dilatation. In one of these cats the threshold dose of nicotine was 0.5 mg., which produced a very small dilatation lasting 30 sec.; 0.6 mg. had the same effect; 0.7 mg., however, produced a dilatation of 4 mm. lasting for 16 min.

In contrast to nicotine, intravenous adrenaline produced consistently a transitory dilatation of both pupils, thus showing that the iris muscle would be sensitive to adrenaline liberated at the nerve endings by stimulation of sympathetic elements.

In 8 experiments, 1.25 mg. hexamethonium bromide was given to paralyse the ciliary ganglion, and this produced a dilatation of the innervated pupil which lasted 30 min. Nicotine given after hexamethonium had no effect, except in 2 cats in which there was a brief constriction of the innervated pupil. Adrenaline, however, still produced a dilatation.

In order to eliminate the influence of the cholinergic nerves on the pupil, 4 mg. atropine was injected intravenously, and this caused the innervated pupil to dilate. Again there was room for further dilatation, but nicotine now had no dilator action on the pupil.

Ergotoxine ethanesulphonate (B.P.1932) was administered in doses sufficient to reverse the action of adrenaline on the blood pressure, thus eliminating possible sympathetic effects in the pupil. This resulted in a steady diminution in the size of the denervated pupil. In the innervated pupil nicotine still produced a dilatation, and, although this effect was smaller than before, it lasted for the same length of time (20 min.) (Fig. 3). Adrenaline had no effect on either pupil.

In one experiment the phenyl ether of choline (Hey, 1952) produced in both pupils a dilatation which was abolished by hexamethonium bromide, and dilated

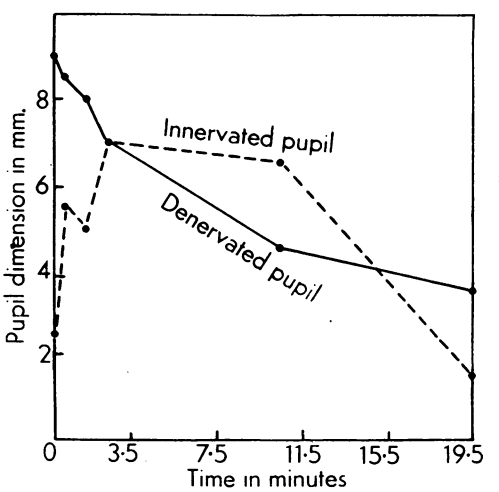

FIG. 3.—Graph showing the effect of nicotine (2 mg. base injected intravenously at zero time) on the cat's pupil after ergotoxine (5 mg.). The innervated pupil has an intact parasympathetic supply only.

the isolated pupil. This substance also produced a large rise in the cat's blood pressure when several large doses of nicotine had been given previously and 15 mg. of nicotine had no effect. Tubocurarine (3–5 mg.) in one experiment dilated both pupils, and the effect on the innervated pupil lasted for the rest of the experiment.

In four additional experiments nicotine (1 g. base/100 ml.) painted on the ciliary ganglion produced a dilatation of the pupil, and this effect was observed whether the superior cervical ganglia and suprarenal glands were intact or excised. In the eserinized animal acetylcholine (1 g. chloride/100 ml.) produced similar effects. Stimulation of the 3rd nerve caused the pupil to constrict, and this effect was blocked by painting the ciliary ganglion with nicotine or in the eserinized animal with acetylcholine. After section of the 3rd nerve, neither nicotine nor acetylcholine painted on the ganglion had any effect on the pupil.

In experiments on the isolated iris in which temperature and *p*H were carefully controlled, nicotine had no effect on pupil size except in very high concentrations (3 mg./ml.) when the effect could not be considered as specific.

Discussion

These experiments indicate that the dilator action of nicotine on the pupil after sympathetic denervation is manifest for the most part through the ciliary ganglion, and the small effects sometimes seen on the completely denervated pupil might be due to a few stray ganglion cells remaining after removal of the ciliary ganglion. It seems clear that the main dilator action of nicotine is no longer seen after removal of the ciliary ganglion, or after paralysing the ciliary ganglion with hexamethonium bromide.

If we assume that, after removal of the superior cervical ganglion, nicotine acts solely through the ciliary ganglion, there are two ways in which it might produce its effects: (1) by stimulation of cells having adrenergic postganglionic fibres; (2) by paralysis of the cholinergic elements, which would result in a passive dilatation of the pupil. Adrenaline produces only a very transient dilatation; thus, if nicotine acts by stimulating adrenergic elements, its effect would last for 20 min. until the pupil dilatation had worn off. This seems unlikely, since the stimulant action of nicotine on sympathetic ganglia, as recorded on the blood pressure, lasts for only a few minutes. Hexamethonium bromide, which, so far as is known, has no ganglion-stimulating properties, produces similar effects to nicotine, and the evidence suggests that these two drugs produce their effects on the pupil by a paralytic action on the cholinergic elements in the ciliary ganglion.

After atropine in doses sufficient to block the cholinergic mechanism, nicotine produces no dilatation, which indicates that there are no active adrenergic elements present, since these would be unaffected by atropine. After adrenaline-like substances had been antagonized with ergotoxine, nicotine still had a dilator effect on the innervated pupil. The dilatation was less after ergotoxine, probably because of its direct constrictor action on the iris muscle seen in the right pupil, which would affect the degree of dilatation after nicotine, but not the duration.

Phenyl ether of choline does not yield any information with regard to the action of nicotine-like drugs on the ciliary ganglion, since it has sympathomimetic properties.

The fact that the innervated pupil, which is not fully constricted in the first place, does not show any trace of constriction after small doses of nicotine suggests that

nicotine has no stimulant action on the cells of the ciliary ganglion. This hypothesis would explain why section of the third nerve abolishes the effects of nicotine painted on the ciliary ganglion. If the only action of nicotine on the ganglion is a paralytic effect which blocks impulses coming from the brain, then when these impulses have already been cut off nicotine can have no further effect. There is no evidence that nicotine stimulates the cells of the ciliary ganglion under these conditions.

The experiments reported above thus produce no evidence to indicate the presence in the ciliary ganglion of cells having adrenergic postganglionic fibres, and one might conclude, therefore, that all the cells contained in the ganglion have cholinergic postganglionic fibres.

SUMMARY

1. In cats the effect of nicotine on the pupils was recorded after removal of the right ciliary ganglion, both superior cervical ganglia, and the suprarenal glands.

2. Nicotine produced in the pupil with ciliary ganglion intact a dilatation lasting 20 min. in all 17 cats used, and in the denervated pupil a small transient dilatation in 5 of the cats. Both effects were abolished by hexamethonium bromide.

3. After ergotoxine, nicotine still produced a dilatation of the innervated pupil, but after atropine nicotine had no effect.

4. Hexamethonium bromide had similar effects to nicotine and dilated only the pupil with ciliary ganglion intact.

5. Nicotine and, in the eserinized animal, acetylcholine painted on the ciliary ganglion dilated the pupil and blocked the constrictor response to stimulation of the 3rd nerve. After section of the 3rd nerve, nicotine and acetylcholine painted on the ganglion had no effect.

6. It is concluded that the dilator effect of nicotine on the cat's pupil deprived of the sympathetic nerve supply is produced entirely by a paralytic action on the cholinergic nerve elements in the ciliary ganglion which results in a passive dilatation of the pupil. There is no evidence to indicate that some cells in the ciliary ganglion have adrenergic postganglionic fibres.

I should like to thank Professor J. H. Burn and Dr. E. Bülbring for their help and advice with this work.

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Note added in proof.—Since this paper was submitted, W. L. M. Perry and J. Talesnik have given a communication at the July, 1952, meeting of the British Pharmacological Society in Edinburgh in which they reported that nicotine, injected into the lingual artery of the cat, produces a constriction of the pupil; this occurred after section of the third nerve and was apparently due to a stimulant action of nicotine on the cells of the ciliary ganglion. It remains, however, to be explained why nicotine, which stimulates a sympathetic ganglion such as the superior cervical ganglion, both on intravenous injection and on direct application, fails to stimulate the ciliary ganglion when applied in these ways.