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Temperature responses and other effects of 5-hydroxytryptophan and 5-hydroxytryptamine when acting from the liquor space in unanaesthetized rabbits

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Summary

1. In unanaesthetized rabbits 5-hydroxytryptophan (5-HTP) and 5-hydroxytryptamine (5-HT) were injected into the cisterna magna or into the cannulated left lateral cerebral ventricle while rectal temperature was recorded.

2. 5-HTP injected intracisternally in a dose of 1·5–3 mg produced a fall in temperature often followed by a rise beyond the pre-injection level. With 6 mg the main effect was a rise in temperature. The intraventricular injection of 1–2 mg 5-HTP usually produced a fall followed by a rise.

3. 5-HT injected intracisternally in a dose of 0·2 mg produced a fall in temperature similar to that produced with this dose injected intraventricularly. Following an intracisternal injection of 1–4 mg 5-HT there was either a fall, or a fall followed by a rise, but in a few experiments the effect consisted mainly of a rise in temperature.

4. Additional effects regularly observed with these injections were tachypnoea, ear twitching, rapid movements of the vibrissae, shaking of the head, wiping and scratching movements, ataxia, nodding and sideways movements of the head and long-lasting catalepsy.

5. The sites where 5-HTP and 5-HT act when producing the temperature responses and the various behavioural effects are discussed.

Introduction

In unanaesthetized rabbits an injection of 5-hydroxytryptamine (5-HT) into the cerebral ventricles or directly into the anterior hypothalamus causes a fall in rectal temperature as first shown by Cooper, Cranston & Honour (1965). This effect, which is small and not regularly obtained (Feldberg & Lotti, 1967), contrasts with the strong hyperthermia observed by Canal & Ornesi (1961) on injection of 5-HT or its precursor 5-hydroxytryptophan (5-HTP) into the cisterna magna. Hyperthermia is also produced when large doses of 5-HTP are injected intravenously (Horita & Gogerty, 1958; Pletscher, Besendorf, Bächtold & Gey, 1959), and according to Bächtold & Pletscher (1957) small doses of 5-HT injected subcutaneously into rabbits treated with a monoamine oxidase (MAO) inhibitor produce hyperthermia as well. As different functions have been postulated from these

results concerning the role of 5-HT as mediator of temperature responses in the central nervous system of rabbits, it seemed necessary to repeat the experiments and to compare the effect of the different routes of administration in more detail and, further, to determine the spread of substances injected intraventricularly and intracisternally in the liquor space. To do so, the dye bromophenol blue was injected instead of the amine or its precursor, and the staining of the exposed brain, brain stem and spinal cord was observed following perfusion of the brain with formalin.

Methods

The experiments were performed on unanaesthetized New Zealand White and Dutch rabbits of either sex, weighing between 1·8 and 3 kg. The methods for injection into the cannulated left lateral cerebral ventricle and into the cisterna magna, for recording rectal temperature and for perfusing the brain with formalin after injections of bromophenol blue were the same as described previously (Banerjee, Burks, Feldberg & Goodrich, 1968).

Drugs used were DL-5-hydroxytryptophan anhydrous (Roche Products), and 5-hydroxytryptamine creatinine sulphate (May & Baker). The doses of 5-HT given in the text refer to the salt. The drugs were dissolved in pyrogen-free 0·9% NaCl solution and injected, if not otherwise stated, in a volume of 0·1 or 0·2 ml into the cisterna and in a volume of 0·1 ml into the lateral ventricle followed immediately by an injection of 0·05 ml of 0·9% NaCl solution. The bromophenol blue injected was a 0·2% solution prepared as described by Feldberg & Fleischhauer (1960a).

Results

Injections of 5-HTP into the cisterna magna

The injection of 0·1 or 0·2 ml of 0·9% NaCl solution either did not affect rectal temperature, or produced a short-lasting fall, usually of less than 0·5° C, once of 0·7° C. These brief responses were associated with vasodilatation in the ears.

An intracisternal injection of 1·5–3 mg of 5-HTP usually produced a fall in rectal temperature which was greater and longer lasting than the fall produced in the same rabbit by the same volume of 0·9% NaCl solution ; the fall produced by 5-HTP was often followed by a rise above the pre-injection level. In some experiments the period of falling temperature was interrupted several times by a rise due to excitement and bouts of struggling. Two typical experiments uncomplicated by excitement and struggling are illustrated in Figs. 1A and B.

In experiment A, the injection of 1·5 mg of 5-HTP produced a fall of 1·7° C during the first 1·5 h ; temperature remained at this low level for 0·5 h and then gradually rose to nearly the pre-injection level during the following 2 hours. A subsequent injection of the same volume of 0·9% NaCl solution (0·1 ml) caused a fall of 0·2° C only. In experiment B, 3 mg of 5-HTP produced a fall of 1·5° C followed by a rise of nearly 1° C above the preinjection level ; the same volume of 0·9% NaCl solution (0·2 ml) injected a few days earlier had produced no effect on temperature in this animal. A late after-rise often occurred also with 1·5 mg ; on the other hand, it was not always obtained with 3 mg 5-HTP.

In two experiments the main effect following an intracisternal injection of 2 mg 5-HTP was hyperthermia. Even in these experiments, the immediate effect was a

tendency for temperature to fall during the first few minutes and the rise began only half an hour after the injection. In one of these experiments, illustrated in Fig. 1C, temperature reached 42·6° C within 2 h, a rise of 3·5° C, and then fell again.

In two rabbits in which 6 mg 5-HTP (in 0·3 ml) was injected intracisternally, the main effect was again hyperthermia. In the one, the temperature response resembled that shown in Fig. 1C, in the other, illustrated in Fig. 1D, the rise was preceded during the first half hour by a fall of nearly one degree.

When large rises in temperature occurred, such as in experiments Fig. 1C and D, there was widespread vigorous tremor, the rabbits became excited, tried to escape, and when restrained, struggled vigorously. The struggling sometimes assumed a near convulsive character and, in the experiment of Fig. 1D, short-lasting periods of convulsions occurred 2·5 h after the injection, recurred several times, and the animal finally died during a seizure.

The fall in temperature produced by 5-HTP was associated with dilatation of the ear vessels, tachypnoea and decreased muscle tone. Dilatation of the ear vessels preceded the onset of hypothermia ; the dilatation often began within the first

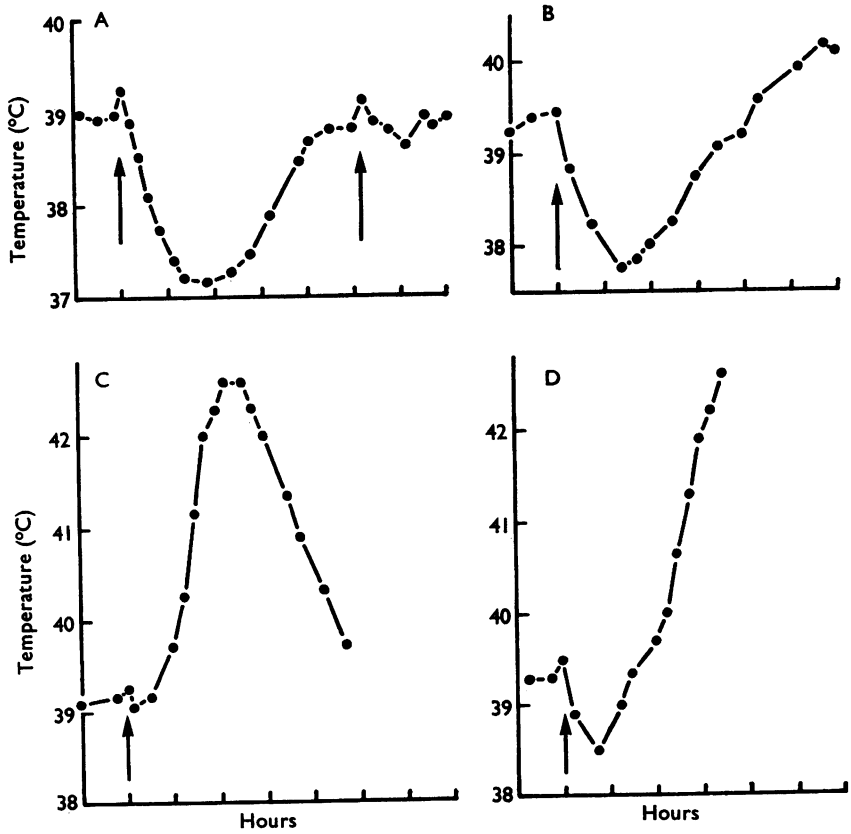

FIG. 1. Records of rectal temperature from four anaesthetized rabbits. In rabbit A, injection into the cisterna magna of 1·5 mg 5-HTP at the first, and of 0·1 ml 0·9% NaCl solution at the second arrow. The short-lasting rises immediately before the injections were the result of slight struggling due to restraining the rabbit for making the injections. In rabbits B to D, at the arrows, injections into the cisterna magna of 5-HTP ; in rabbit B, 3 mg, rabbit C, 2 mg and in rabbit D, 6 mg.

minute of the injection and rapidly became maximal, so that the ears felt hot. Pronounced tachypnoea followed a minute or two later and continued for 1–2 h. Low muscle tone became evident as resistance to forepaw abduction diminished, and within a few minutes the rabbit lay on its belly, often with its hind legs half or fully extended behind it. During this time the rabbit was unable to sit up, and did not succeed when it struggled to do so. Another early sign was continuous rapid movements of the vibrissae with quivering of the nose, which began 5–10 min after the injection and became increasingly pronounced. The movements of the vibrissae were not related to the respiratory movements.

When temperature began to rise, the vasodilatation in the ears usually diminished and the rabbit gradually became able to sit up. It then adopted the posture illustrated in Fig. 2. It sat on its hindquarters with forelegs extended and sometimes slightly spread, with the head bent down and the ears laid back. The half open eyes had a peculiar posteriorly directed gaze, with the lower and posterior parts of the iris and pupil covered by the eyelids. The weight was primarily on the hindquarters, the forelegs often barely touching the ground. The head moved from side to side and nodded up and down, resembling the movements of a doll with a loosely pivoted head. The rapid movements of the vibrissae with quivering of the nose continued during this phase and there was fine tremor of the ears, often extending to the facial and neck muscles: sometimes there was shivering in the flanks as well. This posture, together with the peculiar gaze and the continuous movements of head, vibrissae and ears, characterized the appearance of the rabbit in this condition. In addition, there were from time to time brief periods of flutter of the ears, and, less frequently, shaking of the head, wiping of the face, or incomplete wiping movements. When the rabbit occasionally tried to move, ataxia, particularly in the forelegs, was evident from the way it staggered and swayed. Later, the ataxia diminished and full motor co-ordination was regained. There

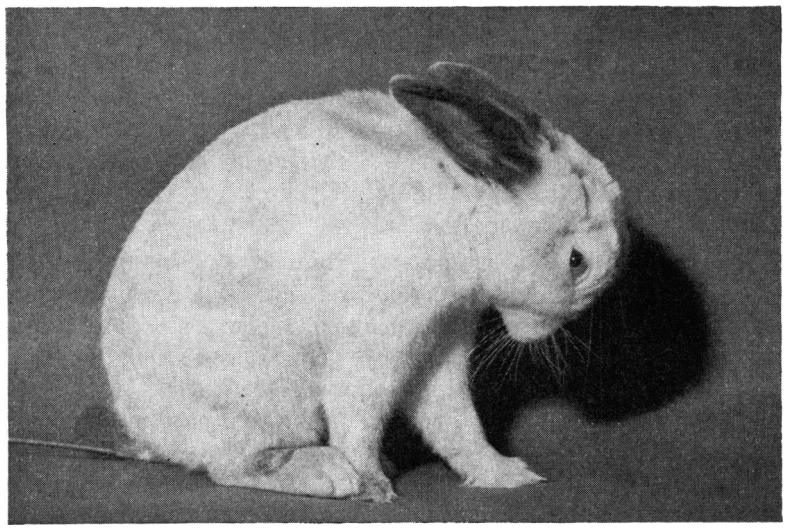

FIG. 2. Posture adopted about 1 h after an injection of 1·5 mg 5-HTP into the cisterna magna of an unanaesthetized rabbit.

were bouts of drumming with the forelegs, and occasional scratching with the hind legs.

Another feature of the response to intracisternal 5-HTP was catalepsy, which developed whilst temperature was still low and then persisted for several hours. When, during this time, the rabbit was placed in a nearly erect posture with its forepaws over a horizontal bar 20–24 cm high, it made no effort to return its forepaws to the ground, but maintained the abnormal posture for several minutes until it slowly sagged from the bar. Sometimes one paw slipped first, and then the rabbit hung on with the other for up to a minute. When it later moved away it did so in a well co-ordinated manner. If the test for catalepsy was carried out while the rabbit showed the side-to-side and nodding movements of the head, the continuous vibrissae movements with quivering of the nose and the tremor of the ears, these movements continued unabated while the rabbit maintained its nearly erect posture. Catalepsy was still present after these movements had disappeared.

Injections of 5-HTP into a lateral cerebral ventricle

The temperature effects resembled those produced by intracisternal injections. With 1 or 2 mg there was a fall in rectal temperature followed in most experiments by a rise above the pre-injection level. Experiment A in Fig. 3 shows the more usual response, a fall of a little over half a degree followed 2·5 h later by a gradual rise to about 41° C, whereas experiment B shows a particularly large fall of 1·5° C followed by a more rapid rise to about 1° C above the pre-injection level. In some experiments a late rise occurred without a preceding fall, or with little lowering of temperature during the first hour or two.

The fall in temperature was associated with dilatation of the ear vessels, rapid shallow breathing up to 250/min and loss of muscle tone followed by muscular weakness. In addition, the animal became quiet, as if sedated. Loss of muscle tone appeared to be the main cause of the hypothermia because temperature also fell when the ear vessels were dilated before the injection, and the fall usually began a few minutes before the onset of tachypnoea, which continued as temperature recovered.

When muscular weakness was pronounced the animal lay on its side or on its belly, unable to support its head or to maintain a sitting position. When lying on its belly the hindquarters could be turned to the side without the rabbit resisting; yet it reacted to being handled and to noise. The eyes were wide open and showed a variable degree of exophthalmos.

During the rising phase of temperature, muscle tone returned; the animal resumed a sitting position or moved about, but with some degree of ataxia. The ear vessels contracted and there was fine tremor of the ears whilst shallow rapid respiration continued. There were bursts of vigorous head shaking with or without licking movements, short bursts of drumming with the forelegs, wiping of the face and scratching movements. The wiping and scratching movements appeared first and predominantly on the side of injection and occurred more regularly than on intracisternal injection of 5-HTP. Vibrissae movements, tremor and flutter of the ears, as well as initial and late excitation with struggling, did not occur in all experiments and were never as pronounced as after the intracisternal injections. Further, the characteristic posture shown in Fig. 2 was rarely seen to be as fully

developed as after the intracisternal injections. In some experiments the rabbit just sat quietly on the table, but showed signs of ataxia during the infrequent attempts to move. From time to time the head gradually fell forward then was abruptly raised, with signs of ataxia such as a sideways swaying, and held up until it again sagged. At other times, the head dropped a little as soon as it was up, to be immediately raised by another jerk. This was the beginning of nodding which appears to be the result of muscular weakness and ataxia which interfered with the animal's ability to maintain a head-up posture. The fully developed nodding and side-to-side movements of the head regularly observed after intracisternal injections may also result from muscular weakness.

Catalepsy could be demonstrated by placing the rabbit in a nearly erect posture with its forepaws over a horizontal bar 20–24 cm high. It was not as pronounced as after intracisternal injections, for the animals maintained the abnormal posture for shorter periods of time.

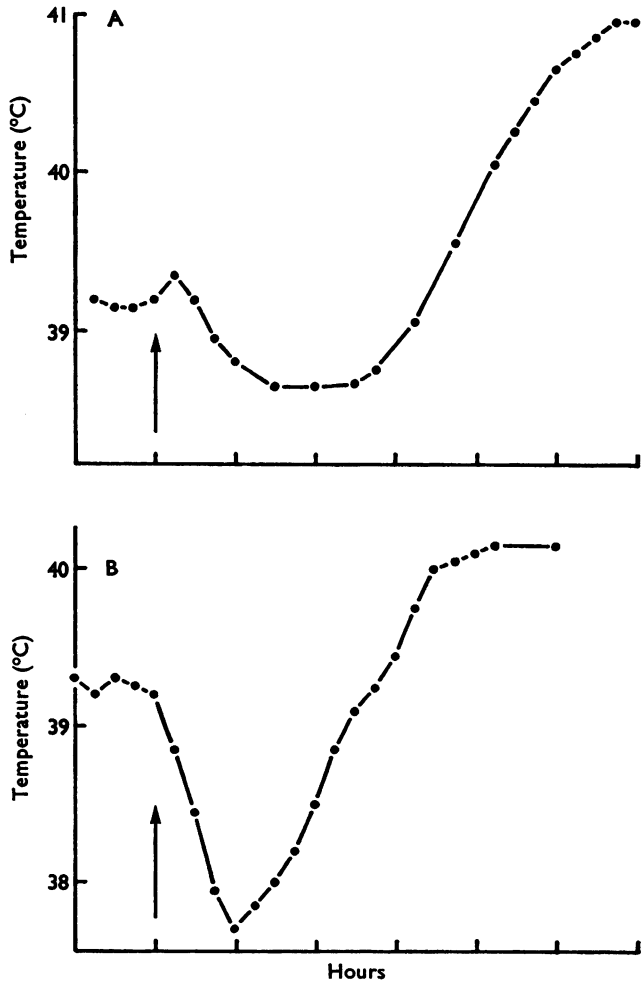

FIG. 3. Records of rectal temperature from two unanaesthetized rabbits. At the arrow in A, 1 mg, in B, 2 mg 5-HTP injected into the cannulated left lateral ventricle.

Intravenous injections of 5-HTP

The temperature effects obtained on injection of a few milligrams of 5-HTP into the cisterna magna or into a lateral cerebral ventricle cannot be attributed to a peripheral action of 5-HTP because even larger doses could be injected intravenously without affecting temperature. This is illustrated in Fig. 4 by the records B and C obtained from different rabbits, each weighing 2·3 kg. The amount of 5-HTP injected into each rabbit was 5 mg/kg, that is 11·5 mg. Before the injection temperature tended to rise in record B and to fall in record C. The rise in record B was interrupted by a transient fall of 0·2° C and the fall in record C continued after the injection.

Hyperthermia, however, was obtained when much larger doses of 5-HTP were injected intravenously. Record A of Fig. 4 shows a rise of 2·8° C following an injection of 70 mg/kg into the marginal ear vein. This result is in agreement with the observation of Horita & Gogerty (1958) who had obtained high, sometimes lethal, fever with 50–100 mg/kg, and of Pletscher, Besendorf, Bächtold & Gey (1959), who had obtained a mean rise of a little over half a degree with 10 mg/kg.

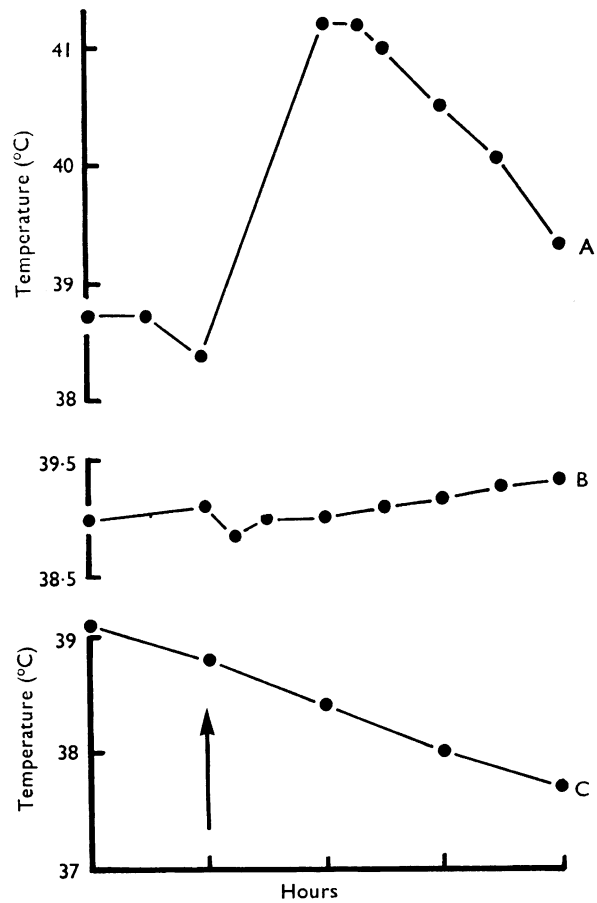

FIG. 4. Records of rectal temperature from three unanaesthetized rabbits, each weighing 2·3 kg. At the arrow, intravenous injection of 5-HTP, 70 mg/kg in A, and 5 mg/kg in B and C.

Injections of 5-HT into the cisterna magna

Cooper *et al.* (1965) obtained a fall in temperature when they injected 0·2 mg 5-HT into the cerebral ventricles of unanaesthetized rabbits. As illustrated in Fig. 5, a similar effect was obtained when this dose of 5-HT was injected into the cisterna magna. An injection of 0·2 ml saline solution had no effect in this rabbit (record A) but 0·2 mg 5-HT injected a few days later (record B) caused a fall of 0·6° C followed by a rise of about half a degree above the pre-injection level. Such an after-rise was not always obtained.

With larger doses of 5-HT the temperature responses varied from rabbit to rabbit. The responses to 4 mg are shown for three experiments in Fig. 6. In record A, the response consisted of a long-lasting fall followed by a rise above the pre-injection level. In record B the initial fall was interrupted during the first hour by two periods of rising temperature followed in the next 2·5 h by a steady fall from 39·4° to 37·8° C, whereas in record C the main effect was a rise.

The other effects produced by 5-HT also resembled those observed with intracisternal 5-HTP though not in every detail, and the described variations in temperature after the larger doses depended on which of these effects predominated. The fall in temperature was associated with maximal dilatation of the ear vessels. Following the injection of the smaller dose (0·2 mg) tachypnoea did not occur, there were no signs of reduced muscle tone and the ear vessels constricted during the return of temperature. Following the injection of the larger doses pronounced tachypnoea developed, the rate of respiration increased to more than 200 and sometimes to more than 250/min, muscle tone decreased and the ear vessels remained dilated for a few hours. With all doses there were rapid movements of the vibrissae with quivering of the nose, muscle tremor or shivering. Tremor was more pronounced than after cisternal injections of 5-HTP and was particularly strong in the anterior part of the body: when the rabbit was lifted off the ground by the scruff of its neck there was strong myoclonus-like tremor in the forelegs.

With larger doses, frequent short periods of flutter of the ears, with and without vigorous shaking of the head occurred regularly 10 to 20 min after the injection, whereas wiping of the face, licking of the forelegs and occasional scratching were late features. Several rabbits became extremely excited or restless shortly after the

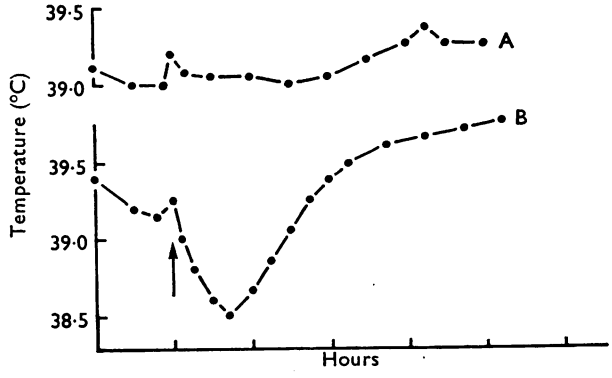

FIG. 5. Records of rectal temperature from an unanaesthetized rabbit, obtained on different days. At the arrow, injection into the cisterna magna of 0·2 ml 0·9% NaCl solution (A) and of 0·2 mg 5-HT (B).

injection. They struggled violently and, with jerking movements, tried to escape from restraint. This condition usually persisted for minutes only, but sometimes for up to an hour. The two initial rises in temperature which interrupted the fall in experiment B and Fig. 6 were associated with such periods of struggling and probably due to it; struggling probably contributed to the steep rise in experiment A of Fig. 6.

Reduction in muscle tone occurred either after the period of restlessness, or soon after the injection, while temperature was falling; it was particularly pronounced in the hind legs. The rabbit lay on its belly with its head resting on the table and its hind legs half or fully extended behind its body. When the animal moved it did so without lifting its body from the ground. With the return of muscle tone, the rabbit would sit up and adopt the position shown in Fig. 2. Nodding and side-to-side movements of the head were not as pronounced as with 5-HTP, the ears were not always laid back, the peculiar gaze was not regularly observed, and in contrast to the condition seen after 5-HTP, this position was not maintained continuously but for periods of several minutes only. Tremor and the vibrissae movements ceased earlier than after 5-HTP so that the rabbit would later sit motionless for an hour or longer with its neck slightly bent and its eyes half open. The ears remained hot.

When tested for catalepsy by placing its forepaws over a horizontal bar at a height of 20 or 24 cm, the rabbit remained in this nearly erect posture for several

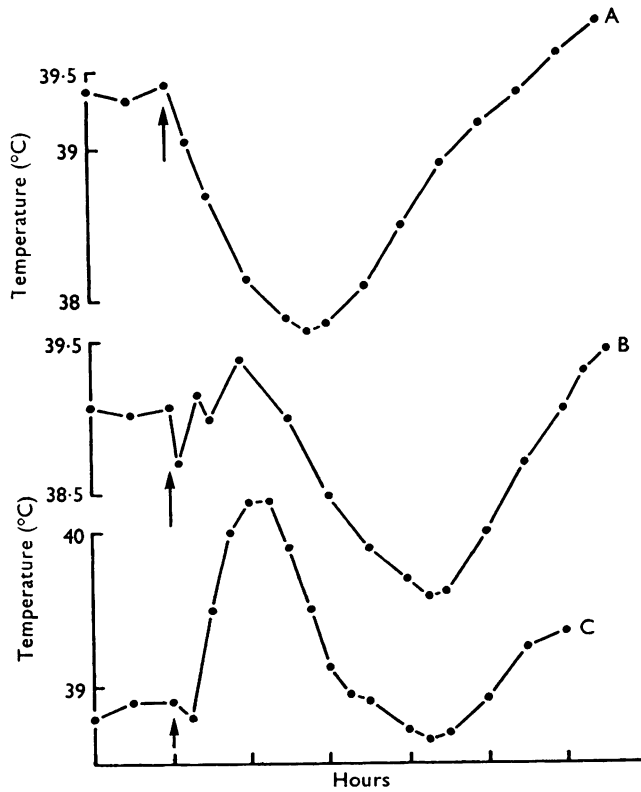

FIG. 6. Records of rectal temperature from three unanaesthetized rabbits. At the arrows, injection of 4 mg 5-HT into the cisterna magna.

minutes and when the paws slipped off and the rabbit moved away, it did so in a well co-ordinated manner. The test for catalepsy was positive before the rabbit resumed a sitting position and remained positive for some time after tremor and other movements had ceased.

Injections of bromophenol blue into the cisterna magna and into a lateral cerebral ventricle

Within a minute or two of the injections (0·1 or 0·2 ml), the ear vessels dilated and tachypnoea occurred; a few minutes later there were bouts of scratching, shaking of the head and wiping of the face. With intraventricular injections, scratching occurred more frequently on the left side—the side of injection—than on the right. The effects were still present 20–30 min after the injection when the rabbits were killed in pentobarbitone sodium anaesthesia in order to perfuse their brains with formalin.

Essentially the same pattern of staining was found as in previous experiments (Banerjee *et al.*, 1968). The main differences following an intracisternal or intraventricular injection were:

(1) The spread of the dye in the subarachnoid space along the spinal cord as well as along the ventral and lateral surface of the cerebrum was greater after intracisternal than after intraventricular injection. After an intracisternal injection of 0·2 ml of the bromophenol blue solution, the spinal cord was found to be stained as far down as the lower lumbar cord; after an injection of 0·1 ml the staining faded in the region of the lower thoracic cord, whereas following an intraventricular injection (0·1 ml dye solution washed in by 0·05 ml 0·9% NaCl solution) it faded in the region of the upper thoracic cord. Following the intracisternal injections, the pyriform cortex became stained and as the dye passed dorsally along the lateral surface of the cerebrum the parietal cortex also became stained. Following the intraventricular injections these regions were not stained. Otherwise the pattern of staining resulting from the dye in the subarachnoid space was the same with both kinds of injection, with particularly deep staining of the outer surface of the walls of the third ventricle around the infundibulum, and of the olfactory bulbs, the most anterior part of the brain.

(2) Following the intracisternal injections, the dye did not enter the cerebral ventricles, their walls were not stained, but if the outer surface of the parietal cortex was deeply stained some of this dye shone through the thin lateral wall of the inferior horn. Following the intraventricular injection, the walls of the third ventricle, aqueduct and fourth ventricle were deeply stained. The staining in the two lateral ventricles differed in intensity. In the left (the side of injection) the walls in front of the cannula—that is in the anterior horn, particularly the caudate nucleus—were stained more deeply than the walls behind the cannula—that is in the inferior horn. The walls of the right lateral ventricle were stained faintly, or not at all.

Discussion

For the effects obtained in the present experiments on injection of 5-HTP and 5-HT into the cisterna magna or into the cerebral ventricles of unanaesthetized rabbits, a peripheral action of these substances can be excluded because they were injected in doses too small to be effective when given intravenously.

The temperature responses to injections of 5-HTP and 5-HT into the cisterna magna differed somewhat from those obtained by Canal & Ornesi (1961). These authors stressed the hyperthermic response to these injections, although it is evident from one of their published temperature records that the rise was preceded by a fall during the first 1·5 hours. The results of the present experiments confirm the hyperthermic action of cisternal injections of 5-HTP and 5-HT, but show that this is not the only effect. The injections nearly always produced first a fall in temperature ; in some experiments, particularly with the smaller doses, a fall was the sole or main effect. In other experiments, however, particularly with the larger doses, the fall was not pronounced and was followed by an intense, sometimes lethal, hyperthermia. From the present results it would thus appear that 5-HTP and 5-HT have a two-fold effect on temperature when injected intracisternally: a temperature lowering effect more readily obtained with smaller and a temperature raising effect more readily obtained with larger doses.

For the effects obtained with intraventricular injections, the same conclusions can be drawn because the effects as far as they have been examined resembled those obtained on intracisternal injection. In the present experiments the intraventricular route was used only for 5-HTP which, administered in this way, usually produced a fall followed by a rise. With 5-HT, Cooper *et al.* (1965) obtained a temperature lowering effect when they injected it in a dose of 0·2 mg intraventricularly, and in the present experiments the same dose given intracisternally also produced a fall. Thus when the temperature effect of the same dose is compared, 5-HT does not appear to act differently when injected intraventricularly or intracisternally.

Cooper *et al.* (1965) have shown that in rabbits, 5-HT lowers temperature when injected directly into the anterior hypothalamus, which must also be the site where 5-HT acts when injected intraventricularly and penetrates the walls of the third ventricle. It can be assumed that 5-HTP acts at the same site when lowering temperature on intraventricular injection. Although a direct 5-HT-like effect of the acid on the central thermoregulatory mechanisms cannot be excluded, it probably acts mainly if not wholly after having been converted into the amine by the dopa decarboxylase or the aromatic-l-amino acid decarboxylase which is known to be present in high concentration in the hypothalamus and in the brain stem (Gaddum & Giarman, 1956 ; Bogdanski, Weissbach & Udenfriend, 1957, 1958 ; Kuntzman, Shore, Bogdanski & Brodie, 1961).

The temperature lowering effect of intracisternal 5-HTP and 5-HT can also be explained by an action on the anterior hypothalamus, although substances injected in this way do not enter the cerebral ventricles. However, from the deep staining around the infundibulum found after intracisternal injections of bromophenol blue we may conclude that they penetrate the ventricular wall deeply enough from the outer surface of the brain to reach the 5-HT sensitive cells in the anterior hypothalamus.

The rise in temperature obtained by the intraventricular and intracisternal injections may be due to either an action on some other part of the hypothalamus reached both from the cerebral ventricles and the subarachnoid space, or to an action on superficial structures in the brain stem or even in the spinal cord reached in both conditions from the subarachnoid space. The present experiments do not distinguish between these two possibilities. If the action were on brain stem or spinal cord structures, it would be readily explained on the assumption that 5-HT

is a transmitter not only of neurones ending on the cells in the anterior hypothalamus which, when acted upon by 5-HT, cause a fall in temperature in the rabbit, but also of interneurones lying in the central pathway for the temperature raising mechanisms activated from the anterior hypothalamus. The cells innervated by these interneurones would naturally be sensitive to 5-HT. There is yet another possibility in that the 5-HT is acting at synapses not lying in the central pathway of the temperature regulating mechanisms. Part of the hyperthermia is certainly explained by the muscular activity of the struggling, excitation and convulsion, and is thus not mediated by an action on the temperature regulating centres or pathways. The hyperthermic effect produced when much larger doses of 5-HTP are injected intravenously is probably due to an action on the same structures in the central nervous system on which 5-HTP and 5-HT act when producing their hyperthermic effects on intracisternal injection.

The tachypnoea as well as behavioural effects obtained with 5-HTP and 5-HT must be attributed to an action on structures which can be reached from the subarachnoid space because they were obtained not only on intraventricular but also on intracisternal injection. Again the possibility cannot be excluded that 5-HTP has a direct action and that some of the effects observed are independent of its decarboxylation to 5-HT.

The tachypnoea may result from an action on the chemosensitive structures at the ventro-lateral surface of the medulla from where profound respiratory changes are produced by various drugs (Loeschke & Koepchen, 1958 ; Mitchell, Loeschke, Massion & Severinghaus, 1963).

Ear twitching, shaking of the head, wiping and scratching movements are obtained in response to intraventricular and intracisternal injection of such widely different substances as morphine (Mehes, 1938 ; Königstein, 1939 ; Banerjee, Feldberg & Lotti, 1968), anticholinesterases (Kelen & McEachern, 1949), tubocurarine and bromophenol blue (Feldberg & Fleischhauer, 1960b ; Domer & Feldberg, 1960). With nicotine only ear twitching but no wiping or scratching movements are obtained (Hall & Reit, 1966 ; Armitage, Milton & Morrison, 1966). In all instances in which the site of action for these motor effects was examined, the drugs were found to act on superficial structures in the upper cervical cord. With 5-HTP itself, wiping and scratching movements had hitherto been observed only in unanaesthetized cats on intraventricular injection (El Hawary & Feldberg, 1966). The fact that in the present experiments these movements occurred more regularly on intraventricular than on intracisternal injection of 5-HTP may be due to the fact that the structures from which these movements are elicited lie in the direct pathway of substances as they pass from the ventricle through the foramina of Luschka into the subarachnoid space, whereas when injected intracisternally they spread more uniformly within this space.

The catalepsy must also be attributed to an action on superficial structures which can be reached from the subarachnoid space and which are either activated or paralysed by 5-HTP and 5-HT. The same explanation applies to the ataxia which may be the cause also of the nodding and sideways movements of the head.

Catalepsy can be obtained by a number of substances injected intraventricularly or intracisternally, and in a previous paper (Banerjee *et al.*, 1968) the site on which these substances act has been discussed for the catalepsy produced by morphine.

It was pointed out that catalepsy is produced not only by drugs but also by discrete lesions of brain stem regions, and as these regions are readily reached by substances penetrating the brain from the ventral part of the third ventricle and from the interpeduncular cisterna of the subarachnoid space, they are probably also those on which drugs act when producing this condition on intraventricular and intracisternal injections. It was also pointed out that some of the actions of morphine may result from release of 5-HT. However, apart from the fact that 5-HT produces catalepsy, as shown in the present experiments, there is no evidence that this is the mechanism by which morphine produces catalepsy.

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