EFFECT OF INTRACEREBROVENTRICULAR INJECTION OF HISTAMINE ON BLOOD SUGAR LEVEL AND HYPOTHALAMO-PITUITARY ADRENAL AXIS OF RATS

C. P. TRIVEDI, N. T. MODI AND R. K. BALOTHIA

Department of Pharmacology, G. R. Medical College, Gwalior (M.P.)

Summary: Intraventricular injection of histamine and normal saline in rats caused a marked fall in adrenal ascorbic acid indicating a stimulatory effect of both on pituitary adrenal axis. Intraventricularly injected histamine caused significant hypoglycaemia also in rats as compared to control series.

Key words: histamine, intraventricular, hypothalamopituitary adrenal axis, ascorbic acid, blood sugar

INTRODUCTION

One of the important sites in the central nervous system with which a drug comes in contact when administered intra-cerebro-ventricularly (IVT) is the hypothalamus (3). Since hypothalamus is involved in the regulation of blood sugar and ACTH secretion, it was considered of interest to investigate the effect of intraventricularly injected histamine on blood sugar level and adrenal ascorbic acid level as the latter is considered to be a reliable index of ACTH secretion(7).

MATERIALS AND METHODS

Sixty Albino rats weighing 100-150 g were selected and divided in three groups (A, B, and C) of twenty each. Group A was kept as control and received nothing. Rats in Group B were administered normal saline 0.05 *ml* IVT and Group C rats were given histamine in a dose 1 *mg/kg* in 0.05 *ml* IVT. The intra-cerebro-ventricular injection was made by Haley's technique (4). The rat was firmly grasped by loose skin behind the head. The skin was pulled taut. For injection an insulin needle to which a guard at 2 mm above the tip was fixed for ensuring entry of needle in the lateral ventricles of the rat was used. The needle was inserted perpendicularly through scalp at a site which was 2 mm from either side of midline on a line drawn through anterior base of the ears. That the drugs reached the ventricles when injected by the above method was confirmed in a few preliminary experiments by injecting methylene blue and dissecting the brain thereafter. Staining of ventricles by the dye confirmed the correctness of the approach and method.

The rats of all the groups were sacrificed fifteen minutes after the administration of the particular solution by decapitation. The blood was collected in vials containing sodium citrate 1% to prevent coagulation. This was used for the estimation of blood sugar.

The suprarenal glands of both sides were taken out, weighed and homogenised with 2 *ml* of trichloroacetic acid. The homogenate, 2 *ml* was shaken with 7% trichloroacetic acid and mixed well with 0.3 *g* of activated charcoal. It was then centrifuged and supernatant liquid was filtered. The filterate (0.5 *ml*) was taken in a tube marked at 5 *ml* and treated with 0.1 *ml* of thiourea and 0.5 *ml* of dinitrophenyl hydrazine. The tube was stoppered and kept at 37°C for three hours. It was then cooled in ice water and 1 *ml* of sulphuric acid was added drop by drop with stirring. The colour was allowed to develop for 30 minutes and the volume of the liquid was raised to 5 *ml* by adding water.

Three standards corresponding to 0.002, 0.004, 0.008 *mg* of ascorbic acid were treated like the test solution as described above. Two *ml* of distilled water was used instead of 2 *ml* of ascorbic acid solution as the blank for test and the standard solution. The blanks were prepared in the same way as the test except that dinitrophenyl hydrazine was added after sulphuric acid.

A standard curve was prepared by taking the readings of the standard solution on a Uvispeck spectrophotometer (Hilger and Watts) at 520 mu. The readings of the unknown solutions were taken at the same wave length and concentration was found out by reference to the standard curve.

Blood sugar determinations were done by the method of Asatoor and King (2) using a Luminteron (Model 401 A) Colorimeter with Ilford red (608) filter.

RESULTS

As shown in Table I, a marked fall of ascorbic acid in both the saline and histamine treated rats was observed. However, the fall was significantly less in histamine treated Group C as compared to that in saline treated Group B.

It is evident from Table II that blood sugar of histamine treated rats was much lower as compared with that of both the control groups. However, the blood sugar level of saline treated rats was significantly higher than that of control group which did not receive any treatment.

DISCUSSION

Certian interesting results have emerged from the present study . A marked fall in the adrenal ascorbic acid of rats injected with normal saline alone signifies that the technique of IVT injection itself acted as a strong stressful stimulus activating the pituitary adrenal axis. Histamine also exerted a marked stimulatory effect on the pituitary adrenal axis as judged by the above parameter though its effect was siginficantly less than that of normal saline. Intravenous

TABLE I: Showing the effect of intraventricularly injected histamine on ascorbic acid in *mg*/100 g of adrenalgland of rats.

S. No.	*Group A* *No drug*	*Group B* *Normal saline* 0.05 *ml*	*Group C* *Histamine* 1 *mg/kg* 0.05 *ml*
1.	104.16	13.33	11.11
2.	101.59	11.76	14.70
3.	117.14	15.23	31.81
4.	133.33	12.50	30.43
5.	121.08	9.37	20.17
6.	114.28	12.50	20.00
7.	114.28	20.00	29.26
8.	121.90	12.50	28.57
9.	98.41	11.53	26.66
10.	97.96	14.28	24.76
11.	121.90	12.50	23.80
12.	110.92	10.00	25.00
13.	100.00	11.42	18.77
14.	114.28	11.90	35.29
15.	96.22	18.75	22.61
16.	97.95	10.00	33.33
17.	95.89	17.85	37.50
18.	114.28	16.60	34.50
19.	121.90	17.58	30.00
20.	117.46	19.04	35.00
Total	2214.93	278.64	533.25
Average	110.746	13.932	26.662
SE	±2.31	±0.734	±1.658
P Value		<0.001	<0.001

TABLE II: Showing the effects of intraventricularly injected histamine on blood sugar level of rats.

S.No.	*Group A* *No drug*	*Group B* *Normal saline* 0.05 *ml*	*Group C* *Histamine* 1 *mg/kg* 0.05 *ml*
1.	160.00	175.00	120.00
2.	160.00	208.00	96.00
3.	150.00	120.00	80.00
4.	140.00	165.00	80.00
5.	150.00	97.00	66.00
6.	133.30	66.00	80.00
7.	133.40	180.00	140.00
8.	160.00	160.00	100.00
9.	160.00	160.00	80.00
10.	186.00	140.00	40.00
11.	146.00	120.00	100.00
12.	130.00	100.00	80.00
13.	135.00	160.00	120.00
14.	120.00	180.00	120.00
15.	100.00	180.00	140.00
16.	100.00	200.00	100.00
17.	148.00	220.00	140.00
18.	120.00	117.00	130.00
19.	125.00	140.00	120.00
20.	140.00	170.00	80.00
Total	2806.60	3131.00	2012.00
Average	140.33	156.55	100.60
SE	±4.39	±8.931	±6.578
P Value	<0.01	<0.001	

injection of histamine has also been shown to act as a strong stressful stimulus causing activation of pituitary adrenel axis (5), however as histamine does not cross the blood brain barrier (1,8) the stimulatory effect of intravenously injected histamine on pituitary adrenal axis could be attributed to an indirect effect medicated through the widespread physiological disturbances resulting from it. Thus one of the physiological functions of histamine might be to act as a neuro-humoral trigger for initiating chain of reactions involved in the stimulation of the hypothalamopituitary adrenal axis when the animal is exposed to sudden stress.

The effect of IVT administration of histamine on the blood sugar level is rather interesting and intriguing. A highly significant fall in blood sugar level of histamine treated groups of rats as compared to that of both the control groups (A & B) indicates that histamine has centrally mediated hypoglycaemic effect. Since peripheral administration of histamine is known to cause hyperglycaemia by causing release of adrenaline from adrenal medulla, this effect of histamine on the central nervous system is opposite to its peripheral effect. It may be noted that the blood sugar level of saline treated rats was significantly more than those rats which were not administered any drug. This could be attributed to relaese of adrenal corticoids resulting from activation of pituitary adrenal axis. As histamine had also been found to stimulate pituitary adrenal axis in our studies, this rather parodoxical hypoglycemic effect of IVT injected histamine could be explained only by presuming that the centrally medicated hypoglycaemic effect of histamine is specific and potent enough to overcome the hyperglycaemia which might result from the activation of pituitary adrenal axis.

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