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THE CENTRAL VASOMOTOR EFFECTS OF 5-HYDROXYTRYPTAMINE

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In the dog, injection of 5-hydroxytryptamine into the cerebral ventricles caused hypotension, inhibition of the pressor response to occlusion of the carotid artery and inhibition of the pressor or depressor response evoked by electrical stimulation of the central end of the cut vagus. Hypotension and inhibition of the vagal vasomotor response also occurred in dogs in which the carotid sinuses had been denervated and the vagi cut. The site of action was central. Local cerebral vascular changes could not have been responsible for the action. The central vasomotor effects of 5-hydroxytryptamine are mediated through the sympathetic outflow. Implications of these findings are discussed in relation to the effects of intravenous 5-hydroxytryptamine and the mechanism of action of reserpine.

Feldberg and Sherwood (1954) studied the effects of drugs introduced into the ventricular system of cats through an implanted metallic cannula. Using a simple polyethylene cannula for injecting drugs into the lateral cerebral ventricles of dogs, we have studied the central vasomotor effects of 5-hydroxytryptamine in this species.

It is generally believed that the quantity of 5-hydroxytryptamine which penetrates the blood-brain barrier after parenteral administration is too small to produce central effects. However, a measurable rise of brain 5-hydroxytryptamine occurs on parenteral administration into mice (Shore, Pletscher, Tomich, Carlsson, Kuntzman, and Brodie, 1957). In this species an intraperitoneal injection of 5-hydroxytryptamine produces, like reserpine, general depression of muscular activity, sedation, and potentiation of the hypnotic action of barbiturates and ethanol (Shore, Silver, and Brodie, 1955). A direct inhibition of central synaptic transmission was observed by Marrazzi and Hart (1955) after the intracarotid injection of small doses of 5-hydroxytryptamine into cats, and Malcolm (1958) showed that intracarotid injection of 5-hydroxytryptamine into cats depressed the cortical response evoked by sensory nerve stimulation, but only with large doses. There are a few observations which show that 5-hydroxytryptamine, by a central action, can influence blood pressure and its responses. Bhargava and Borison (1957) found that, in cats, pressor responses elicited by threshold electrical stimulation of the medulla oblongata were depressed by large doses of 5-hydroxytryptamine given intravenously. The effect was similar to that after reserpine. Costa and Aprison (1957) observed in cross-circulation experiments that perfusion of the isolated head with 5-hydroxytryptamine caused a fall of arterial blood pressure in the recipient. A central depressor action of 5-hydroxytryptamine had previously been suggested by Ginzel and Kottegoda (1954) to explain the depressor effect obtained on its injection into the subclavian artery.

The present experiments show that 5-hydroxytryptamine injected into the cerebral ventricles of dogs caused a fall in arterial blood pressure, probably due to inhibition of sympathetic vasoconstrictor tone and, in addition, it inhibited the blood pressure responses produced by carotid occlusion and by central vagal stimulation.

METHODS

Dogs were anaesthetized with 30 mg./kg. of pentobarbitone sodium given intravenously. Usually both vagi were cut in the neck and the animals were maintained on artificial ventilation. Blood pressure was measured by means of a mercury manometer connected to the left carotid artery.

Reflex vasomotor responses were evoked by occlusion of the right common carotid artery or by electrical stimulation of the central end of a cut vagus nerve. A tubular electrode consisting of a 2 cm. long

polyethylene tube of 5 mm. bore in which platinum wires were embedded was used to stimulate the nerve. The stimuli were obtained from a Stoelting Electronic Stimulator delivering rectangular pulses. The nerve was kept under a pool of medicinal liquid paraffin.

Injections into the lateral cerebral ventricles were made through a polyethylene cannula introduced into a ventricle soon after the animal was anaesthetized. The cannula was 5 cm. long and 2 mm. in bore. The tube was passed through the centre of a pliable metal plate and fixed rigidly to the plate with the inner end projecting 1.5 cm. below it. Two holes were provided on the metal plate to screw it on the skull. A suitable incision of the scalp was made to expose the parietal bone. A burr hole (2 mm. in diameter) was made into the bone at a point 5 cm. rostral and 3 cm. lateral to the occipital protuberance. The dura was punctured through the burr hole and the inner end of the cannula was passed anteromedially into the lateral cerebral ventricle. The metal plate was then screwed snugly on the bone. To ensure further against leakage, a paste made of plaster of Paris was used to seal the plate on to the bone. The small amount of cerebral tissue which entered the cannula was sucked out. The correct placing of the cannula was indicated by the appearance of cerebrospinal fluid on suction. Pulsations of the cerebrospinal fluid could be observed through the transparent plastic cannula. Not more than 1 ml. of drug solution was injected into the ventricle at any one time. At the end of the experiment the position of the cannula was confirmed by cutting a coronal section of the head at the level of the cannula.

Effects of intraventricular injection of drugs were observed on the systemic blood pressure. The effect of a drug was considered valid only when followed by recovery to control values.

Freshly prepared solutions of 5-hydroxytryptamine creatinine sulphate (*p*H 6.5) were used.

Results

Blood Pressure Changes after 5-Hydroxytryptamine.—It is well known from the experiments of Page and McCubbin (1953) that, in dogs, an intravenous injection of 5-hydroxytryptamine causes an initial fall followed by a transient rise with finally a secondary prolonged fall in blood pressure. These three phases occurred in the present experiments on intravenous injection of 5-hydroxytryptamine (1 mg. in dogs weighing about 12 kg.). Intraventricular injection of 5-hydroxytryptamine, on the other hand, caused only a prolonged fall in arterial blood pressure. In a dog of about 12 kg., 1 to 2 mg. of 5-hydroxytryptamine caused a fall of 25 to 50 mm. Hg, and 0.5 mg. a fall of about 10 mm. Hg. These average values were calculated from the results of thirty-six injections. A more pronounced depressor effect was obtained with intraventricular 5-hydroxytryptamine when the carotid sinuses were denervated and the vagi cut. Then a dose of 0.5 mg. produced about the same effect as 1 mg. in a dog with normally innervated carotid sinuses.

The depressor action of intraventricular 5-hydroxytryptamine is probably due to central inhibition of sympathetic vasoconstrictor tone, since it no longer occurred when the autonomic

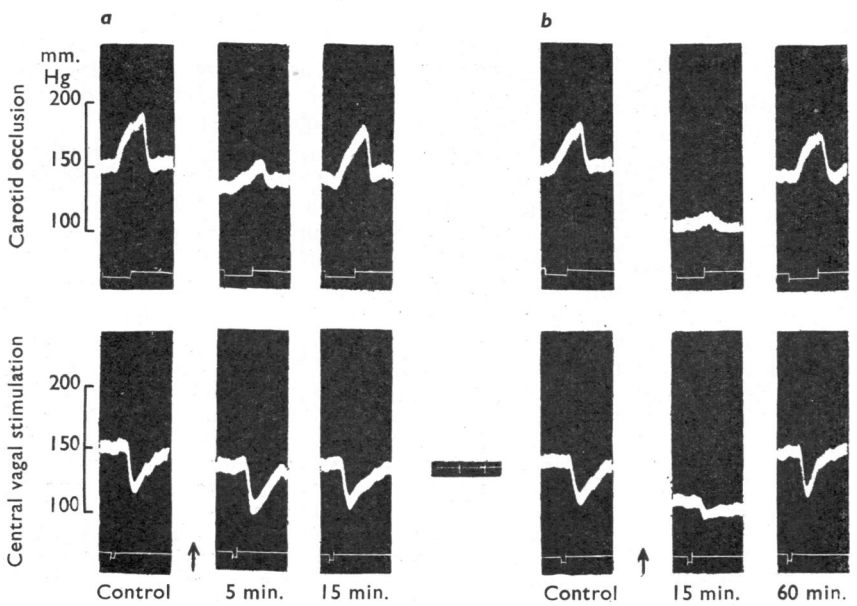

FIG. 1.—Dog, 12.5 kg. Blood pressure records. Comparison of effects of, *a*, intravenous and, *b*, intraventricular injections of 1 mg. of 5-hydroxytryptamine respectively at the arrows on the pressor response to carotid occlusion (upper records) and depressor response to electrical stimulation (30 V., 240/sec.) of afferent vagus nerve (lower records). Note the marked fall in blood pressure and the inhibition of both vasomotor responses on intraventricular administration at 15 min. Time, 1 min.

ganglia were blocked by an intravenous injection of 1 mg./kg. of pentolinium or when the vessels were rendered insensitive to the transmitter of the adrenergic vasoconstrictor fibres by the intravenous injection of 2 mg./kg. of hydrallazine. The presence of ganglionic block after pentolinium was confirmed by the absence of retraction of the nictitating membrane in response to electrical stimulation of the preganglionic cervical sympathetic nerve.

The centrally-induced hypotension produced by intraventricular 5-hydroxytryptamine is unlikely to be due to local vasoconstriction of cerebral vessels, since certain vasoconstrictor and vasodilator agents, when given intraventricularly. did not significantly change the arterial blood pressure nor did they modify the vascular reflexes. The substances tested were noradrenaline (5 μg. to 1 mg.), vasopressin (2 to 4 units) and histamine (50 to 750 μg.).

Effects of 5-Hydroxytryptamine on Vascular Reflexes.—Fig. 1 shows the effect of 1 mg. of 5-hydroxytryptamine given intravenously and intraventricularly in the same dog on the pressor response to occlusion of the carotid artery and on the depressor response to central vagal stimulation. During the secondary depressor phase, about 5 min. after the intravenous injection, the pressor response to the occlusion of the carotid was greatly reduced, but the depressor response to central vagal stimulation was unchanged. About 15 min. after the injection, the pressor response to occlusion of the carotid had recovered. When both tests were carried out about 15 min. after the intraventricular injection when the blood pressure was still low, both the pressor response to carotid occlusion and the depressor response to central vagal stimulation were abolished. Recovery of both responses was complete in 1 hr.

When the carotid sinuses were denervated and the vagi cut, electrical stimulation of the central end of the left vagus elicited a pressor response which was greatly reduced when the vagus was again stimulated 15 min. after an intraventricular injection of 0.5 mg. of 5-hydroxytryptamine. Recovery was complete after 1 hr. (Fig. 2).

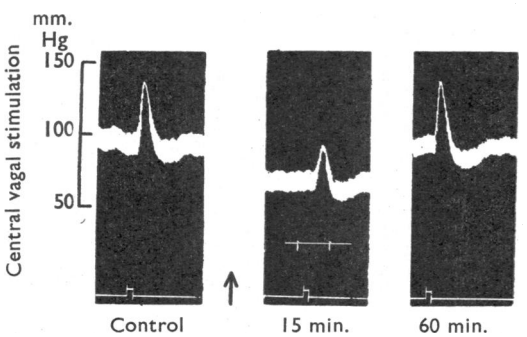

FIG. 2.—Dog, 12.0 kg. Carotid sinus and vagus nerves cut. Record of blood pressure. Effect of intraventricular injection of 0.5 mg. of 5-hydroxytryptamine at the arrow on pressor response to electrical stimulation (7 V., 60/sec.) of central cut end of vagus nerve. Note the fall in blood pressure and diminution of the vagal response at 15 min. Recovery complete at 60 min. Time, 1 min.

DISCUSSION

Ginzel (1958) failed to observe vasomotor effects on intraventricular injection of 5-hydroxytryptamine into cats in doses comparable to those employed in the present experiments on dogs. This may be due to a species difference. In dogs, hypotension occurs regularly on intraventricular injection of 5-hydroxytryptamine but only with relatively high doses. These doses abolish reflex pressor and depressor responses. A direct neuronal action of 5-hydroxytryptamine is assumed to be responsible for these central effects. The existence of a local vasoconstrictor action on the brain vessels is unlikely because intraventricular noradrenaline, vasopressin and histamine did not influence the arterial blood pressure nor did they affect the vascular reflexes.

The effects of intraventricular 5-hydroxytryptamine, namely the hypotension as well as the abolition of the reflex blood pressure responses to carotid occlusion and to central vagal stimulation, suggest depression at the brain stem level, probably on the vasomotor centres. That these effects no longer occur when the autonomic ganglia are blocked or the vessel wall is rendered insensitive to the mediator of adrenergic sympathetic fibres by hydrallazine shows that the depressant effect of 5-hydroxytryptamine is exerted via the sympathetic outflow.

After intravenous injection of 5-hydroxytryptamine the response to central vagal stimulation remained unimpaired, whereas the response to carotid occlusion was greatly reduced. It is unlikely that this effect of 5-hydroxytryptamine is also due to central depression, because it would then be difficult to explain the unchanged response to central vagal stimulation. The depression of the response to carotid occlusion on intravenous injection of 5-hydroxytryptamine is probably due to its action on the carotid sinus receptors which are known to be vulnerable to this drug when given intravenously (Ginzel and Kottegoda, 1954).

Centrally-induced inhibition of sympathetic vasoconstrictor tone, which appears to be the

cause of the prolonged fall in arterial pressure on intraventricular injection of 5-hydroxytryptamine, may well produce the secondary prolonged hypotension when this substance is injected intravenously. This hypotension has never been satisfactorily explained and, although it is generally assumed to be due to a peripheral action of 5-hydroxytryptamine, the evidence for this assumption is anything but convincing. Page and McCubbin (1956) attributed this hypotension to peripheral inhibition of neurogenic vasoconstrictor tone. They were able to block the effect with large doses of promethazine and thus considered release of endogenous histamine to be a contributory factor in the causation of the hypotension. However, promethazine in large doses also abolishes adrenergic nerve effects (Gengoux, 1956). On the assumption that the hypotension results from centrally-induced inhibition of vasoconstrictor tone this property of promethazine would also explain why it prevents the hypotension. Furthermore, histamine release has actually been excluded as a possible mechanism since Reid (1952) found that the hypotension was not prevented by diphenhydramine or mepyramine. In his opinion, the cause for the hypotension has not been satisfactorily elucidated, but by elimination he assumes that it may result from impaired performance of the cardiac muscle as a result of coronary arterial constriction. It seems to us more likely that central inhibition of vasoconstrictor tone is responsible for both the hypotension after intraventricular injection of 5-hydroxytryptamine and the secondary prolonged hypotension after its intravenous injection. This view is strengthened by the fact that a centrally-induced hypotension is also observed when the 5-hydroxytryptamine is injected into the subclavian artery (Ginzel and Kottegoda, 1954) or when the head is perfused with it in cross-circulation experiments (Costa and Aprison, 1957).

Reserpine is known to release 5-hydroxytryptamine from the brain in addition to other sites (Pletscher, Shore and Brodie, 1956) and the hypotension produced by reserpine has been shown to correspond well with this action (Deming, Bogdanski, Udenfriend, Shore and Brodie, 1956). That 5-hydroxytryptamine in the cerebrospinal fluid is capable of inducing hypotension by a central action suggests the possibility that, when reserpine releases 5-hydroxytryptamine from the brain, the free 5-hydroxytryptamine acts directly on the vasomotor centre and depresses it.

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