THE ACTION OF OPTICAL ISOMERS. II. HYOSCINES.

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(Two Figures in the Text.)

IN a former paper[1] it was shown that the two hyoscyamines differ to a marked extent in their pharmacological action, the lævorotary natural base possessing a very powerful action on the terminations of the nerves in the salivary glands, heart, and iris, while the dextrorotary artificial base is almost devoid of effect on these organs, but exercises a stronger stimulating action on the central nervous system of the frog. The action of atropine (racemic hyoscyamine) is the resultant of the action of its two components, lævo- and dextro-hyoscyamine, and it thus affects the nerve terminations about half as strongly as lævo-hyoscyamine, while possessing a more distinct stimulant action on the central nervous system. The difference in the effect of lævo-hyoscyamine and the dextrorotary alkaloid was first inferred from a comparison of the action of atropine and hyoscyamine, and was then confirmed by the study of dextro-hyoscyamine.

A review of the literature concerning the action of optical isomers on vertebrates was given in that paper but two further examples of differentiation between the isomers have since been added. Mayor[2] states that lævo-nicotine, the natural alkaloid, is twice as toxic to guinea-pigs as the artificial dextro-nicotine. The lævorotary base induces pain when injected hypodermically, while the dextrorotary has no such effect, and there appears to be some difference in the nature of the convulsions, those following dextro-nicotine having a prevailing tremulous character, while those induced by lævo-nicotine are more violent and set in more abruptly. Neuberg and Mayer[3] found that d-mannose undergoes more rapid oxidation in the tissues of the rabbit than l-mannose, and that the injection of inactive mannose is followed by the appearance of l- and inactive mannose in the urine. Glycogen is formed from inactive

[1] This *Journal*, xxx. p. 176. 1904.

[2] *Ber. d. Deutsch. chem. Gesellsch.* xxxvii. p. 1234. 1904.

[3] *Zeitsch. f. physiol. Chemie*, xxxvii. p. 530. 1903.

and l-mannose as well as from d-mannose. An instance of similar differentiation which was overlooked in the former paper is offered by β-oxybutyric acid examined by McKenzie[1], who states that the dextrorotary acid is more readily decomposed in the tissues than the lævorotary and that the injection of inactive β-oxybutyric salts is followed by the excretion of a mixture of inactive and lævorotary acid in the urine.

The study of atropine and hyoscyamine led naturally to that of lævorotary and racemic hyoscine[2], and the fact that the presence of the dextrorotary body in atropine lends it a more excitant action on the central nervous system than is possessed by hyoscyamine suggested that racemised hyoscine might have less hypnotic action than the lævorotary base and that this might explain the frequent failure of hyoscine to act in insomnia. The only experiments hitherto performed on the comparative activity of these two isomers are those of Meyer[3] and Königshöfer[4], who applied dilute solutions to the eye and describe the effects of the alkaloids as very similar, each causing dilation of the pupil of approximately the same duration; racemic hyoscine appeared to act more quickly on the accommodation than the natural base according to Königshöfer, and Meyer seems to consider that it acts more strongly in some pathological conditions. The method of application adopted in these investigations, however, scarcely allows of any accurate comparison of the effects of the alkaloids.

A very pure specimen of hyoscine hydrobromate was kindly supplied us by the Merck Co., who stated that the $(a)_D$ was $-24{\cdot}62°$. This was recrystallized out of 80 % alcohol, and the first crop of crystals dried gave a rotation of $-25{\cdot}47°$. The highest rotation hitherto observed was $-25{\cdot}9$ (Hesse)[5], and our preparation was therefore 98 % pure lævohyoscine. Racemic hyoscine hydrobromate was prepared by Gadamer's[6] method, and recrystallized repeatedly. It was quite devoid of rotation. These two preparations were compared in our experiments, fresh solutions being made every day to preclude the possibility of decomposition.

The action of hyoscine or scopolamine has been investigated by a

[1] *Journal of the Chemical Society*, LXXXI. Part ii. p. 1409. 1902.

[2] Lævorotary hyoscine has been called scopolamine by Schmidt, and racemic hyoscine atroscine by Hesse, but hyoscine ought to have the preference over scopolamine from a historical point of view, and atroscine has not received general recognition.

[3] See E. Schmidt, *Arch. der Pharm.* CCXXXVI. p. 71. 1898.

[4] See Hesse, *Ber. d. Deutsch. chem. Gesellsch.* XXIX. p. 1782. 1896.

[5] *Journ. f. prakt. Chem.* LXIV. p. 353. 1901.

[6] *Arch. der Pharm.* CCXXXIX. p. 294. 1901.

number of writers[1] who agree in regard to most of the changes observed. Our attention has been directed only to certain limited points in the action, and we need only refer to the literature of the subject when our results bear upon disputed questions. The first point we investigated was the influence of the alkaloids on salivary secretion, and the method was the same as that employed in the case of atropine and the hyoscyamines. The same dog with permanent salivary fistula was used and the experiments consisted in injecting one or other hyoscine, observing its effect for 30 minutes and then injecting 5 mg. pilocarpine and measuring the saliva secreted every 5 minutes for about an hour. The saliva was collected on pledgets of cotton-wool for each 5 minutes and weighed. L-hyoscine and r-hyoscine were injected on alternate days. It was found that 0·05 mg. l-hyoscine was sufficient to arrest the secretion when the dog was lying still, and that 0·1 mg. r-hyoscine had an equal effect. Sometimes the secretion ceased after 0·05 mg. r-hyoscine, but in other experiments this was insufficient. The effects of the injection of 5 mg. pilocarpine hydrochlorate 30 minutes after the hyoscine injection are given graphically in Figs. 1 and 2, in which the numbers along the abscissa indicate the time after the pilocarpine injection, while the numbers along the ordinate give the number of decigrammes of saliva secreted per minute. In one experiment, marked I, pilocarpine was injected alone as a control. The doses of

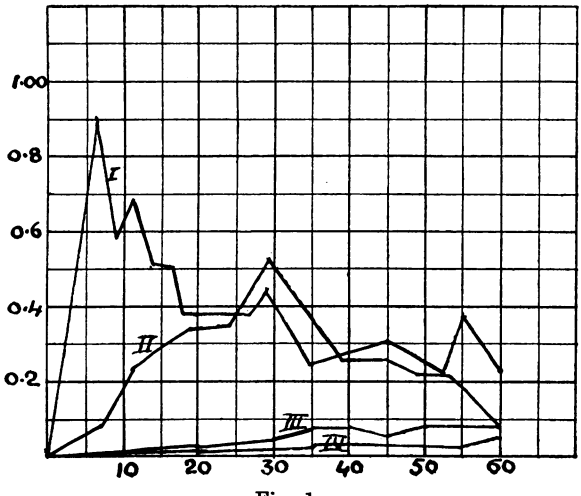

Fig. 1.

[1] See De Stella. *Arch. de Pharmacodyn.* III. p. 381, 1892. Kochmann. *Arch. internat. de Pharmacodyn. et de Therap.* XII. p. 99. 1903.

l-hyoscine hydrobromate (Fig. 1) were 0·05 (II), 0·1 (III), and 0·2 (IV) mg.; those of r-hyoscine hydrobromate (Fig. 2) were 0·05 (II), 0·1 (III), and 0·2 (IV) mg.

In Fig. 2 it is shown that 0·05 mg. r-hyoscine had no antagonistic effect to pilocarpine: 0·1 mg. reduced the salivary secretion to about one-half, while after 0·2 mg. it scarcely exceeded the normal amount with-

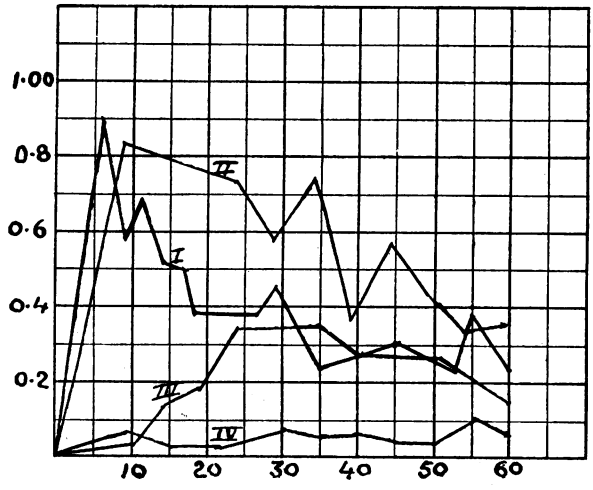

Fig. 2.

out pilocarpine. In Fig. 1, 0·05 mg. l-hyoscine has about the same effect as 0·1 mg. r-hyoscine, and 0·1 mg. l-hyoscine as 0·2 r-hyoscine, while after 0·2 mg. l-hyoscine there was practically no secretion for about 45 minutes. Another series of experiments gave similar results. The lævorotary hyoscine thus acts about twice as powerfully on the salivary secretion as the racemic form. One injection of atropine hydrobromate was interpolated in this series, when it was found that atropine has approximately the same power of antagonizing pilocarpine as r-hyoscine. In comparing these results with those given in the former paper, it is to be noted that the doses there given are those of the base, while in this series we have calculated them as the hydrobromate.

The relative activity of the two hyoscines on the inhibitory fibres of the heart was tested by injecting them hypodermically in a medium-sized dog, and counting the heart-beats. At intervals inhibition was induced by holding a piece of cotton soaked in ether to the nostrils. The normal pulse-rate of this dog was 80—90 per minute. When

inhibition was completely paralysed by a large dose of atropine the rate was about 130. After small doses the rate often rose to 110—120, but distinct slowing could be made out when ether was approached to the nose. The pulse was generally rather slower at first after the injection, as has been noted by most previous investigators, who have ascribed it to preliminary stimulation of the inhibitory apparatus. This slowing was generally more marked after small doses than after larger ones, which tended to paralyse the inhibition very soon. 0·2 mg. l-hyoscine hydrobromate had no effect on the pulse-rate, 0·45 mg. caused distinct acceleration, but no complete failure of inhibition, while after 0·7 mg. the application of ether to the nostrils had no effect on the rate. R-hyoscine hydrobromate 0·5 mg. quickened the heart very slightly, if at all, while the acceleration was marked after 1·0 mg. but 1·2 mg. was required to completely paralyse the inhibition. The estimations could not be made so exactly as in the case of the salivary secretion, but the general result was the same, that the lævorotary form was about twice as active as the racemic variety.

These results indicate that the two active hyoscines bear the same relation to each other as the two hyoscyamines; *i.e.* the lævorotary alkaloid is intensely poisonous to the terminations of certain peripheral neurons, while the dextrorotary is almost or entirely devoid of effect on them. The racemic form owes its pharmacological action on these terminations to the presence of the lævorotary variety, and in the tissues and in solutions in general must be dissociated into its two optically active components.

The terminations of these neurons thus differentiate between the two optical isomers, reacting to the lævorotary much more strongly than to that of the opposite sign. A similar elective affinity for one of two optical isomers is shown by some pure chemical substances which are themselves optically active, as for example when dextro-tartaric acid crystallizes more readily with d-coniine than with l-coniine[1]. Analogy would suggest the presence in the nerve ends of some optically active substance of an acid nature which exhibits a similar preference for the lævorotary bases, or which perhaps may deposit dextrorotary bases in a non-poisonous form.

The general action of the two alkaloids was examined first in frogs, two not differing more than 2 g. in weight being used in each experiment; l-hyoscine hydrobromate was injected into the abdominal

[1] A list of these reactions is given by Landolt, *Das optische Drehungsvermögen*, 2te Auflage, p. 61. 1898.

lymph sac of one, and an equal amount of r-hyoscine hydrobromate into that of the other. The effects induced by the two alkaloids proved to be identical, no such differences being noted as in the case of hyoscyamine and atropine. No distinct action was induced in 25 g. frogs by the injection of 5 mg.; after 10 mg. the frog sat still and made few spontaneous movements, but when touched hopped normally at first. In about 10 minutes after the injection a certain clumsiness in the movements became apparent, the frog alighting more flatly and the head swaying forward. This became more marked when the leaps were repeated, and often the animal crawled away instead of leaping. It recovered its normal posture when put on its back although with some difficulty, and this became very evident when it was put in this abnormal position repeatedly. After two or three hours the effect of the drug began to pass off and in less than twenty-four hours recovery was complete. No distinct increase in the reflex irritability and no loss of sensation could be made out at any time. After 20 mgs. the symptoms were the same in kind but more marked. The frog lay stretched out and could no longer hop on irritation but could crawl at first. In a short time it could no longer crawl although it made efforts to do so. When put on its back at this stage the frog always struggled to return to its normal posture, but often failed to do so and invariably failed the second or third time. The animal drew away its foot when pinched or touched with acid, but the movements were much less energetic than in a normal frog. Very often the movement was accompanied or followed by coarse tremors. When the lumbar plexus was stimulated with rapid induced electric shocks the legs were shot out as in a normal frog, but no complete muscular tetanus was elicited, but a series of rapid contractions and relaxations. The muscles gave the normal tetanus on direct stimulation. The recovery was complete within 24 hours.

30—40 mgs. injected into the lymph sac induced more marked manifestations of the same kind, and the recovery was complete in 24 hours, and in fact appeared almost complete within 12 hours in some instances.

These symptoms appear to be due to action on the terminations of the motor nerves in the voluntary muscles, and the usual Claude Bernard experiment showed that these were affected in the same way as by curara. Complete paralysis of the nerve ends was not elicited even by the largest doses employed (40 mgs. in 25 g. frogs), the hyoscines in this respect resembling a number of other alkaloids such as atropine, hyoscyamine and gelseminine. This imperfect paralysis of the nerve

ends is always marked by tremor and clumsiness accompanying muscular movements, and these are obviously due to the failure of a certain number of impulses to reach the muscles, and consequently imperfect coordination. Not infrequently these tremulous movements simulate convulsions, and in fact they have in some cases been ascribed to some central action. This peripheral action is always accompanied by a certain degree of inactivity and sometimes by the complete failure of spontaneous movements, and this has also been stated to indicate depression of the central nervous system. But exactly the same absence of spontaneous movements may be seen after the injection of quantities of curara too small to elicit complete paralysis of the nerve terminations. We have looked with care for evidence of central action from hyoscine because of its well-known hypnotic action in man, and also because Kochmann states that the general paralysis elicited by scopolamine is due to central action. We were unable to find any evidence of the central nervous system being affected in any way by either of the hyoscines examined. It is true that it is difficult to determine this point in the presence of the marked peripheral action. But we could elicit immediate reflex movement by pinching or touching with dilute acid at all stages, and some effort, however futile, was always made to return from the back position. The complete central paralysis described by Kochmann was certainly not present in our frogs, while the peripheral paralysis which was the only striking feature in our experiments is not recorded by him, though De Stella noted it in his work. Sohrt[1] on the other hand observed no changes in the motor functions after 60 mgs. Wood's[2] description of the symptoms in frogs corresponds in almost every detail with those in our experiments, but we consider that his inference that hyoscine acts on the frog as a motor spinal depressant is erroneous. The discrepancies in these observations may perhaps be explained by different species of frogs having been employed, the *Rana temporaria* and *esculenta* used by European observers showing distinct effects on the spinal cord, while the *Rana virescens* and *catesbiana* employed by us, and presumably by Wood, exhibit only symptoms of peripheral action. The cardiac action also seems to have been much more marked in the experiments of Kochmann than in those of Wood and ourselves.

In mammals the lethal dose of hyoscine is very large, though symptoms of cerebral action are induced by smaller quantities and are obtained in

[1] *Pharmacotherapeutische Studien über das Hyoscin., Inaug. Diss.* Dorpat. 1886.

[2] *Therapeutic Gazette*, p. 1. 1885.

man after fractions of a milligramme. We have made a number of experiments on white mice to find whether the lævorotary and the racemic base were equally poisonous. 10—15 mgs. of either base proved fatal when injected hypodermically into small mice (about 10 g. weight) and no definite difference could be made out in the onset of symptoms or in their character and duration. The features observed in mice under hyoscine have been described by Wood, and we have nothing essential to add to his account. A certain amount of depression was present, as shown by lessened spontaneous movements and imperfect coordination, but this was accompanied at first by occasional sudden jerks and later by well-marked clonic convulsions. The intervals between these became shorter and the spasms became more severe for some time. Then the intervals of rest became longer and the respiration was very slow and laboured and finally disappeared. Larger doses (up to 40 mgs.) induced the same symptoms in a more acute form. Quantities which were too small to cause convulsions (5 mgs.) were followed by no very distinct effects except perhaps some decrease in spontaneous movement, which was not sufficiently regular in its appearance to justify us in stating that a true narcotic action was present.

The two bases thus appear to act equally strongly on the nervous systems in frogs and the lower mammals, and the symptoms induced are identical. In this the hyoscines offer a contrast to atropine and hyoscyamine, for in the frog atropine stimulates the spinal cord much more powerfully than hyoscyamine. We would suggest as a possible explanation of the failure of the corresponding racemic hyoscine to stimulate the cord the fact that this alkaloid is excreted too rapidly. The marked change in the reflex excitability under atropine occurs only twelve hours or more after the injection of the drug. At this time the hyoscine whether lævorotary or racemic is in large part excreted. It seems probable therefore that the failure of racemic hyoscine to influence the reflex irritability of the frog in the same way as atropine is to be attributed to its shorter stay in the body, rather than to any essential difference in its relation to the nervous tissues.

In these experiments no unquestionable evidence of a depressant action on the central nervous system was obtained, and in order to determine whether the natural base and the racemic form were equally available as hypnotics a number of trials of their usefulness for this purpose were made in the Michigan Asylum for insane at Kalamazoo. The harmlessness of small doses of both alkaloids was first ascertained on ourselves, and then a number of tablets each containing 0·6 mg. of

l-hyoscine or r-hyoscine hydrobromate were used as hypnotics in the wards of Drs Richards and Light under the general supervision of Dr W. M. Edwards. We are much indebted to these physicians for the results recorded by them. Instead of hyoscine, a certain number of tablets contained 0·6 mg. of hyoscyamine hydrobromate, as its usefulness as a hypnotic has not yet been determined. In all, ten patients were treated with the tablets.

As a general rule a tablet was given on each alternate evening, and the duration of sleep and other features noted and compared with those of the intervening control night on which no hypnotic was given. Hyoscyamine was thus used on three occasions, and then racemic hyoscine, and then lævo-hyoscine. Then a tablet was given each evening for a week or more, the different alkaloids following each other in succession. The results may be given shortly in tabular form, details being reserved for publication elsewhere.

TABLE I.

	Controls (no hypnotic)		0·6 mg. L-Hyoscyamine HBr.			0·6 mg. L-Hyoscine HBr.			0·6 mg. R-Hyoscine HBr.		
Patient	No. of observations	Average hours of sleep	No. of observations	Average hours of sleep	Increase over controls	No. of observations	Average hours of sleep	Increase over controls	No. of observations	Average hours of sleep	Increase over controls
1	9	0·6	6	1·3	0·7	6	2·5	1·9	6	2·1	1·5
2	9	3·0	6	1·4	−1·6	6	3·8	0·8	6	4·4	1·4
3	8	4·7	6	4·5	−0·2	6	5·8	1·1	6	4·7	0·0
4	9	5·5	3	4·3	−1·2	3	5·6	0·1	3	4·8	−0·7
5	9	6·2	3	6·1	−0·1	3	6·1	−0·1	3	6·7	0·5
6	8	3·2	4	6·6	3·4	3	7·6	4·4	3	8·3	5·1
7	8	2·5	3	6·2	3·7	3	8·0	5·5	3	8·2	5·7
8	7	2·8	6	3·6	0·8	6	4·4	1·6	5	4·3	1·5
9	8	1·1	5	1·1	0·0	6	5·7	4·6	5	5·8	4·7
10	9	2·9	5	4·9	2·0	5	6·3	3·4	6	6·4	3·5
11	—	—	2	6·3	—	2	6·8	—	2	7·3	—

From these results it is evident that hyoscyamine is of no value in the dose given as a hypnotic, while the lævorotary and racemic forms of hyoscine have about the same influence in inducing sleep. In one or two cases the patient complained of thirst or dryness of the mouth. The pulse generally became slower, and slight dilation of the pupil appeared in some instances from each of the drugs. In other cases acceleration of the pulse was noted. It may be questioned whether these changes in the pulse and pupil were direct effects of the drug or merely accompanied drowsiness.

SUMMARY.

1. Lævo-hyoscine acts twice as strongly as the racemic base on the terminations of the secretory nerves in the salivary glands and of the inhibitory fibres in the heart. It may be inferred that a similar ratio holds in other analogous terminations.

2. Lævo-hyoscine and racemic hyoscine have the same effect on the central nervous system in man and mammals, and on the terminations of the motor nerves in the frog, in which they do not seem to affect the central nervous system.

3. From this it would appear that as in the case of the hyoscyamines, the dextrorotary hyoscine is practically inactive on the terminations of the secretory and cardiac inhibitory terminations, while it acts equally strongly with the lævorotary base on the central nervous system in mammals and on the motor nerve ends in frogs. On the other hand dextro-hyoscine differs from dextro-hyoscyamine in not stimulating the spinal cord in the frog, but this may be due to its being very rapidly excreted.

4. Hyoscyamine is practically devoid of hypnotic action in man, when given in doses which do not affect the peripheral organs.

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