Stimulation of Sympathetic Centers by Histamine

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Contraction of the nictitating membrane of the cat following intravenous injections of histamine persisted after adrenalectomy when cocaine had been injected. Since histamine has no direct effect on the nictitating membrane and since its action on the superior cervical ganglion is abolished by cocaine, the effect seemed to be due to an action of histamine in the central nervous system. Proof has been obtained that it has such an action. In addition, injections of small doses of histamine into the ventricles of the cat's brain have been found to cause a rise of systemic blood pressure which was of central origin.

HISTAMINE has long been known to liberate sympathin from the adrenal medulla1-3 and from chromaffin tissue of the heart1-5 by a direct action on the cells. My recent experiments5 have shown that the ganglion cells of the superior cervical ganglion of the cat are also stimulated by intra-arterial ganglionic injections of histamine in amounts approximating those of nicotine required to stimulate the ganglion by intra-arterial injections. Much smaller amounts of histamine (0.01-0.1 μg.) were found to potentiate the response of the nictitating membrane to sub-maximal preganglionic stimulation,7 and it has recently been confirmed that this potentiating effect was due to an action on the ganglion cells of the superior cervical ganglion.5 Furthermore, the pressor response which follows the intravenous injection of 20 μg. histamine into spinal cats, has been found to be partly due to general stimulation of peripheral sympathetic ganglia.7

A central action of histamine was suggested by its effects when injected into the blood supply of the superior cervical ganglion; these differ, depending on whether its central connections are intact or cut. Pure ganglionic actions were obtained only after section of the preganglionic fibers. The nature of the impulses reaching the superior cervical ganglion from higher sympathetic centers after intravenous injections of histamine was, therefore, investigated as was the response of the systemic blood pressure to injections of histamine into the ventricles of the cat's brain.

METHODS

Cats of 2-4 Kg. were used. After inducing anesthesia with ether, 80 mg./Kg. chloralose was injected intravenously. Intra-arterial injections of histamine were made through the central end of the lingual artery during occlusion of the external carotid artery. The injected substance was thus diverted to the superior cervical ganglion. The movements of the nictitating membranes were recorded by attaching them to isotonic levers fitted with frontal writing points.

For intraventricular injections a permanent cannula was inserted into the lateral or fourth ventricle of cats under chloralose anesthesia, as described by Feldberg and Sherwood.9 Histamine dihydrochloride, cocaine hydrochloride, hexamethonium bromide and mepyramine maleate were the substances used. (Weights given refer to the salts.) The solutions were neutralised for intra-arterial and intraventricular injections.

RESULTS

Intra-Arterial Injections of Histamine to the Superior Cervical Ganglion. Intra-arterial injections of 2-40 μg. histamine into the blood supply of the superior cervical ganglion have been found to cause a contraction of the nictitating membrane, by stimulating the ganglion cells. Intravenous injections of cocaine (0.1 mg. and more) were found to abolish the response of the ganglion to histamine without affecting ganglionic transmission. This was observed in preparations whose central connections had been severed by cutting the preganglionic fibers, excluding any central effects.4

In the present experiments the preganglionic fibers were left intact. Small amounts of cocaine (0.1-1 mg. injected intravenously) again antagonized the stimulant effect of intra-arterial injections of 10-40 μg. histamine on
the superior cervical ganglion. These small amounts of cocaine scarcely increased the sensitivity of the nictitating membrane; when, however, larger amounts of cocaine (2.5 mg. and more) were injected intravenously, the response of the nictitating membrane to intrarterial injections of histamine was unchanged or even increased. This always happened when cocaine had caused hypersensitivity of the nictitating membrane to adrenalin and noradrenalin. The observation suggested that although the action of histamine on the superior cervical ganglion was abolished by cocaine, the sensitized nictitating membrane responded to impulses originating in the higher sympathetic centers which were reached by histamine via the blood stream. Section of the preganglionic fibers abolishes the contractions of the nictitating membrane caused by intrarterial injections of histamine into cocainized preparations, supporting this assumption.

Intravenous Injections of Histamine. The stimulation by histamine of the centers responsible for the contraction of the nictitating membrane was studied in more detail by injecting histamine intravenously. For this purpose experiments were performed in previously adrenalectomized cats under chloralose anesthesia. Figure 1 shows a comparison of the action on the nictitating membrane of intravenous injections of 15 µg. histamine and of 1 µg. norepinephrine. Both substances failed to cause a response of the nictitating membrane when the central connections were left intact (fig. 1a and b). Thirty minutes after the intramuscular injection of 8 mg./Kg. cocaine, full sensitization of the nictitating membrane was observed. Both histamine and noradrenalin then caused a contraction of the membrane (fig. 1c and f). The contraction caused by histamine was then abolished by section of the preganglionic fibers (fig. 1h).

Injections of hexamethonium had the same effect as section of the preganglionic fibers. After sensitization of the nictitating membrane by cocaine, the intravenous injection of 10 mg. hexamethonium abolished the response of the membrane to the intravenous injection of 20 µg.
Fig. 2. Cat under chloralose, 3.3 Kg., adrenals removed. Normal nictitating membrane with its central connections intact (upper trace) and other side, with its preganglionic fibers cut (lower trace). Intravenous injections of 50 μg. histamine at arrow. In (a) and (c) submaximal preganglionic stimulation of one side (lower trace), as indicated by solid line. No stimulation in (b). Intramuscular injection of 8 mg./Kg. cocaine 30 min. before (c).

histamine, recovery being observed during the following 40 min. Section of the preganglionic fibers finally abolished the response of the nictitating membrane to histamine.

The contraction of the nictitating membrane of the cocainized and adrenalectomized cat after intravenous injections of histamine was not necessarily due to central stimulation. A similar response could have been caused by the potentiating effect of histamine on transmission of tonic impulses through the superior cervical ganglion. This potentiating effect, however, is abolished by cocaine.

The experiment shown in figure 2 excludes the possibility that histamine potentiated ganglionic transmission in the presence of cocaine. The central connections were left intact on one side (upper trace), while they were cut on the other (lower trace). In figure 2a submaximal preganglionic stimulation was applied for the period indicated. The intravenous injection of 50 μg. histamine caused a contraction superimposed on the plateau recorded (lower trace). This contraction was greater than the response of the nictitating membrane when no preganglionic stimulation was applied (fig. 2b, lower trace). The larger response in figure 2a (lower trace) was due to potentiation of ganglionic transmission by histamine, while the smaller responses in figure 2a (upper trace) and figure 2b (both traces) were due to stimulation of the superior cervical ganglion by histamine. Thirty minutes after the intramuscular injection of 8 mg./Kg. cocaine, however, both the stimulation of the ganglion and the potentiation of ganglionic transmission by histamine were abolished (fig. 2c, lower trace), but the contraction of the centrally connected nictitating membrane was not abolished (fig. 2c, upper trace) and was thus due to an outburst of impulses from sympathetic centers.

This central stimulation could have been caused either by a direct action of histamine on sympathetic centers or by vascular changes caused by the intravenous injection of histamine (central anoxia or reflex activation of sympathetic centers). Figure 3 shows that the contraction of the nictitating membrane was not related to the fall of blood pressure. Four intravenous injections of 10 μg. histamine caused identical responses of the blood pressure, but the second failed to cause central stimulation. This second injection (fig. 3b) was given 10 min. after the first, the time interval between the other injections being 20 min. Histamine thus failed to cause central stimulation if the time interval between injections was only 10 min., although this time interval was sufficiently long for full recovery of the blood
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Pressure and although the response of the blood pressure to histamine was identical with that to the initial injection. Section of the pre-ganglionic fibers also abolished the contraction of the nictitating membrane (fig. 3c).

The influence of section of the spinal cord at the level of the second vertebra was studied in 1 experiment. The response of the nictitating membrane to the intravenous injection of 10 μg histamine was found to be reduced by section of the spinal cord and abolished by section of the pre-ganglionic fibers. The central actions of histamine were thus exerted both on the higher sympathetic centers and on the centers of the spinal cord.

**Intraventricular Injections.** When the cannula through which injections were made communicated with the subarachnoid space, the injection of 10 μg histamine failed to cause a rise of systemic blood pressure (fig. 4a). When, however, a similar amount of histamine was injected into the lateral ventricle, a prolonged rise of blood pressure was observed (fig. 4c). Injection of the same volume of saline failed to cause a response of the blood pressure (fig. 4b).

Intraventricular injections of 5–40 μg histamine caused a rise of blood pressure in 20 out of 24 preparations. The response increased with the injection of increasing amounts of histamine; 5, 10 and 20 μg histamine were injected into the lateral ventricle and caused pressor responses increasing both in height and duration, while control injections of saline solution had little or no effect on the blood pressure (fig. 5). The last injection of 20 μg histamine was then repeated after an intraventricular injection of 40 μg mepyramine (fig. 5, lowest trace). The very small and transient response of the blood pressure to this injection was indistinguishable from that to an injection of 0.2 ml saline solution.

Such small amounts of mepyramine abolished the response to intraventricular injections of histamine only when injected into the ventricle. Intravenous injections of similar amounts of mepyramine failed to antagonise the response to histamine. When, on the other hand, large amounts (1.5 mg.) were injected intravenously, they abolished the pressor response to the histamine.

The pressor response to the intraventricular injection of 10 μg histamine was abolished after the intravenous injection of 7.5 mg hexamethonium; partial recovery was observed 40 min. later. Section of the spinal cord similarly abolished the pressor response.

**Discussion**

Since histamine has no direct action on the smooth muscle of the nictitating membrane, its injection into adrenalectomized and cocainized cats should not cause a contraction of the nictitating membrane. However, Gaddum and...
Goodwin reported that under these conditions histamine caused a contraction of both the normal and the previously denervated nictitating membrane. Interestingly enough, they observed a larger contraction of the normal than of the supersensitive denervated nictitating membrane, when larger amounts were injected. This suggested that the innervated nictitating membrane received nervous impulses initiated by histamine, while the hypersensitive denervated membrane responded to the liberation of sympathin from some distant organ or organs.

The present results have shown that intravenous injections of 10–40 μg histamine caused an outburst of impulses from sympathetic centers, which caused a contraction of the nictitating membrane. These impulses were normally weak and might easily have been masked by the ganglionic actions of histamine. They were, however, demonstrated after injections of cocaine into adrenalectomized cats. Cocaine had a double action, it sensitized the nictitating membrane and antagonized the ganglionic actions of histamine. These two actions unmasked the stimulation by histamine of sympathetic centers. Both section of the preganglionic fibers and hexamethonium abolished the contraction caused by the histamine. It was concluded, therefore, that the contractions of the nictitating membrane obtained under these conditions were of purely central origin.

The nictitating membrane is known to be innervated by the group of fibers which also innervate other structures of the orbit, while the blood vessels of the head are innervated by another group also originating in the superior cervical ganglion. Therefore, the higher centers responsible for contraction of the nictitating membrane are probably closely connected with those responsible for dilatation of the pupil. The preganglionic fibers of the superior cervical ganglion, which send impulses to the pupil, originate from the “centrum ciliopinale (Budge)” which lies in the lateral column of the spinal cord at the junction of its dorsal and cervical region. The next higher center for pupillary dilatation lies in the medial and frontal part of the hypothalamus.

It has been found that section of the spinal cord at the level of the second vertebra (i.e., above the centrum ciliopinale) reduced the response of the nictitating membrane to histamine after adrenalectomy and cocaineization. It is therefore suggested that the preganglionic fibers conducting impulses to the nictitating membrane originate from a part of the spinal cord below the second vertebra; probably from the centrum ciliopinale. The present experiments showed that impulses from this as well as from higher sympathetic centers play a part in the response of the nictitating membrane.

There is evidence that liberation of sympathin is not confined to the nictitating membrane: Gaddum and Goodwin observed that the previously denervated membrane of the adrenalectomized and cocainized cat responded as well. Pilcher and Sollmann in perfusion studies of the spleen with intact nervous connection, found that injections of histamine decreased the perfusion flow due to the stimulation of the vasomotor center. They concluded that this action was presumably secondary to anemia of the center. In the present experiments it was found that with short time intervals between intravenous injections of histamine, the blood pressure responses were identical, but no contraction of the nictitating membrane was obtained. This suggested that neither reflex stimulation of the sympathetic centers nor anemia of the central ganglion cells could explain the stimulation observed after intravenous injections of histamine, but suggested rather a direct action of histamine on sympathetic centers. Since histamine stimulates the peripheral ganglion cells, such a central action did not seem improbable, especially as the superior cervical ganglion also failed to respond to repeated injections of histamine, when the time interval between injections was less than 20 min.

The present results suggest that the contraction of the nictitating membrane following intravenous histamine is mediated by one or all of the following: stimulation of the adrenal medulla, the superior cervical ganglion, sympathetic centers and potentiation of impulses on their way through the superior cervical ganglion.

Injection of histamine into the brain ventricles indicated that the rise of systemic blood
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Pressure was of central origin, for it was abolished both by section of the spinal cord and by intravenous injections of hexamethonium. This prevented central impulses from reaching the periphery, but did not antagonise the peripheral action of histamine. The pressor response to histamine was also abolished by intraventricular injections of small amounts of mepyramine. The present data obviously do not furnish information as to whether the central effect is direct or indirect or data on the location of centers stimulated. However, our observations that contraction of the nictitating membrane were obtained after intravenous but not after intraventricular injection of histamine do support the inference of Rosenblueth and Schwartz that responses of the nictitating membrane and blood pressure are mediated by independent centers.

The present series of experiments suggest that histamine exerts a direct action on specific ganglion cells of the central nervous system. Furthermore, the sympathetic ganglion cells located in the central nervous system have about the same sensitivity to histamine as the peripheral ganglion cells.

Summario in Interlingua

Le contraction del membrana nictitante del catto post injectiones intravenose de histamina persiste post adrenalectomia si injectiones de cocaina ha essete effectuate. Proque histamina ha nulle directe effecto super le membrana nictitante e proque su action super le ganglion supero-cervical es abolite per cocaina, le persistentia del contraction del membrana nictitante sub le supra-describite conditiones pareva esser le effecto de un action de histamina in le systeema nervous central. Esseva obtenite le prova que histamina ha de facto un tal action. In plus, injectiones de parvo doses de histamina in le ventriculos cerebral del catto se provava le causa de un augmento del pression systemic de sanguine que esseva de origine central.

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