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Mechanism of histamine-induced antidiuretic response

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Summary

1. In dogs anaesthetized with α-chloralose, intracerebroventricular (i.c.v.) injection of histamine induced antidiuresis and increase in jugular vein blood antidiuretic hormone (ADH) level but no change in urinary electrolytes. The mechanism of the histamine-induced antidiuretic response was analysed by the use of pharmacological agents.

2. Histamine (i.c.v.) in 1–20 μg doses produced a variable effect on urine outflow as well as on the blood ADH concentration; however, higher doses (25–500 μg) of histamine elicited a dose-dependent antidiuretic response with concomitant rise in blood ADH titre.

3. Repeated administration of high doses of i.c.v. histamine (400 μg) elicited a diminishing antidiuretic response which was not observable after the fourth dose, thus exhibiting tachyphylaxis. The antidiuretic response to histamine could be restored by central administration of noradrenaline (500 μg).

4. Central pretreatment with mepyramine (5 mg) prevented the histamine-induced antidiuresis. Atropine (2 mg i.c.v.) was ineffective in blocking the antidiuretic effect of histamine. A diuretic response to histamine (400 μg i.c.v.) was obtained in phenoxybenzamine (i.c.v.) pretreated animals; this response could be blocked by i.c.v. injection of propranolol. Tetrabenazine pretreatment prevented the antidiuretic response to histamine.

5. The results of the study lead us to conclude that histamine releases central catecholamines which activate the central adrenergic mechanism for the release of antidiuretic hormone.

Introduction

In a previous communication from this laboratory, the role of central cholinergic and adrenergic mechanisms in the control of antidiuretic hormone (ADH) release was described (Bhargava, Kulshrestha & Srivastava, 1972). The pharmacological analysis employing adrenoceptor and cholinoceptor agonists and antagonists demonstrated that the central muscarinic cholinoceptors and α-adrenoceptors are facilitatory and the β-adrenoceptors are inhibitory for ADH release.

Dale & Laidlaw (1910) were the first to report an antidiuretic response to intravenous histamine. This finding was confirmed by other investigators (Gilman & Kidd, 1938; Reubi & Futcher, 1949; Blackmore & Cherry, 1955). The decrease in urine flow could be the consequence of a fall in blood pressure but this possibility

was ruled out by Pickford (1952). Since Blackmore & Cherry (1955) failed to evoke the antidiuretic response to intravenous infusion of histamine in unanaesthetized, hypophysectomized dogs, they concluded that the action of histamine may be related to a central release of ADH from the hypophysis.

Histamine has been located in different brain areas including the hypothalamus and the hypophysis (Crossland, 1960; Adam, 1961; Adam & Hye, 1966). The enzymes necessary for its synthesis and catabolism are also found in the central nervous system (Adam, Hye & Waton, 1964). Intraneuronal association of histamine with the synaptic vesicles (Kataoka & de Robertis, 1967) may suggest a neurotransmitter role for histamine, similar to acetylcholine and catecholamines in the central nervous system.

The present study was undertaken to determine the mechanism of histamine-induced antidiuresis and to study the possibility of a neurotransmitter function for histamine in the release of ADH. The antidiuretic response was induced by intracerebroventricular injection of histamine and pharmacological agents were employed to analyse the mechanism of the antidiuretic response.

Methods

Thirty-eight dogs of either sex were used, weighing between 10–15 kg. Animals were fasted for 24 h but were allowed water *ad libitum*. The procedure adopted for anaesthesia, hydration and recording of urine outflow was similar to that described by Bhargava *et al.* (1972).

One of the external jugular veins was cannulated to collect the blood for ADH estimation. ADH from the blood was extracted on a column of XE–64 resin (Weinstein, Berne & Sachs, 1960) as modified by Yoshida, Motohashi, Ibayashi & Okinaka (1963). The recovery of ADH by this method was 80%. Necessary correction for the loss of ADH during extraction was made in the results. The ADH in the eluate was estimated by the antidiuretic assay method in rats following the technique of Jeffers, Livezy & Austin (1942) as modified by Dicker (1953). Arginine vasopressin (Pitressin, Parke Davis) was used as a standard, for the bioassay.

Electrolytes (Na and K) were estimated in plasma and urine by flame photometry (Wootton, 1964).

Drugs were administered intracerebroventricularly (i.c.v.) through a cannula implanted by the technique of Bhargava & Tangri (1959). The proper placement of the cannula was confirmed at autopsy. The volume of fluid injected (drug followed by 0·25 ml 0·9% w/v NaCl solution (saline)) never exceeded 0·5 ml; this volume of saline (i.c.v.) did not influence the urine flow.

Drugs

Histamine dihydrochloride (Ward-Blenkinsop), (−)-noradrenaline hydrochloride (Sigma), mepyramine maleate (May & Baker), atropine sulphate (E. Merck), phenoxybenzamine hydrochloride (S.K.F.), (±)-propranolol hydrochloride (I.C.I.), tetrabenazine (Roche) and arginine vasopressin (Parke Davis).

The doses of compounds used refer to their salts.

Results

Effect of i.c.v. histamine on urine outflow

Intracerebroventricular (i.c.v.) administration of graded doses of histamine, 25–500 μg, consistently produced a decrease in urine outflow with a concomitant increase in ADH concentration in the jugular vein blood. With the higher doses of histamine (200–500 μg) there was a fall of blood pressure (5–10 mmHg) which lasted 10–15 minutes. Lower doses of histamine (1–20 μg i.c.v.) produced a variable response: diuresis (10–30%) was obtained in 2 animals and antidiuresis (20–40%) in 4 animals. In these experiments, blood ADH concentration also showed corresponding changes. Only in the dose range of 25–500 μg of histamine was an approximately linear dose-response relationship obtainable (see Fig. 1).

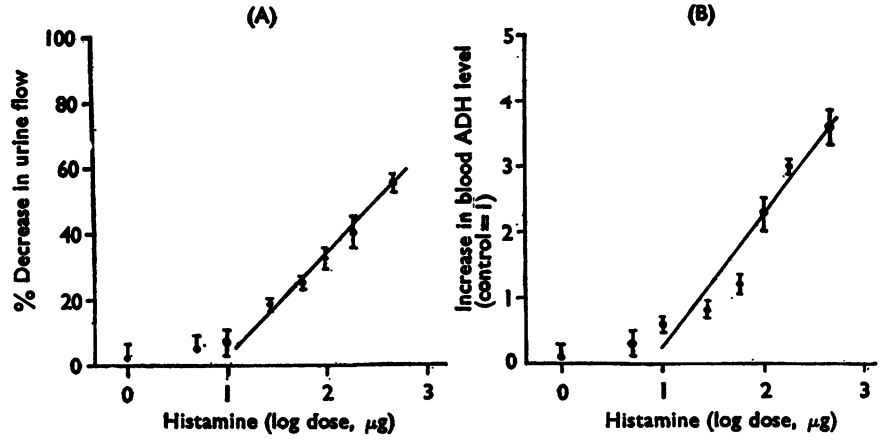

FIG. 1. Effect of intracerebroventricular administration of graded doses of histamine on the urine outflow (A) and blood ADH concentration (B) in dog. Histamine (1–20 μg) produced a variable response; higher doses of histamine (25–500 μg) produced a dose-dependent decrease in the urine outflow and increase in the blood ADH concentration. Note near-linearity of log dose-response regression lines in the 25–500 μg dose-range of histamine. Vertical bars indicate ±S.E.M. ($n=10$.)

Following i.c.v. histamine (200–500 μg) the antidiuretic response appeared within 10 min and the peak effect was observed within 20–30 min, complete recovery occurred between 60–90 minutes. However, with doses lower than 200 μg the time-course of the antidiuretic response was shortened.

Intracerebroventricular administration of histamine did not produce any significant change ($P>0.05$) in the excretion rate of electrolytes.

Effect of repeated administration of high doses of histamine (400 μg i.c.v.) on urine outflow

The results of these experiments are shown in Figure 2. The first injection of histamine (400 μg i.c.v.) produced 50% inhibition of urine flow. When this dose of histamine was repeated a number of times, after obtaining recovery from the preceding dose, the antidiuretic response gradually declined and by the fourth dose, it was completely abolished (2 experiments) or there was a mild diuretic response (10–20%) in two out of four experiments. At this stage i.c.v. noradrenaline

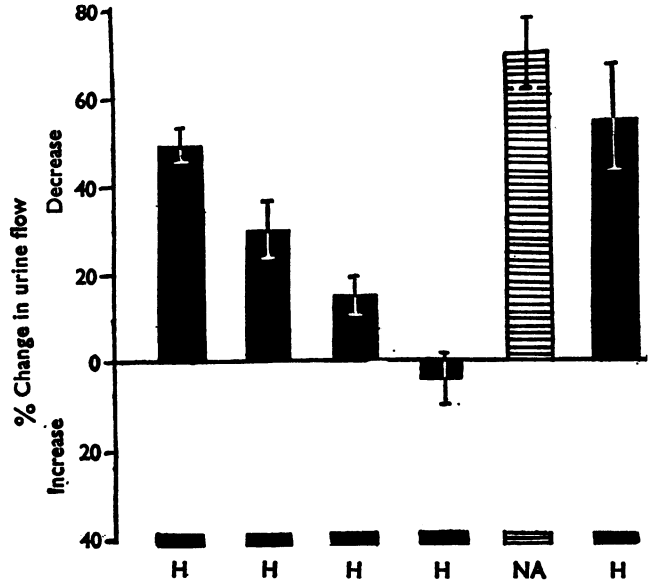

FIG. 2. Effect of repeated i.c.v. administration of histamine (H, 400 μg) on urine outflow in dog. The antidiuretic response gradually declined with successive doses of histamine, and could not be obtained with the fourth dose. Note complete restoration of the antidiuretic response to histamine after noradrenaline (NA, 500 μg i.c.v.) pretreatment. Vertical bars indicate $\pm$S.E.M. (n=6.)

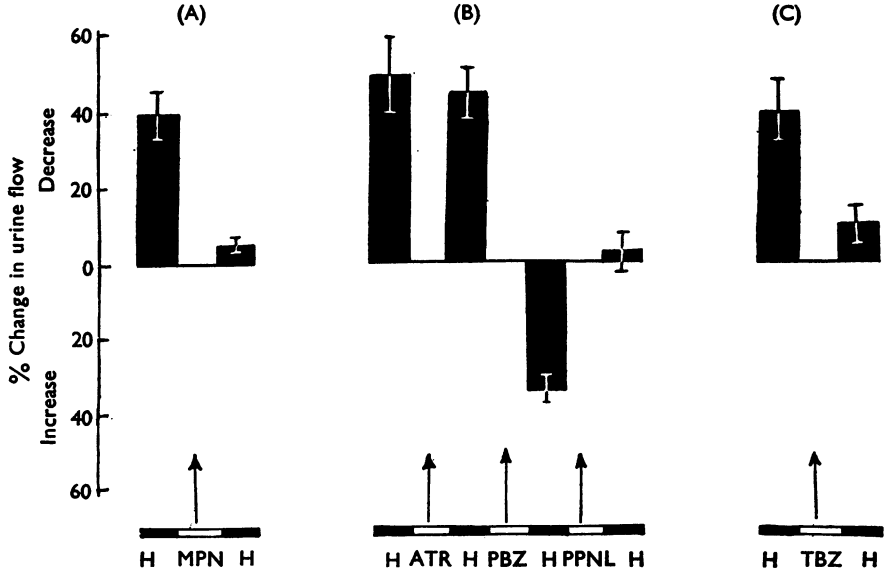

FIG. 3. Histogram depicting changes in the i.c.v. histamine (H, 400 μg)-induced antidiuretic response following central pretreatment with drugs. The results obtained are from three different groups of experiments each with 5 dogs. (A) Mepyramine (MPN, 5 mg i.c.v.) blocked the antidiuretic response to histamine. (B) Pretreatment with atropine (ATR, 2 mg i.c.v.) failed to block the antidiuretic response to histamine. Phenoxybenzamine (PBZ, 2 mg i.c.v.) blocked the antidiuretic response to histamine and converted it to a mild diuretic response. Propranolol (PPNL, 2 mg i.c.v.) completely blocked this diuretic effect of histamine. (C) The antidiuretic response to i.c.v. histamine (400 μg) was completely blocked by treatment with tetrabenazine (TBZ, 30 mg/kg i.p.) 3 h beforehand.

(500 μg) elicited a 70% decrease in the urine outflow and a concomitant increase in blood ADH concentration. One hour after noradrenaline injection, the antidiuretic response to i.c.v. histamine (400 μg) was fully restored. These experiments demonstrate the phenomenon of tachyphylaxis to i.c.v. histamine and its restoration by i.c.v. noradrenaline.

Effect of central pretreatment with drugs on histamine (400 μg i.c.v.)-induced antidiuresis

The results obtained in three different groups of animals are summarized in Figure 3. Mepyramine (5 mg i.c.v.) pretreatment completely blocked the antidiuretic effect as well as the rise in blood ADH concentration induced by i.c.v. histamine (400 μg) as shown in Figure 3A. In one experiment out of five, however, a small (8%) increase in urine outflow was observed. Figure 3B shows that atropine (2 mg i.c.v.) did not significantly alter the antidiuretic response to i.c.v. histamine ($P>0{\cdot}05$). Further pretreatment with i.c.v. phenoxybenzamine (2 mg), an α-adrenoceptor antagonist, converted the antidiuretic effect of i.c.v. histamine (400 μg) to a diuretic effect which was successfully blocked by propranolol (2 mg). In all these experiments, changes in blood ADH concentration corresponded with the urine outflow. In another group of five dogs (see Fig. 3C) control antidiuretic responses to i.c.v. histamine (400 μg) were obtained. These animals were given tetrabenazine (30 mg/kg i.p.) to deplete central catecholamines and were left for three hours. This tetrabenazine pretreatment effectively ($P<0{\cdot}001$) blocked the antidiuretic effect as well as the rise in blood ADH that normally occurred in response to i.c.v. histamine (400 μg).

Discussion

That the antidiuretic action of histamine was central is supported by the increase in ADH concentration in the jugular vein blood when histamine was localized in the cerebral ventricles. These findings support the suggestion of Blackmore & Cherry (1955) that the antidiuretic response to intravenous histamine may result from a central release of ADH. Although the centrally induced histamine-antidiuresis could be successfully blocked by i.c.v. injection of mepyramine, other results of our study do not support a direct participation of the histaminergic mechanism in the release of ADH.

We have earlier provided proof for central cholinergic (muscarinic) and α-adrenergic mechanisms for facilitation of ADH release which may be responsible for the antidiuretic response. It is conceivable that i.c.v. histamine may be activating the central cholinergic or adrenergic mechanism to elicit the antidiuretic response. No evidence for the activation of cholinergic mechanisms by histamine is available. The histamine-induced antidiuretic response, unlike the acetylcholine response, was not altered by central atropinization.

Since tachyphylaxis to the antidiuretic effect of i.c.v. histamine was observed, an indirect action of histamine is suggested. Histamine is found in association with the adrenergic transmitter in nerve terminals (Kwiatkowski, 1943 ; von Euler, 1949 ; Werle & Weicken, 1949 ; Werle & Palm, 1950) and simultaneous release of histamine as well as noradrenaline has been reported at certain peripheral synapses (von Euler & Astrom, 1948). Furthermore, histamine is known to release catechol-

amines centrally as well as peripherally (Burn & Dale, 1926 ; Burn & Trendelenburg, 1954 ; Trendelenburg, 1955 ; 1957a, b ; Rocha e Silva, 1959 ; Halobut, 1966).

Intracerebroventricular injection of noradrenaline successfully reversed the histamine-induced tachyphylaxis to the antidiuretic response. Exogenous noradrenaline (given by i.c.v. injection) is effectively taken up by adrenergic neurones in the central nervous system (Glowinski & Axelrod, 1966). Moreover, depletion of central catecholamines by tetrabenazine treatment effectively blocked the antidiuretic response to i.c.v. histamine. Thus, it is our contention that i.c.v. histamine-induced antidiuresis results from a central release of the adrenergic neurotransmitter. The antidiuretic effect of i.c.v. histamine could be converted into a diuretic effect by i.c.v. phenoxybenzamine treatment in a manner similar to that observed with i.c.v. catecholamine (Bhargava *et al.*, 1972). The diuretic response to histamine in phenoxybenzamine-treated animals is attributed to central β-adrenoceptor activation because propranolol blocked the diuretic response.

These results lend further support to our hypothesis for the participation of central cholinergic and adrenergic mechanisms in ADH release. While a histaminergic mechanism may not be directly concerned in the release of ADH, the histamine-induced antidiuresis probably results from an activation of a central adrenergic mechanism concerned in the release of ADH.

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