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THE ACTION OF 5-HYDROXYTRYPTAMINE ON PULMONARY AND CARDIOVASCULAR VAGAL AFFERENT FIBRES AND ITS REFLEX RESPIRATORY EFFECTS

BY

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The identification of 5-hydroxytryptamine with serotonin (Rapport, 1949) made it of interest to examine further its respiratory effects in cats. Reid and Rand (1951) have reported that 5-hydroxytryptamine may cause apnoea in cats, and Douglas and Toh (1952) found that, in dogs, this compound stimulated the chemoreceptors of the aortic arch and carotid body. Phenyl diguanide also has been shown to cause a reflex inhibition of the respiratory movements, abolished by vagotomy, in cats. This is due to an action on receptors in the lungs (Dawes, Mott, and Widdicombe, 1951). Phenyl diguanide also stimulates the chemoreceptors of the aortic arch and carotid body in dogs (Dawes, Mott, and Widdicombe, 1952). Further, this compound stimulates certain vagal afferent nerve fibres which are normally quiescent and whose mean conduction velocity is 6 m./sec. (Paintal, 1953c). This low conduction velocity corresponds with the low temperature (below 3° C.) to which the vagi must be cooled to block the respiratory reflex. It seemed possible that the apnoea caused by 5-hydroxytryptamine in cats might be a reflex due to the stimulation of those receptors which are stimulated by phenyl diguanide and other amidine compounds. Reid (1951) found that the apnoea caused by tryptamine in cats was abolished by vagotomy, but Page (1952) states that the respiratory effects of 5-hydroxytryptamine are not modified by vagotomy.

METHODS

The experiments to be described were performed on cats of 2.1–3.3 kg. in weight, anaesthetized with chloralose (60–80 mg./kg. body weight).

The technique of dissecting single units of the vagus and determining their conduction velocity has been described elsewhere (Paintal, 1953b). The right venous pressure was recorded with a semirigid catheter passed down the external jugular vein and connected to a saline-filled capacitance manometer. Intrapleural pressure was recorded with a wide-bore needle connected to a mirror membrane manometer. The electrocardiogram (lead 1) was recorded, using a condenser-coupled amplifier and cathode-ray oscilloscope. Various kinds of afferent fibres were dissected and, after identification, 5-hydroxytryptamine was injected intravenously into the femoral vein while the activity of the fibre was being recorded. The phenyl-diguanide-sensitive fibres were isolated by a method to be described elsewhere (Paintal, 1953c), and the effect of 5-hydroxytryptamine on them was tested by injecting the drug about 15 minutes after the injection of 100 μg. phenyl diguanide.

Carotid blood pressure was recorded by a mercury manometer. The left auricular appendage was cannulated in six cats, and the vagi prepared for cooling in three cats; the respiratory movements were recorded by a body plethysmograph (Dawes, Mott, and Widdicombe, 1951), and the 5-hydroxytryptamine was injected intravenously into a jugular vein. All doses are in terms of 5-hydroxytryptamine. The depressor effect of this compound was found to be very great. In order to obtain apnoea without too much cardiovascular disturbance, it was necessary to give atropine 1 mg./kg. body weight.

RESULTS

Localization of Receptor Area.—In six cats equal doses of 5-hydroxytryptamine were injected alternately intravenously and into the left atrium, and the effects on the respiratory movements observed. In four cats 45–90 μg. of 5-hydroxytryptamine caused apnoea (almost always in the expiratory position) when injected intravenously, but not when injected into the left atrium; this inhibition of the respiratory movements was abolished by vagotomy (Fig. 1). In a fifth cat, on one occasion, 22.5 μg. of 5-hydroxytryptamine, injected into the left atrium, failed to cause inhibition of respiratory movements, although this

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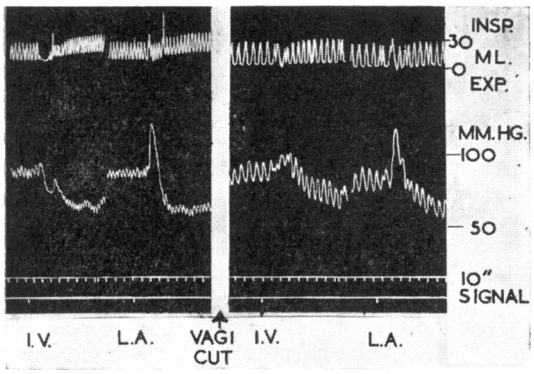

FIG. 1.—Cat 2 kg. Chloralose 60 mg./kg., atropine 2 mg. Upper record, respiration; lower record, carotid blood pressure. At the signal marks 90 μg. of 5-hydroxytryptamine was injected intravenously (I.V.) or into the left atrium (L.A.).

dose injected intravenously had previously caused a transient cessation of respiratory movements. In two of the six cats the apnoea seen on intravenous injection of 5-hydroxytryptamine was not abolished by vagotomy.

Effect of Vagal Cooling on the Reflex Apnoea.—The effect of vagal cooling on the apnoea caused by intravenous injection of 5-hydroxytryptamine was examined in three cats; in two of them vagotomy did not completely abolish the apnoea caused by the intravenous injection of 5-hydroxytryptamine, and the results were therefore equivocal. In a third cat the apnoea caused by the intravenous injection of 45 μg. 5-hydroxytryptamine survived cooling of the vagi to 2.5° C., but was abolished by vagotomy (Fig. 2). This figure also shows that the apnoea caused by an intravenous injection of 100 μg. of 2-α-napthyl ethyl isothiourea (another amidine compound whose actions in the cat resemble closely those of phenyl diguanide) likewise survived cooling of the vagi to 2.5° C. and was also abolished by vagotomy.

Effect of 5-Hydroxytryptamine on Discharge of Afferent Vagal Fibres.—There was no significant change of activity in four of five slowly adapting pulmonary stretch fibres on which the effect of 5-hydroxytryptamine was tested. In one (Fig. 3) a continuous low frequency discharge occurred 9 sec. after injection of 50 μg. during the initial period of respiratory inhibition. On plotting frequency of impulses before and after injection of the drug against intrapleural pressure no evidence of sensitization was found; other factors appear to have been concerned. It seems, therefore, that 5-hydroxytryptamine, like phenyl diguanide, does not sensitize or stimulate the pulmonary stretch receptors.

The drug had no significant effect on one depressor fibre and one right atrial type B fibre (Paintal, 1953a). In one left atrial type B fibre there occurred a threefold increase in activity (Fig. 3) beginning 9 sec. after injection of the drug. This happened some time after bradycardia and respiratory inhibition had started, and was preceded by a decrease in activity. It could not be ascertained with certainty whether this was due to sensitization of the receptor, as there was no record of left intra-atrial pressure.

On three occasions in three different cats 5-hydroxytryptamine aroused activity in previously inactive fibres (Fig. 4). The character of the response was in all instances the same as the response of these fibres to 100 μg. phenyl diguanide (Paintal,

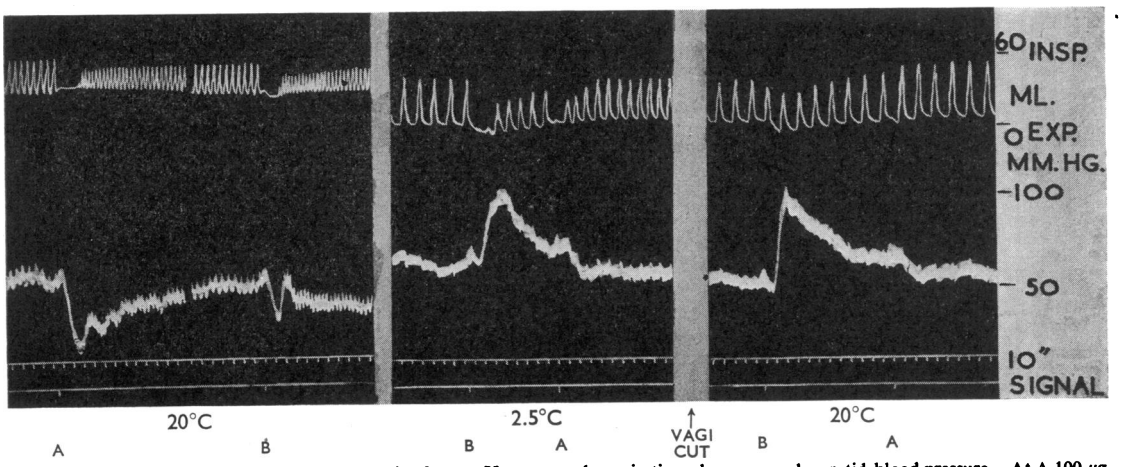

FIG. 2.—Cat 2.6 kg. Chloralose 60 mg./kg., atropine 3 mg. Upper record, respiration; lower record, carotid blood pressure. At A 100 μg. of 2-α-naphthyl ethyl isothiourea, and at B 45 μg. of 5-hydroxytryptamine, were injected. The first section is at 20° C., the second with the vagi cooled for 2 min. to 2.5° C., and the third after vagotomy at 20° C.

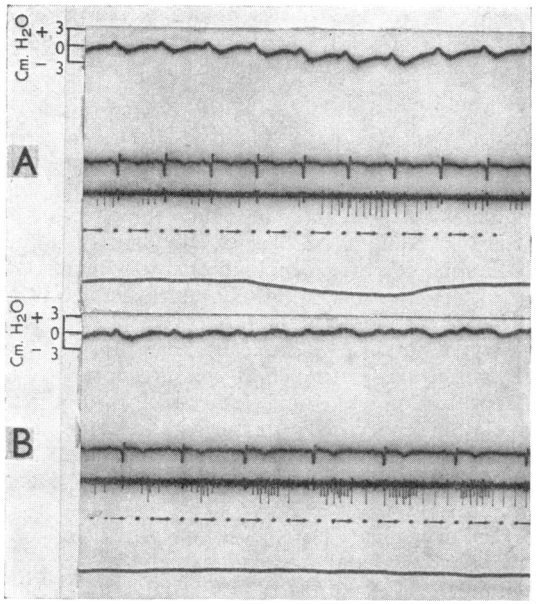

FIG. 3.—Cat, chloralose 80 mg./kg. Effect of 50 μg. 5-hydroxytryptamine on vagal afferent discharges; A before, B after intravenous injection. From above downwards, right venous pressure; E.C.G.; impulses in a vagal strip; time in 1/10 sec.; intrapleural pressure, inspiration downwards. The fibre with a small spike discharge is a left atrial fibre, the one with large spikes arises from a pulmonary stretch receptor. Note that the increase in atrial fibre activity in B follows the rise in right venous pressure.

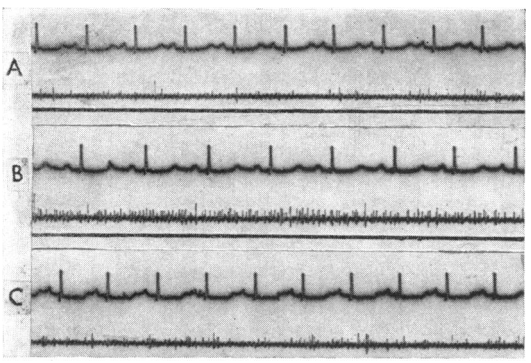

FIG. 4.—Cat, chloralose 80 mg./kg. Vagal afferent fibres stimulated by an intravenous injection of 25 μg. 5-hydroxytryptamine. Upper record, E.C.G.; lower record, activity in a vagal strip. A before, B 13 sec. after, and C 24 sec. after injection.

1953c). One single active unit was affected in the same way by both phenyl diguanide and 5-hydroxytryptamine. The response, as with phenyl diguanide, could be repeated several times, but the effect of 5-hydroxytryptamine differed from that of phenyl diguanide in that the degree of respiratory inhibition did not seem to be related to the frequency and number of units contributing to the discharge. Although the discharge resembled that evoked by phenyl diguanide in that it started 2 to 4 sec. after injection, it always lasted longer. On the other hand, respiratory inhibition was much more prolonged with phenyl diguanide than with 5-hydroxytryptamine, and with the latter the discharge always outlasted the respiratory inhibition by several seconds. The conduction velocity of one of these fibres was 5 m./sec. As with units stimulated by phenyl diguanide, none of these fibres was affected by gradual or rapid inflations of the lungs, suction of air from the trachea, administration of 100% nitrogen or a mixture of 90% oxygen + 10% carbon dioxide, or by intratracheal inhalation of ammonia. The effect of 5-hydroxytryptamine was only investigated in fibres stimulated by phenyl diguanide and such others as have been mentioned; the possibility therefore exists that the drug might excite fibres not affected by phenyl diguanide.

DISCUSSION

It is clear that 5-hydroxytryptamine can cause a reflex apnoea in cats by the stimulation of receptors situated in the circulation between the great veins and the left atrium. As this response is abolished by vagotomy, the afferent path must run in the vagi, but since the reflex survives vagal cooling to 2.5° C. it cannot be due to the stimulation of pulmonary stretch endings whose activity is abolished by cooling the vagi to 10–12° C. (Dawes, Mott, and Widdicombe, 1951). The respiratory reflex described in this paper could be due to the stimulation of those pulmonary receptors responding to various amidine compounds which also cause a reflex apnoea in expiration, abolished by vagotomy but not by cooling the vagi to 2.5° C. and unaffected by thoracic sympathectomy (Dawes, Mott, and Widdicombe, 1951). Further weight is added to this hypothesis by the observation that 5-hydroxytryptamine excites those vagal fibres which are otherwise excited only by phenyl diguanide. The analysis of the respiratory effects of 5-hydroxytryptamine is complicated by the fact that doses sufficient to cause the reflex apnoea may also cause an apnoea, possibly of central origin, and not abolished by vagotomy; an examination of the records suggests that other respiratory phenomena may occur as well.

The fact that the fibre activity produced by 5-hydroxytryptamine is greater and more prolonged than that produced by phenyl diguanide, while the inhibition of respiratory movements produced by the former is much less, also suggests that the mechanisms concerned with 5-hydroxytryptamine are less simple than with phenyl diguanide. 5-Hydroxytryptamine has, among other effects, a

direct action on bronchial musculature and the pulmonary vessels (Gaddum and Swan, personal communication).

The variability of the results of our pharmacological experiments recalls the experience of Douglas and Toh (1952) with this compound in dogs. Page (1952) states that 5-hydroxytryptamine in cats causes an apnoea followed by hyperpnoea which is not influenced by vagotomy. This result is not necessarily inconsistent with the findings of this paper.

There therefore seems little doubt that the mechanism of the reflex apnoea caused by 5-hydroxytryptamine in cats is identical with that evoked by phenyl diguanide. There is no evidence that the slowly adapting pulmonary stretch receptors, or the endings of the depressor or right or left atrial fibres, are involved.

The normal function of the nerve endings stimulated by phenyl diguanide and 5-hydroxytryptamine is not known. 5-Hydroxytryptamine is known to stimulate pain receptors in man (Armstrong, Dry, Keele, and Markham, 1952), and, if it does so in the cat as well, then it is possible that the fibres sensitive to phenyl diguanide and 5-hydroxytryptamine might arise from pain receptors in the lungs. The evidence for the presence of such receptors in the lungs is small, but it is significant that pain is a prominent feature of bronchogenic carcinoma (Jackson, 1942). Such a hypothesis would explain the fact that these fibres are normally quiescent and also that they are unaffected by procedures that arouse activity in other respiratory and cardiovascular receptors. Further investigation is required to elucidate this point.

Summary

1. 5-Hydroxytryptamine injected intravenously into some cats in doses of 15–45 μg./kg. body weight causes a reflex apnoea which is abolished by vagotomy; in such cats this quantity of 5-hydroxytryptamine has little effect on respiration when injected into the left atrium. In other cats this compound causes an apnoea which is not abolished by vagotomy.

2. The reflex apnoea caused by 5-hydroxytryptamine resembles that described for various amidine compounds in the following features: (*a*) it arises from the vessels between the great veins and the left atrium; (*b*) it is abolished by cutting the vagi but not by cooling them to 2°–3° C.

3. Afferent vagal fibres which are stimulated by phenyl diguanide are also stimulated by 5-hydroxytryptamine. These fibres have a conduction velocity of 5–6 m./sec.

4. There is no evidence that 5-hydroxytryptamine stimulates or sensitizes pulmonary stretch, right or left atrial, or depressor nerve endings.

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