

EFFECTS OF CENTRAL ADMINISTRATION OF INSULIN IN NORMAL AND VMH (VENTROMEDIAL HYPOTHALAMUS) LESIONED RATS ON FOOD INTAKE

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Abstract : Central effects of insulin on 20 min. food intake were studied in rats. Insulin administration in the lateral ventricular cerebrospinal fluid (CSF) did not alter food intake in the intact or lesioned ventromedial hypothalamus (VMH) rats. Whereas, after insulin injection in VMH there was a decrease in food intake. In VMH lesioned rats, subcutaneous injection of insulin increased food intake.

The present study suggests that CSF insulin is not implicated in short term regulation of food intake, and secondly, peripheral glucoreceptors may play an important role in influencing hypothalamic feeding mechanisms.

Key words : insulin ventromedial hypothalamus food intake
intracerebroventricular administration intrahypothalamic administration

INTRODUCTION

Hyperphagia and increase in body weight following lesions of ventromedial hypothalamus (VMH) are attributed to the removal of inhibition on the feeding centre. VMH has recently been suggested (1, 2, 3, 4) to play an important role in controlling insulin secretion and release. Chronic administration of insulin in cerebro-spinal fluid (CSF) of baboons (5) and rats (6) suppressed their body weight gain. Evidence is accumulating to suggest that receptors for insulin like growth factors (IGF I & II) and insulin are present in the hypothalamus (7, 8). Insulin is also known to influence glucose uptake in the neurons of VMH (9). These studies and increased levels of insulin in plasma and CSF postprandially are in favour of its being an

endogenous satiety substance. Suppression of food intake has been reported (5, 6, 9) after chronic administration of insulin.

The present study was, therefore, planned to evaluate the acute effects of intracerebroventricular (ICV) administrations of insulin on food intake, before and after VMH lesions.

METHODS

Institute bred male albino rats ($n=36$) were used in this study (BW 200-250 g).

Surgical procedures : Under ether anaesthesia bilateral VMH lesions were produced by passing 2 mA anodal current for 15 Sec, through stainless steel electrodes insulated except at the tips using a

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lesion maker (INCO). Stereotaxic coordinates for VMH were A-4.5 mm, L-0.5 mm and H-0.6 mm above the base of the skull according to König & Klippel (10).

In some animals stainless steel cannulae (20 gauge) were introduced stereotaxically either into the lateral ventricle or into VMH, unilaterally under ether anaesthesia. With the help of tiny screws in the skull, cannulae were anchored to the animals skull with dental cement. Coordinates for LV were A-3.4 mm, L-3.5 mm and H-2.0 mm (10).

Groups : Control animals (Group-I, n=6) were not subjected to any surgical procedures. In fifteen rats cannulae were introduced either in LV (Group II, n=7) or in VMH (Group III, n=8). After inducing bilateral VMH lesions in the remaining 15 animals, only some received LV cannulation (Group IV, n=7). Other VMH lesioned rats were not cannulated (Group V, n=8).

Food intake : Food and tap water was available adlib to all the animals housed in individual cages. Food intake for each day (24 h) was recorded. Body weight was recorded every week. Daily food intake and weekly body weight were monitored till the animals were sacrificed except during the post-surgical recovery period of 5-6 days.

Insulin administration : Insulin or saline were administered into LV or VMH with the help of microsyringe (Hamilton) and a slow injector. The volume injected never exceeded 4 μ l.

Effect of Insulin on 20 min. food intake : After two hours of food deprivation in the morning, 20 min food intake was measured 30 min following insulin administration. Insulin lente (Boots Co.) in doses of 0.04U, 0.08U and 0.16U per Kg. b. w. in 4 μ l volume or saline (4 μ l) was administered slowly either into CSF (LV) (Group II) or into the VMH

(Group III). In each group rats received any one of the insulin doses or saline in random sequence. These measurements were repeated for four consecutive days to determine the mean values for each dose and saline.

Using the above procedure, 20 min. food intake was estimated in VMH lesioned rats (Group IV) after ICV administration of insulin or saline. The test procedure was carried out after the VMH lesioned rats attained the static phase of food intake, i.e. 3-4 weeks after the lesion. Subcutaneous injections of insulin were given to VMH lesioned rats (Group V) in doses of 1.0, 2.0 and 4.0 U/kg. bw and 20 min. food intake was measured.

Lesion and cannulation sites were later confirmed histologically at the end of the study.

RESULTS

There was a significant increase in bw and 24 hr food intake after VMH lesion in rats. This progressive increase in hyperphagia (dynamic phase) ceased after 21-28 days and the food intake stabilised at a higher level (Fig. 1).

Effect of Insulin on 20 min food intake : (a) The results of effect of insulin injection on 20 min. food intake are depicted in Table I. In non-lesioned animals, 20 min. food intake showed slight but in significant increase only with higher doses of insulin given ICV. VMH lesions did not alter this effect of insulin given ICV.

When the dose of intra VMH insulin was increased, there was progressive and significant decrease in 20 min. food intake. Subcutaneous insulin administration in VMH lesioned rats resulted in elevation of 20 min. food intake.

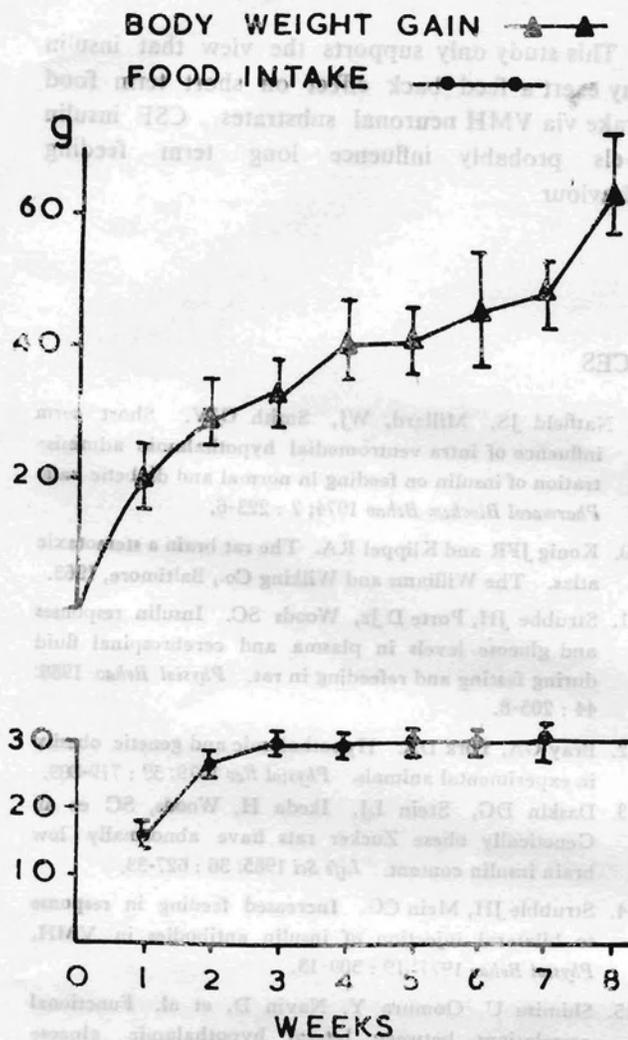


Fig. 1 : Figure showing body weight gain and food intake in VMH lesioned rats. The abscissa indicates the period in weeks after the VMH lesion at "0". Body weight (bw) gain is the difference between the bw before and after the lesion. Vertical bars show \pm SEM.

TABLE I : Effect of intracerebro-ventricular (ICV), intra VMH and subcutaneous (s/c) insulin in ventromedial hypothalamus lesioned (VMHX) and non-lesioned rats (NL) on food intake.

Insulin/Saline	Food intake after ICV Insulin		Food intake after VMH insulin NL (n=8)	Food intake after s/c insulin in VMHX (n=8)
	NL (n=7)	VMHX (n=7)		
Saline	4.83 \pm 0.09	3.38 \pm 1.13	5.00 \pm 0.38	2.25 \pm 0.75
0.04 U (1U)	5.40 \pm 0.58	3.41 \pm 1.09	2.57 \pm 0.35***	5.25 \pm 0.63*
0.08 U (2U)	5.90 \pm 0.66	4.09 \pm 1.25	2.29 \pm 0.57**	6.50 \pm 2.02
0.16 U (4U)	6.66 \pm 0.44*	6.16 \pm 1.57	1.79 \pm 0.49***	7.25 \pm 1.38**

Insulin in U/kg bw; figures in paranthesis denote subcutaneous dose.
 Food intake for 20 m in g (mean \pm SEM), 30 m after insulin administration.
 *P<0.05, **P<0.02, ***P<0.001 compared to saline, other values not significant.

DISCUSSION

Results of central administration of insulin demonstrates that it fails to alter the short term food intake neither, in the intact nor lesioned hypothalamus rats. Chronic infusion of insulin in CSF has been reported to reduce body weight and food intake (5, 6). No conclusion can, therefore, be drawn regarding the effects of CSF insulin on VMH neurones by this study.

It is likely that CSF insulin concentration have to be maintained at high levels for the penetration of insulin around circum ventricular areas or the hormone may reach the VMH neurones after long delay to exert its action. The possibility of slow penetration of insulin molecules into periventricular areas after VMH lesion cannot be ruled out (11).

It is also possible that circum-ventricular areas do not possess insulin specific receptors. It is shown earlier (7) that these areas are rich in receptors for IGF I & II, but not for insulin. The hypothalamic obesity may also lead to low insulin receptor levels or sensitivity as observed in obese rats (12, 13).

The immediate effect of reduced food intake after insulin administration in VMH is an evidence in favour of these neurones being influenced by this hormone. Earlier study (9) has demonstrated similar effects and injection of insulin antibodies in VMH (14) increased food intake in rats.

Elevation in food intake after S/C injections of insulin is due to hypoglycaemia, although blood glucose levels were not estimated in our animals. That the hypoglycaemia could increase the food intake in the absence of VMH supports the view that the blood glucose may be monitored by peripheral gluco-receptors (15, 16) or by receptors in lateral hypothalamus.

This study only supports the view that insulin may exert a feed back effect on short term food intake via VMH neuronal substrates. CSF insulin levels probably influence long term feeding behaviour

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VMH	VMH	VMH	VMH
(n=8)	(n=8)	(n=7)	(n=7)
2.00 ± 0.38	2.00 ± 0.38	2.00 ± 0.38	2.00 ± 0.38
2.27 ± 0.32***	2.27 ± 0.32***	2.27 ± 0.32***	2.27 ± 0.32***
2.50 ± 0.31***	2.50 ± 0.31***	2.50 ± 0.31***	2.50 ± 0.31***
2.73 ± 0.29***	2.73 ± 0.29***	2.73 ± 0.29***	2.73 ± 0.29***

TABLE I: Effect of intracerebroventricular (ICV) insulin (10 μg) on food intake (g) in VMH-lesioned (VMH) and pair-fed (PF) rats. Values are mean ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001 compared to saline. Input values not significant.