HYPOGLYCÆMIC SHOCK AND THE GRASP-REFLEX

THE EFFECT OF INSULIN SHOCK ON BULBOCAPNINE CATALEPSY IN MONKEYS

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IN a previous communication (Kennedy, 1939) an account has been given of the effects of cardiazol convulsions, such as are used in the treatment of clinical catatonic states, upon the catalepsy-like condition seen in bulbocapnine intoxication in monkeys. A study was made of the effects of convulsions on the grasp-reflex which is invariably present with this state in the bulbocapninized monkey, the intensity of the response being measured by the hanging-time method of Richter (1931). It was shown that the effect of the convulsions was to increase very considerably the cataleptic component of the state produced by bulbocapnine in much the same way as does the inhalation of a high concentration of carbon dioxide (Paterson and Richter, 1932), and that the period during which the grasp-reflex was present was greatly prolonged, though the convulsions alone produced only a transient hanging-response.

The purpose of the work to be described was to compare these effects of the induced convulsion with those of hypoglycæmic shock. The first object, therefore, was to reproduce in monkeys a condition as nearly as possible resembling therapeutic insulin shock and to determine its effect on motility and upon the grasp-reflex. Having thus standardized the effects of insulin on each animal used, it was then possible to investigate the effects of the hypoglycæmic state on the catalepsy and grasp-reflex phenomena produced by bulbocapnine.

Technique

The animals used for these experiments were six adults of the *Macacus Rhesus* species, each weighing about 3.5 kilos. The apparatus for measuring the duration of the hanging-response has been described in detail previously (Richter, 1931; Richter and Paterson, 1932), and consists of an horizontal brass bar, $\frac{3}{8}$ in. in diameter, held by two upright stands about 4 ft. above a net stretched over a frame, into which the animals fall when they cease to grip the bar. During the experiments trials of the

hanging-response were made every 10 minutes, and on each occasion both hands were tested separately, the one which was not being tried being tied down, with the feet, by means of a strip of muslin, in order to prevent the animal from using them to grip the bar. At each trial the monkey was held by the head, while the palm of its free hand was allowed to come into contact with the bar, when, if the response was present, grasping occurred and the animal was allowed to hang free. The time from releasing the animal and its falling into the net was taken with a stopwatch and recorded as the hanging-time. Before the experiments the six monkeys were tested on several occasions and it was found that the response was not present and that on being put to the bar they dropped at once and attempted to escape.

In previous experiments with the grasp-reflex (Richter and Paterson, 1932) the insulin was given intravenously, but it was found that its effects were far less constant and uniform than by the subcutaneous route, and this was employed in the present series. Preliminary experiments were made in order to find a dosage which would produce a state as nearly as possible resembling therapeutic hypoglycæmic shock as seen clinically, and it was found that under carefully controlled conditions a dosage of one unit per kilo produced the most uniform results. It was found that these results could be obtained only if the animals had been starved for 24 hours and if elaborate precautions were taken to preclude access to small quantities of carbohydrate, such as might be obtained by chewing the sawdust in the cages. It was also found necessary to reduce their activity to a minimum by reducing the amount of light and extraneous noises. To this end the six monkeys were kept in a row of cages in the same room as the apparatus for 24 hours before the experiments, so that they were not unduly stimulated and could be taken out one by one with a minimum of struggling, examined, and at once put back. The experiments were carried out at weekly intervals, the weight and activity of the animals being recorded in the interval.

Fig. 1.—Graphs showing the effects of insulin on the hanging-time in four monkeys. The reflex appears 80–110 minutes after the administration of insulin and continues until the onset of coma. On interruption of the coma with glucose given by stomach-tube the reflex appears again briefly during recovery. The times given are the average hanging-times from the two hands.

After the insulin had been given, the activities, appearance, and results of examinations of the animals, as well as the hanging-times, were recorded in relation to the times at which they occurred. With the times after injection as abscissæ and the hanging-times as ordinates, graphs were made (Fig. 1) to illustrate the changes in the hanging-response. When the hypoglycæmic shock had progressed to the stage of deep coma, it was interrupted by giving 10 c.c. of a 50 per cent. solution of glucose by means of a stomach tube, which offered no difficulties in the unconscious animal. The bulbocapnine was injected subcutaneously as a 10 per cent. solution, and a dosage of 15 mg./Kilo was used as this gave the most uniform results.

Procedure

In the first part of the experiment the behaviour and reflex changes, including the hanging-response, were studied after the subcutaneous injection of insulin. In the second part the object was to study the effects of hypoglycæmic shock on the behaviour, cataleptoid phenomena, akinesia, tremors, and grasp-reflex changes produced by bulbocapnine, and for this purpose the effect of bulbocapnine alone was first determined and hanging-curves obtained, and then the drug was injected at different periods during the action of insulin, a week elapsing between each experiment. Thus from each animal a record and curve was obtained of the action of insulin alone, of the action of bulbocapnine alone, of the effect of giving both simultaneously, of the effect of giving bulbocapnine just as the pre-comatose stage was commencing, and of the effect of giving it at the time that the coma was interrupted by giving glucose. It was thus possible to compare the effects by a parallel series of observations.

Results

Effect of Insulin on the Normal Monkey

The following account is based on the observations common to the records of all of the six animals used. No effect was noted for about 50 minutes after the injection, the animals sitting quietly in their cages. At the end of this period some restlessness appeared, and they would begin to scratch the floor of the cage in search of scraps of sawdust which they would put in their mouths and chew, or they would reach into the next cage to explore their neighbour's back for food. This activity was intermittent and would be succeeded by periods in which their heads would nod and eyelids droop and they would blink frequently. From this drowsiness they could at first be readily aroused by handling or by making a noise or exhibiting food, but the active periods soon became shorter, and at the end of 70 minutes their heads were bowed down and their eyes closed for most of the time. Even when very drowsy, however, the animals would frequently lick their lips and put their hands to their mouths as if hungry. At this stage the muscles had become hypotonic and the tendon reflexes were rather more brisk than normal.

Between 80 and 100 minutes after the injection, the hanging-response appeared when the hand was allowed to grasp the bar, thus stretching the flexor tendons of the forearm, but no grasping was elicited by stroking the palm lightly with a brush. The mean hanging-times for the two hands at different periods after the injection of insulin for four of the animals are shown in Fig. 1.

In this figure the period of the hypoglycæmia has been divided arbitrarily into four stages of drowsiness, pre-coma, and recovery, the pre-coma stage commencing with the appearance of the hanging-response.

Shortly after the hanging-response had appeared, the animals once more showed short periods of excitement in which, without otherwise moving very much, they glanced rapidly from side to side and at the same time showed muscular irritability and increased tendon reflexes. The glancing movements then lost their apparently purposeful character and almost imperceptibly developed into a marked spontaneous nystagmus which later, in some of the animals, was of the scintillating type. This stage was reached some twenty minutes after the appearance of the hanging-response.

With the nystagmus, twitching and sudden movements of the limbs began to appear at intervals of 3 to 5 minutes, and in the intervals muscular hypotonia became very profound, though the tendon reflexes were very brisk and individual muscles would contract on being lightly tapped. Soon these periods of muscular irritability became more intense and somewhat more frequent, occurring at intervals of 2 to 3 minutes. The movements gradually became more widespread and assumed the character of convulsions. If the monkeys were handled at the time when such a convulsion was expected, the stimulation attendant on handling would bring it on. When this stage of intermittent convulsions had been reached, the animals showed no appreciation of visual or auditory stimuli and were evidently unconscious. Immediately after each bout of convulsions the muscular hypotonia was extreme. In two animals short periods of clonic movements occurred, of about 5 seconds' duration. At 160–170 minutes after the injection a rapid change came over all the animals. The muscles became toneless, cyanosis and frothing at the mouth appeared, together with drenching perspiration and a rapid collapse in which the tendon reflexes and the hanging-response disappeared. This stage of deep coma came on in the course of less than 5 minutes and necessitated the giving of glucose. This was given by means of a stomach-tube and syringe, and within a minute consciousness returned and the animals began to look about. The hanging-response also reappeared transiently during this stage of recovery, to disappear again as behaviour became normal. After the experiment the animals did not seem very exhausted and had voracious appetites. At no phase of the action of insulin were any cataleptic phenomena observed.

Effect of Hypoglycæmia on Bulbocapnine Catalepsy

Effect of Bulbocapnine alone.—The effects of bulbocapnine in the monkey have been previously described (Kennedy, 1939) and will not be given in detail. Shortly after the injection, the hanging-response appeared, accompanied by the akinesia, tremors, and salivation. No marked catalepsy was observed, but there was a slight tendency to maintain impressed postures about 40 minutes after the injections. The duration of the hanging-response was recorded graphically as before (Fig. 2, A). For simplicity the average hanging-time for the two hands is given, there being usually no great difference between them.

Effect of Bulbocapnine and Insulin : when given simultaneously.—For the first 40 minutes the effects observed resembled those brought about by bulbocapnine alone, except that at the first trials the hanging-response was in all the animals appreciably longer (Fig. 2, C). As the effects of the bulbocapnine

Fig. 2.—Graphs from two animals showing the effects of the administration of insulin and bulbocapnine in different time relations on the hanging-response. The vertical arrangement enables the summation of the effects to be appreciated.

began to wear off, the tremors disappeared and the hanging-times became shorter, the animals began to blink and to nod as the effect of the insulin became evident. The hanging-times then increased again and the nystagmus, muscular irritability, and convulsive movements appeared in the same time-relations as when insulin was given alone, and were followed by the stage of deep coma and collapse. Upon interruption the grasp-reflex reappeared or increased almost exactly as before. In respect of the hanging-response, apart from the high level at the commencement, the curves obtained may be regarded

as summations of those obtained with bulbo-carpine and insulin separately (Fig. 2, A and B).

When Bulbo-carpine was given as the Hanging-Response appeared.—In these experiments the effects of the insulin were observed up to the time of the appearance of the hanging-response and found to have very similar time-relations to those recorded 2 weeks previously. As soon as the grasp-reflex became evident, bulbo-carpine was injected and at once the hanging-time increased to a level higher than obtained when either drug was given separately. At the same time a number of new phenomena were observed.

The animals were very still and the tremor which might have been expected at this time from the bulbo-carpine was notably absent in four and only slightly present in two of the animals, in both of which it later disappeared.

In the table (Fig. 3) it is seen that a considerable tremor-free period was

NO. OF ANIMAL	TREMOR			CATALEPSY	GRASPING	
	MINUTES AFTER ONSET OF BULBOCAPNINE EFFECT				SPONTANEOUS	ON STIMULATION OF PALM
	15	30	45			
I	X	—	—	—	X	X
II	X	—	—	—	X	X
III	—	X	X	XX	—	X
IV	—	—	X	—	X	X
V	—	—	X	X	X	X
VI	—	—	—	X	X	X

Fig. 3.—Table showing differences in the phenomena observed in the six monkeys in the period following the injection of bulbo-carpine during insulin pre-coma (see also Fig. 2, D). In all the animals there was an inhibition of the tremors for at least 10 minutes of the period during which it was present with bulbo-carpine alone.

present in all the animals at a time when, had they been under the influence of bulbo-carpine alone, tremors would have been well marked. In three animals slight catalepsy was present, but they would not maintain impressed postures against gravity to any extent. When the hands were put to the bar, grasping occurred very readily in all and within 15 minutes of the injection of bulbo-carpine, in five of the six animals the hands and forearms spontaneously took up a flexed position and grasping occurred without any local stimulus. In all, grasping occurred at this period when the skin of the palm was lightly touched with a brush. The spontaneous grasping was accompanied by a flexed position of the arms, extreme muscular irritability, and drawing up of the knees and forward bending of the trunk. This condition persisted for 20–30 minutes, during the latter part of which time nystagmus developed and was followed by intermittent convulsive movements which increased in frequency and magnitude until the stage of sweating, cyanosis, and collapse with gross hypotonia supervened and necessitated the giving of glucose. In three animals in which there had been no tremor at first, this appeared as the hanging-time, which had

been greatly prolonged, abruptly became shorter. A summary of the signs evident during this period in the different animals is shown in the table (Fig. 3).

When Bulbocapnine is given as the Hypoglycæmia is interrupted.—The same effects were noted after the injection of insulin as before, and it was observed that the time-relations of the changes and the contour of the hanging curves were roughly the same for each animal on each occasion. After the stage of deep coma, bulbocapnine was given at the same time as the glucose, and it was observed that when the hanging-response appeared, the hanging-times were at first a little longer than when bulbocapnine alone was given. Apart from this there was little difference, the descriptive data and hanging-curves being very similar (Fig. 2, E).

Discussion

From the experiments described it is evident that when insulin is given to monkeys that have been previously starved and kept so that external stimulation is reduced to a minimum, the phenomena observed are closely comparable to those seen in man during hypoglycæmic shock treatment. It is seen that a constant accompaniment of the pre-coma stage in the monkey is the appearance of the hanging-response which disappears with the onset of gross hypotonia and collapse and reappears briefly in the stage of recovery after glucose has been given.

Although, after the action of insulin alone, there was a period during which the animals became drowsy and akinetic, no severe catalepsy was observed such as has been described in cats (de Jong, 1931) and in mice (Divrey and Evrard, 1937). The hanging-response, therefore, was not associated with catalepsy as it is in the monkey after bulbocapnine (Richter, 1931) or bulbocapnine-cardiazol (Kennedy, 1939).

The convulsions seen in monkeys during insulin hypoglycæmia differ in a number of ways from those induced by intravenous injections of cardiazol. They are multiple and intermittent, have a good deal of prodromal twitching, and tend to be precipitated by peripheral stimulation. There is no usual pattern such as is seen in the cardiazol convulsion, and there is no sharp distinction between minor twitches and convulsive movements, all intermediate stages being present. Clonic movements were seen in two of the animals, but they did not occur with every convulsion and were very brief in duration. As seen in these experiments, the seizures could not be described as epileptiform and their occurrence seemed to result from an intermittent exaltation of neuromuscular irritability rather than from a process of spreading cerebral excitation. The occurrence of increased neuromuscular excitability in association with drowsiness and akinesia and with the appearance of the grasp-reflex would suggest that, unlike the cardiazol convulsion, the insulin convulsion is of the nature of a release phenomenon.

The reappearance of the neonatal grasp-reflex in the adult monkey would not appear to be a phenomenon indicative of a single type of dysfunction in the

central nervous system, but rather the common physical sign of a number of abnormal processes in the upper neurons. It appears, together with the drowsiness resulting from the action of some sedatives (Richter and Paterson, 1932) and during the action of a number of substances which have in common the property of producing transient remissions in some catatonic states, and, as already mentioned, it is always present in association with the catalepsy produced by bulbocapnine (Richter, 1931). It has been suggested (Kennedy, 1939) that it is also a part of the extrapyramidal syndrome produced by that drug. It has been further suggested that when it appears as the result of more than one train of causation, the hanging-time is longer than when a single cause is operative. This view receives confirmation in the present experiments where it can be seen that when bulbocapnine and insulin are given to the same animal, either simultaneously or in sequence, the results, so far as the hanging-response is concerned, represent a simple summation of the action of the two agents, as is well seen in the series of curves in Fig. 2. There are, however, two periods during which there is a greater prolongation of the hanging-time than would be expected on this basis. The first of these occurs when the insulin and bulbocapnine are given simultaneously (Fig. 2, C). Here the prolongation of the hanging-time is brief but constant, and it is presumably due to the absorption into veins of a quantity of insulin sufficient to increase the hanging produced by bulbocapnine, though when the insulin is given alone it is insufficient to cause hanging by itself.

The second occasion when the hanging-time may be rather longer than would be expected from simple summation occurs when the bulbocapnine is given at the time the insulin is approaching the height of its effect, in the pre-coma stage, and it is this period which is the greatest theoretical interest. As has been seen, for a period of about 30 minutes phenomena are present which are not brought about by either drug alone, and there is a disappearance of a conspicuous component of the bulbocapnine picture, namely the tremor. During this period, spontaneous grasping occurs and the animal takes up a position with the forearms flexed. This position, with the attendant muscular irritability, is not unlike that seen in tetany. That the presence of tetany as a complicating factor is not to be excluded lightly is indicated by the fact that bulbocapnine causes a considerable fall in the blood calcium of cats (Katzenelbogen and Meehan, 1933), and it is probable that the tendency to tetany is increased by the strong alkalizing action of the insulin. During this critical period a grasp-reflex was obtainable from all the animals by lightly stroking the palm. While this might be taken to indicate the presence of a different type of grasp-reflex initiated by a skin-sensory stimulus, in view of the observation (Bieber and Fulton, 1938) that in the "pre-motor monkey" the grasp reflex can be obtained by lightly touching the palm, even when the cutaneous nerves have been blocked with a local anæsthetic, it seems possible that it may be activated by stimulation of the flexor tendons, just as is the reflex that gives rise to the hanging-response. It is likely, however, that even if a sensorimotor grasp-reflex of the type described by Walshe and Robertson (1933) does not appear, the ease with which grasping is obtained indicates a further process of release.

The presence of spontaneous grasping and of an associated attitude of the forearms is also suggestive of further cortical release, since the grasp-reflex is to be regarded as part of a less localized response, whether this be of the nature of a forced grasping movement (Walshe and Robertson, 1933) or of a postural reflex (Bieber and Fulton, 1938), more of which is revealed when the action of insulin is added to that of bulbo-capnine.

In the table (Fig. 3) it can be seen that at this critical period in the pre-coma stage, in all the animals the tremors are absent for at least 10 minutes at a time when, under the influence of bulbo-capnine alone, they would be unmistakably present. In view of the observation (Schaltenbrand, 1925; Ferraro and Barrera, 1932) that tremor does not occur on the contralateral side in a bulbo-capnized, hemi-decorticate animal, it would seem that the absence of tremor might be explained by a temporary suspension of cortical activity, comparable to that which presumably causes the cessation of extrapyramidal tremors in sleep. This again would suggest that the action of insulin is a depressant one predominantly at the cortical level.

Summary

1. Hypoglycæmic shock was induced in six monkeys. The phenomena observed are essentially similar to those seen in therapeutic hypoglycæmia in man.

2. The hypoglycæmia was accompanied by a reappearance of the neonatal grasp-reflex, which disappeared when coma became deep and reappeared briefly during the phase of recovery.

3. When bulbo-capnine is given at different periods during the action of insulin, the general effects and those in regard to the hanging-response are a summation of the individual effects of the two drugs, except when the peak of action of both drugs coincides, when new phenomena appear.

4. These consist of disappearance of the tremors caused by the bulbo-capnine and the appearance of spontaneous grasping, together with a grasp-reflex obtainable on light stimulation of the palm.

5. Hypoglycæmic shock has no effect on the cataleptic manifestations induced by bulbo-capnine, nor does it itself produce catalepsy in the monkey.

6. Theoretical reasons are adduced from the experiments for the supposition that the action of insulin is predominantly a depressant one on the cerebral cortex.

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