A COMPARATIVE STUDY OF CERTAIN ACTIONS OF ADRENALIN IN THE CAT AND THE RABBIT.

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PLATES 29 TO 31.

(Received for publication, November 9, 1916.)

After unilateral excision of the superior cervical ganglion, certain substances or conditions produce an effect on the side on which the ganglion has been removed, while on the other side on which nothing has been done, or on which the sympathetic nerve has been cut below the ganglion, the pupil is affected but little or remains comparatively unaffected. This is called paradoxical pupil dilatation.

Meltzer and Auer found that subcutaneous injection or instillation in the conjunctival sac, which has no effect upon the pupil of the normal rabbit, produces considerable dilatation of the pupil in the rabbit on the side on which the superior cervical ganglion has been removed, while the pupil on the side on which only the sympathetic nerve has been cut, remains unchanged; in other words, adrenalin causes a paradoxical pupil dilatation in the rabbit. Meltzer found later that the same holds true for the cat, but only when adrenalin is administered by subcutaneous injection. He has not been successful with instillation of adrenalin into the eyes of operated cats, on account, he says, of the “protruding nictitating membrane which would sweep over the entire eye as soon as adrenalin came in contact with it, thus removing the adrenalin.” Meltzer adds that he has not been persistent enough in his attempts.

In a series of experiments on cats we have made many attempts to produce dilatation by instillation of adrenalin in the conjunctival sac on the side on which the ganglion was previously removed and have found that it is difficult to produce dilatation in the cat by this method. While in rabbits dilatation of the pupil is readily obtained

by a single instillation, in cats we obtained in many cases a moderate dilatation only after many instillations in the course of 2 hours, and in many instances we failed. In addition to the action of the nictitating membrane mentioned by Meltzer, it is possible that the conjunctiva of the cat is more dense and does not favor absorption.

However, it seemed doubtful that these mechanical factors alone could sufficiently account for the failure of conjunctival instillation, in view of the ease with which eserine and atropine cause dilatation of the pupil in the cat. There seemed to be no obvious reason why adrenalin should be absorbed less readily than these substances, and we thought that there might be other reasons for the difference in the response of the two species of animals.

Our first problem was to establish whether the responsiveness of the iris differed in the two species, and we believed that some light might be thrown on the matter by studying the effect of adrenalin, given by intravenous injection, on the cat's pupil and comparing this effect with that of similar injections in the rabbit. By this means all differences in the degree of conjunctival absorption would be eliminated.

The solution used for the injection was made by dissolving adrenalin crystals in 0.7 per cent sodium chloride with hydrochloric acid, and diluting until an accurate 0.1 per cent solution was obtained. For the smaller doses this was further diluted before injection. In this way we had a reliable solution at our disposal throughout the experiments.

All the animals used had undergone excision of the superior cervical ganglion, at least several days, and often several weeks before the experiments. Notes were made on the pupil of the intact, as well as on that of the operated side.

The rabbits were either held gently without narcosis and the injection was given into the marginal vein of the ear, or the jugular vein was exposed after anesthetizing the skin with ethyl chloride and the injection given into the vein. No difference was observed between the results of injections into the jugular and the ear vein. Cats were always injected in the jugular vein.

There is some difficulty in obtaining records with cats, on account of the paradoxical dilatation which appears so readily in excited
animals after gangliectomy. If the cat is stroked gently during
the operation, it becomes quiet and the pupils return to normal.
If the needle is then inserted in the vein and a few seconds are per-
mitted to elapse before the injection is given, no dilatation results
from the manipulation alone, as we have observed repeatedly by
injection of saline solution. In a few instances the adrenalin caused
marked disturbance of heart action with dyspnea. The results of
these injections were discarded.

The present study deals exclusively with the size of the pupil;
other effects of adrenalin on the eye were disregarded in the protocols.

The response of the pupil to intravenous injection of adrenalin
has been studied in the cat by Lewandowsky\(^3\) and in the rabbit by
Joseph.\(^4\) Lewandowsky made only qualitative observations and gives
no figures either as to dosage of the adrenal extract or the degree
dilatation of the pupil which it produces. Joseph studied the
quantitative response of the pupil of the rabbit after gangliectomy,
but his observations were limited to the operated side. In the main,
our results agree with Joseph's, the only difference being that in our
experiments the response of the rabbit's pupil to a given dose was
greater, both in degree and duration.

Our results may be briefly stated as follows: In the rabbit the
dilating influence of intravenous injections of adrenalin was not seen
in the eye on the unoperated side with doses smaller than 0.05 mg.
per kilo of body weight; with doses less than 0.1 mg. per kilo the
effect was not constant and when manifest was slight and lasted
only a few minutes. A dose of 0.1 mg. per kilo of body weight
carried, as a rule, moderate or slight dilatation with return to normal
in about 10 minutes. In two animals no dilatation was seen on the
intact side from this quantity. Dilatation of the pupil of the gan-
gliectomized side was noted with doses of 0.01 mg. per kilo of body
weight. With doses below 0.02 mg. however, the effect was slight
and inconstant. The most constant results were obtained with a
dose of 0.1 mg. With this dose a maximal dilatation ensued which
lasted about 10 minutes, followed by a gradual return to normal in
the course of 2 or 3 hours.

\(^3\) Lewandowsky, M., Arch. f. Physiol., 1899, 360.
In the cat the response was found to be much greater. On the eye of the intact side doses of adrenalin as small as 0.01 mg. per kilo of body weight gave a distinct and constant effect, and a dose of 0.1 mg. gave rise to almost maximal dilatation. The duration was, however, brief even with the largest dose, the pupil becoming normal within 5 minutes. Similar relations were found on the operated side. Here minute doses, even as small as 0.002 mg. per kilo of body weight, caused a distinct dilatation, and 0.01 mg. per kilo gave rise to almost maximal dilatation. In both cases the dilatation was transient. A dose of 0.1 mg. per kilo of body weight caused maximal dilatation lasting about 5 minutes with a gradual return to normal within half an hour.

ILLUSTRATIVE PROTOCOLS.

**Rabbit 1.**—White female; weight 1.480 kilos.


Mar. 29, 9.21 a.m. Injected in ear vein, 1 cc. of adrenalin, 1 : 50,000, (0.0135 mg. per kilo).

Before injection, right pupil 5 mm. in diameter; left 5 mm.

<table>
<thead>
<tr>
<th>Time</th>
<th>Right Pupil</th>
<th>Left Pupil</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ min. after injection</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>1½</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>4½</td>
</tr>
<tr>
<td>4</td>
<td>5½</td>
<td>4½</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Apr. 6, 10.00 a.m. Injected intravenously 0.15 cc. of adrenalin, 1 : 1,000 (0.1 mg. per kilo).

Before injection, right pupil 5 mm. in diameter; left 5 mm.

<table>
<thead>
<tr>
<th>Time</th>
<th>Right Pupil</th>
<th>Left Pupil</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ min. after injection</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>6½</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

**Rabbit 2.**—White female; weight 1.910 kilos.


Apr. 5, 3.23 p.m. Injected intravenously 0.19 cc. of adrenalin, 1 : 1,000 (0.1 mg. per kilo).

Before injection, right pupil 4 mm. in diameter; left 4 mm.

<table>
<thead>
<tr>
<th>Time</th>
<th>Right Pupil</th>
<th>Left Pupil</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ min. after injection</td>
<td>8½</td>
<td>3½</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>3½</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>
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10 min. after injection, right pupil 10 mm. in diameter; left 3 mm.
17 " " " " " " 10 " " " " " " 4 " "
57 " " " " " " 8½ " " " " " " 3 " "
77 " " " " " " 6½ " " " " " " 3 " "
100 " " " " " " 5½ " " " " " " 4 " "
112 " " " " " " 4 " " " " " " 2 " "

Cat 1.—Black male; weight 2.660 kilos.
Mar. 27, 1916. Left superior cervical ganglion excised under ether anesthesia.
Mar. 30, 10.13 a.m. Injected intravenously 2 cc. of adrenalin, 1:50,000 (0.014 mg. per kilo).

Before injection, left pupil a slit; right a slit.
½ min. after injection, 10 mm. in diameter; 4 mm.
1 " " " " " " 6 " " " " " " 2 " "
2 " " " " " " 1 " " " " " " 1 " "
10.23 a.m. Second injection. 2 cc. of adrenalin intravenously, 1:50,000 (0.014 mg. per kilo).

Before injection, left pupil 1 mm. in diameter; right 1 mm.
½ min. after injection, 10 " " " " " " 2 " "
1 " " " " " " 8 " " " " " " 1 " "
2 " " " " " " 2 " " " " " " 1 " "
7 " " " " " " 1 " " " " " " 1 mm.
10.45 a.m. Third injection. 2 cc. of adrenalin intravenously, 1:10,000 (0.07 mg. per kilo).

Before injection, left pupil 1 mm. in diameter; right 1 mm.
½ min. after injection, 15 " " " " " " 10 " "
1 " " " " " " 15 " " " " " " 8 " "
2 " " " " " " 12 " " " " " " 6 " "
3 " " " " " " 12 " " " " " " 2 " "
4 " " " " " " 10 " " " " " " 1 " "
6 " " " " " " 6 " " " " " " 2 " 
Apr. 10. Weight unchanged.
10.09 a.m. Injected intravenously 0.285 cc. of adrenalin, 1:1,000 (0.11 mg. per kilo).

Before injection, left pupil 3 mm. in diameter; right 4 mm.
½ min. after injection, 16 " " " " " " 14 " "
1 " " " " " " 16 " " " " " " 10 " "
1½ " " " " " " 16 " " " " " " 6 " "
2 " " " " " " 14 " " " " " " 3 " "
6 " " " " " " 10 " " " " " " 3 " "
8 " " " " " " 6 " " " " " " 3 " "
18 " " " " " " 2 " " " " " " 2 " 

Cat 2.—Gray male; weight 3 kilos.
Mar. 27, 1916. Left superior cervical ganglion excised under ether anesthesia.
Apr. 10, 10.30 a.m. Injected intravenously 3 cc. of adrenalin, 1:1,000 (0.1 mg. per kilo).
Before injection, left pupil 3 mm. in diameter; right 4 mm.

½ min. after injection, left pupil 17 mm.; right 12 mm.
1 min. after injection, left pupil 17 mm.; right 4½ mm.
3 min. after injection, left pupil 17 mm.; right 2½ mm.
5 min. after injection, left pupil 17 mm.; right 2½ mm.
7 min. after injection, left pupil 16 mm.; right 2 mm.
9 min. after injection, left pupil 7 mm.; right 2 mm.
15 min. after injection, left pupil 4 mm.; right 3 mm.
20 min. after injection, left pupil 4 mm.; right 4 mm.
30 min. after injection, left pupil 2 mm.; right 3 mm.

These examples illustrate the type of dilatation seen in the cat and in the rabbit after intravenous injections of adrenalin. The striking differences are the greater degree and briefer duration of the dilatation in the cat. This is true both for the normal and gangliectomized sides, and with all doses.

The following table shows the number of experiments and the average results.

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose per kilo</th>
<th>No. of experiments</th>
<th>Pupil</th>
<th>Time before return to normal</th>
<th>Increase</th>
<th>Maximum size of pupil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit</td>
<td>0.01 mg.</td>
<td>3</td>
<td>Intact side. Operated side.</td>
<td>10 min.</td>
<td>0 mm.</td>
<td>4 mm.</td>
</tr>
<tr>
<td>Rabbit</td>
<td>0.1 mg.</td>
<td>12</td>
<td>Intact side. Operated side.</td>
<td>3 min.</td>
<td>2 mm.</td>
<td>6 mm.</td>
</tr>
<tr>
<td>Cat</td>
<td>0.01 mg.</td>
<td>2</td>
<td>Intact side. Operated side.</td>
<td>1½ min.</td>
<td>7 mm.</td>
<td>9 mm.</td>
</tr>
<tr>
<td>Cat</td>
<td>0.1 mg.</td>
<td>13</td>
<td>Intact side. Operated side.</td>
<td>2 min.</td>
<td>8 mm.</td>
<td>10 mm.</td>
</tr>
</tbody>
</table>

Text-fig. 1 shows graphically the course of the dilatation in the normal and gangliectomized pupils of rabbits and of cats, after injection of 0.1 mg. of adrenalin per kilo.

The cat's pupil, when fully dilated, is from 14 to 16 mm. in diameter, and the rabbit's from 10 to 12 mm. It will be seen that in the cat the pupil on the operated side showed approximately complete dilatation from even the smaller dose, while the rabbit showed full dilatation with the larger dose, but not even approximating it with
the smaller. The pupil of the normal side of the cat also showed a greater response to adrenalin than that of the rabbit. Comparison of the increase in diameter of the pupil of the intact side with that of the operated side, in each species, might seem to show a greater increase in response following gangliectomy in the rabbit, but this is deceptive and due to the marked effect on the pupil of the unoperated side of the cat, which would render a dilatation three times as great, such as occurs in the rabbit, an impossibility.

Our original problem, namely, the question whether the difference in response of the two species to instillation of adrenalin was dependent on a greater responsiveness of the iris of the rabbit, seems, therefore, to be satisfactorily answered. Our experiments seem to show definitely that this is not the case. With intravenous injections it was found that the opposite was true; that is, that the responsiveness of the iris of the cat was greater than that of the rabbit. In other words, a given dose of adrenalin, injected intravenously, will cause wider dilatation of the pupil in the cat than in the rabbit.

The experiments brought out, however, the fact that while the degree of dilatation of the pupil which is brought about by a given dose of adrenalin is greater in the cat than in the rabbit, the duration
of the dilatation is, on the contrary, longer in the rabbit than in the cat. The question arose whether these inverse relations are confined to the iris, or whether it would be met also in the various other effects of adrenalin on the functions of the body.

The most readily observed and best known action of adrenalin is its constricting power on the arterioles. We therefore made a study of the influence of intravenous injections of adrenalin on the blood pressure in the cat and the rabbit, comparing the intensity of the reaction with the duration of the rise in the two species of animals.

The technique in this series of experiments differed from that already described in that all the animals were kept under light narcosis throughout the experiments.

The results showed that with all doses from 0.01 to 0.3 mg. the average effect upon the blood pressure was greater in the rabbits than in the cats, both in regard to the height and the duration of the rise. The actual height reached was greater in the cats, as their original blood pressure was higher, varying from 100 to 110 mm., while in the rabbits the normal blood pressure varied from 60 to 70 mm. With 0.1 mg. of adrenalin per kilo of body weight there was in rabbits an average rise of 85 mm. (actual maximum 150 mm.) with a return to normal in about 6 minutes (Fig. 1); in cats the rise was about 75 mm. (actual maximum 175 mm.) lasting about 3½ minutes (Fig. 2). With 0.03 mg. per kilo, rabbits showed a rise of 70 mm. (maximum 135 mm.) lasting 4 minutes (Fig. 3); cats showed a rise of 45 mm. (maximum 120 mm.) lasting 3½ minutes (Fig. 4). With 0.01 mg. rabbits showed a rise of 55 mm. (maximum 120 mm.) lasting 3 minutes; cats showed a rise of 35 mm. (maximum 140 mm.) lasting 2 minutes.5

It will be seen that the influence of adrenalin on blood pressure differs from that on the iris. In the iris the duration of the effect was at variance with the degree of dilatation, the one being greater in the rabbit the other in the cat. With blood pressure we find that the two differ in the same direction, both the duration and intensity of the effect being greater in the rabbit.

5 In the rabbits the return to the base-line signalized the end of the response. In more than half the cats the return to the base-line was followed by a fall of from 10 to 40 mm. below the line with a gradual return to normal in from 2 to 10 minutes.
DISCUSSION.

The original problem was to determine whether there were other explanations than that suggested by Meltzer to account for the difference of response of the iris of the cat and rabbit to instillations of adrenalin. One possibility was that the iris of the rabbit was more sensitive to this substance. The experiments with intravenous injections showed, however, that the opposite was the case; namely, that the iris of the cat is more sensitive to adrenalin than that of the rabbit.

In these experiments it was, however, found that with regard to the pupil there was a contrast between responsiveness and duration. While in the cat the responsiveness was greater than in the rabbit, the duration of the effect was greater in the rabbit than in the cat. This led to the investigation of the effect of adrenalin on blood pressure in the two species to determine whether it showed the same relation. Here it was found on the contrary, that the responsiveness of the vasoconstrictors as well as the duration of the response was greater in the rabbit than in the cat.

It is possible that the brevity of the dilating effect upon the cat's pupil, seen in the intravenous injections of adrenalin, is an additional factor in the very slight effect of adrenalin on the pupil of these animals, when administered by instillation. The slight absorption which perhaps actually takes place produces no perceptible effect on account of the lack of a cumulative action.

SUMMARY.

The present investigation brought out the facts that the pupil of the cat is little affected by instillation of adrenalin, but shows, nevertheless, a greater responsiveness to adrenalin when given intravenously than does that of the rabbit, and that the duration of the dilatation effected by intravenous injection is, on the contrary, longer in the rabbit.

In regard to the vasoconstricting effect of adrenalin when administered intravenously, it was found that the intensity as well as the duration of the rise of blood pressure was greater in the rabbit than in the cat.
EXPLANATION OF PLATES.

Blood pressure of cats and rabbits after intravenous injection of adrenalin. The upper line shows the blood pressure; the lower line, the base-line with the time in seconds and minutes. The numbers above the base-line show the transverse diameter of the pupil on the gangliectomized side. In Fig. 1 the upper row of numbers shows the normal eye, the lower row, the operated side.

PLATE 29.

FIG. 1. Rabbit 4. Injection of 0.1 mg. per kilo of body weight.

PLATE 30.

FIG. 2. Cat 4. Injection of 0.1 mg. per kilo of body weight.

PLATE 31.

FIG. 3. Rabbit 3. Injection of 0.03 mg. per kilo of body weight.
FIG. 4. Cat 3. Injection of 0.03 mg. per kilo of body weight.
(Githens: Adrenalin in the Cat and the Rabbit.)
FIG. 2.

(Githens: Adrenalin in the Cat and the Rabbit.)
(Gibbons: Adrenalin in the Cat and the Rabbit.)