THE ONSET OF ABSORPTION OF HISTAMINE INJECTED INTO THE LATERAL CEREBRAL VENTRICLES OF CATS

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It has been shown that histamine (μ 500) injected into the lateral cerebral ventricle of the cat gets partly absorbed within 20 minutes into the general blood circulation as evidenced by the production of acid gastric secretion after its intraventricular injection (Bhawe, 1958). It was assumed that the histamine had passed into the endocranial venous sinuses from the ventricles via the subarachnoid space.

Subsequently it was shown by Draskoci *et. al.*, (1960) that histamine also passes into the blood stream from the cerebral ventricles without entering the subarachnoid space. In addition, these authors showed that a part of histamine was taken up by the brain tissue and the choroid plexus.

In view of the foregoing findings, it was thought that more information on the time course of absorption of the intraventricularly injected histamine would be desirable since that might indicate the possible pathways of its passage. An attempt was therefore made to find out how soon within these 20 minutes after intraventricular injection, does histamine get absorbed into the blood circulation.

METHODS

Anaesthetised cats (ether followed by intraperitoneal pentobarbitone sodium 35 mg/kg) weighing between 2.5 and 3 kg. (except one which weighed l. 7 kg) were used. Cannulation of the ventricle was done by using the Collison cannula for intraventricular injection described by Feldberg and Sherwood (1953) with slight modification, as described by Bhawe (1958). At the end of every experiment it was confirmed that the cannula was in the correct position, by injection of the dye and postmortem examination.

Histamine acid phosphate (500 μg base) in 0.25 ml. of normal saline was slowly injected intraventricularly followeds after about 20 second by another slow injection of 0.25 ml. of saline.

Collection of Samples of gastric secretion and estimation of their free HCl. content: Procedure described by Edkins (1906) was followed. Food was witheld from the cats for 24 hours prior to the experiment. Abdomen was opened and duodenum was tied off about 2 cm. below the pylorus. A polythene tube bearing multiple perforations in the sides of the end portion was introduced into the stomach through a small cut in the anti mesenteric border of the doudenum, below the pyloroduodenal junction. The stomach was washed out several times with 10 ml. of warm saline solution introduced through the polythene tube and removed with a pipette and then filled with 10 ml. of warm saline solution. The free end of the polythene tube was closed by a light clamp and the solution allowed to remain in the stomach for 2 minutes (in the case of first 6 samples). It was then removed and replaced with another 10 ml. of saline solution. This procedure was repeated every 2 minutes (in the case of first six samples extending over 12 minutes) and the samples were titrated for their free HCl content against 0.01 N. Na OH solution using Topfer's reagent as the indicator. In the case of the last 2 samples the saline solution from the stomach was drawn after 3 minutes and 5 minutes respectively. Thus, the first 6 samples were taken every 2 minutes, 7th. sample after 3 minutes and the 8th. sample after 5 minutes, i. e. in all 8 samples were taken within the first 20 minutes after intraventricular injection. Cats showing histamine-fast achlorhydria (three) were discarded.

The arterial blood pressure from the carotid artery was recorded during the experiment.

RESULTS

The results of 9 experiments are summarised in the Table No. 1. In 4 experiments, (experiments No. 1, 4, 6, and 7 in the Table) inspite of repeated washings, some slight acidity persisted in the stomach before injecting histamine intraventricularly and this has been shown under the column of initial acidity in the Table.

In all the experiments except one (No. 9) the acidity appeared (or considerably increased if there was some slight initial acidity) in the gastric secretion within 2 minutes after intraventricular injection of histamine. In experiment No. 9, the appearance of acidity was delayed at least upto 12 minutes.

TABLE I

Free gastric acidity in ml. of 0.01 N. HCl in samples drawn after various intervals during the first 20 minutes after intraventricular injection of 500μg of Histamine in cats

Experiment No.	Initial acidity ml.	Samples drawn after 2 min. ml.	4 min. ml.	6 min. ml.	8 min. ml.	10 min. ml.	12 min. ml.	15 min. ml.	20 min. ml.
1	0.05	0.2	0.3	0.8	1.25	1.35	Lost accidentlly		6.0
2	Nil.	0.2	0.3	0.4	0.6	1.00	1.6	2.4	3.2
3	Nil.	0.8	2.4	3.2	3.2	3.2	3.6	4.0	4.8
4	0.1	0.6	0.8	1.2	1.8	1.8	2.0	1.8	2.2
5	Nil.	0.36	0.54	0.54	0.8	0.9	1.4	1.6	2.0
6	0.2	0.3	0.4	0.4	0.72	0.8	1.0	1.44	2.2
7	0.08	0.2	0.4	0.54	1.0	1.2	1.2	1.62	2.0
8	Nil.	0.022	0.14	1.47	3.3	3.43	3.8	3.8	3.47
9	Nil.	Nil.	Nil.	Nil.	Nil.	Nil.	Nil.	0.19	0.19

On the whole, the aciditys howed a progressive increase in the successive samples, as reported previously (Bhawe 1958). Two samples (12 minutes and 15 minutes) in experiment No. 1 were lost accidentally.

The blood pressure changes following intraventricular injection were not any different from those described earlier by Bhawe (1958).

DISCUSSION

It has already been shown that the absorption of intraventricularly injected histamine into the general blood circulation begins within the first 20 minutes after the injectcion as indicated by acid gastric secretion in the first 20 minute sample (Bhawe 1958). It was assumed that the histamine had passed from the lateral ventricles into the subarachnoid space and then into the endocranial venous sinuses. Less than half of the injected histamine (between 18% and 45% of the 500 μg injected) was absorbed in this way over a period of some hours (2 to 5).

Recently Draskoci *et. al.* (1960) showed that the histamine also passed into the blood stream from the cerebral ventricles without entering the subarachnoid space. They perfused the histamine solution (1 : 1000 and 1 : 10,000) through the lateral and third ventricles and collected the effluent from a cannula inserted into the aqueductus Sylvii as described by Bhattacharya and Feldberg (1956) thus excluding the fourth ventricle and the subarachnoid space. This perfusion also resulted in acid gastric secretion. They removed the samples of acid gastric secretion every 20 minutes. They found that during 1 hour perfusion with 6000 μg (1:1000 solution of histamine) or with 600 μg (1 : 10,000 solution) not more than 100 μg or 10 μg respectively could have entered the circulation. Thus not more than 1.66% of the perfused histamine got absorbed in this way. They, in addition, observed that histamine is also absorbed from the subarachnoid space since it produced acid gastric secretion when infused into cisterna magna under conditions in which its entrance into the cerebral ventricles was prevented. Here also it appears that samples of acid gastric secretion were collected every 20 minutes. They further showed that during the one hour perfusion of lateral ventricles with histamine, only a small part (i. e. 100 μg out of 6000 μg) was taken up by the brain tissue.

Before one is able to speculate about the various possible routes of absorption of the intraventricularly injected histamine, some more information on the time-course of absorption of the intraventricularly injected histamine is desirable. How soon after injection, does the absorption begin?

In the present series of 9 experiments, 8 showed that absorption of the intraventricularly injected histamine began within first two minutes after injection. (In one experiment however, the appearance of acidity was delayed at least upto 12 minutes for which no explanation can be offered at present : the cat used in this experiment weighed much less i. e. 1.7 kg. and was young). If one could further narrow down the range and find out how soon within these first two minutes does the absorption begin, that information would be useful. It would be pertinent to obtain similar information about the histamine that is absorbed into the blood stream from the cerebral ventricles without entering the subarachnoid space.

Absorption of intraventricularly injected substances may be a matter of seconds but it may as well not be in view of the 'barrier's if they exist.

Dandy and Blackfan (1913) showed that intraventricularly injected phenolsulphonephthalein appeared in urine within 10 to 12 minutes after injection. When the same dye was injected by them into the subarachnoid space, it appeared in the blood within 3 minutes and in the urine within 6 minutes.

Dixon and Haliburton (1916) found that atropine, histamine, adrenaline, nicotine and pituitary extract injected into the cisterna magna of dogs produced systemic peripheral effects within a very short time, sometimes as quickly as after an intravenous injection. Salicylates and methylene blue injected by them into the cisterna magna were detected within a few minutes in the venous blood of heart. Criticism against these findings came from Bacht (1920) because entirely different results were obtained by Meltzer and Auer (1911) and by Meltzer (1918) in monkeys after intracisternal injection of adrenaline and by Bacht himself after intracisternal injection of adrenaline and nicotine in anaesthetized dogs. The characteristic pressor effects seen with these drugs after intravenous injection did not occur after intracisternal injection. Bacht thought that Dixon and Haliburton's technique was faulty and their results were not valid. On the other hand, Wallace and Brodie (1940 a, 1940 b), injected sodium salt, iodide and bromide into the cisterna magna of dogs and detected them in blood within 13 minutes to 4 hours after injection. Rodrigues (1955) injected the fluorescent dye proflavine into the cisterna magna or into the lateral ventricles of cats, rabbits and rats and demonstrated its absorption into blood stream. Gaitonde (1961) has observed increased acid gastric secretion within 5 minutes of intraventricular injection of histamine in cats. Wustmann (1934) could detect thorium in the blood of sagittal sinus, 2 minutes after intracisternal injection of thorotrast.

Experiments using radioactive histamine may yield more precise information regarding the onset of absorption after intraventricular injection. Bakay and Lindberg (1949) found that P^{32} could be detected in blood within one minute after its intracisternal injection in rabbits. Sweet and Locksley (1953) in their study on two patients with brain tumours (in whom they could isolate the ventricular compartment from the subarachnoid space) found that isotopes K and Cl injected into subarachnoid space passed quickly into the blood stream. They even found a quick absorption of these ions into blood stream when injected into the isolated ventricles and assumed an absorption through the choroid plexus.

Absorption of intraventricularly injected substances may depend on a number of factors including the nature of the substance, its molecular size, etc. Histamine may not behave in the same way as an electrolyte so far as the absorption is concerned. Dixon and Haliburton in their experiments cited above, found that absorption of secretin from the subarachnoid space was much less and larger molecules like Witte's peptone or protein did not enter the blood stream from the subarachnoid space or entered with great difficulty. On the other hand Sweet and Locksley (1953) in their study mentioned above, found that protein (radio iodinated human serum albumin) injected into the subarachnoid space passed through the villi into the blood stream but if injected into the isolated ventricle, it behaved differently from the electrolyte and remained in the ventricle.

Our work described above indicates an approach to the problem and represents an attempt in the direction under a given circumstance. In our series a large dose of histamine (500 μg) was used. Draskoci *et al* (1960), also have used large doses. Gaitonde (1961) has observed an effect on acid gastric secretion of cats following 10 μg of histamine (base) administered intraventricularly and in a few cases even after 2 μg. It would be worthwhile confirming this observation and pursuing the work with such smaller doses and also finding out the smallest dose for intraventricular injection that evokes acid gastric secretion.

SU MMARY

In the present series of 9 experiments on cats, 8 experiments show that absorption of the intraventricularly injected histamine into blood stream begins within first two minutes after the injection.

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