THE GAS EXCHANGE IN EXPERIMENTAL HYPOTHALAMIC ADIPOSITY

Ya. M. Kabak, S. M. Leites, and V. P. Al'khimenyuk

Laboratory of Endocrinology (Head – Prof. Ya. M. Kabak), M. V. Lomonosov Moscow State University; Division of Pathophysiology (Head – Prof. S. M. Leites), All-Union Institute of Experimental Endocrinology (Dir. – Prof. E. A. Vasyukova), Moscow

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A bilateral, symmetrical lesion of the hypothalamus in the region of the ventromedial nuclei or of regions lying immediately lateral thereto causes the development of adiposity in rats [3, 5, 6, 8, 10]. In the pathogenesis of this type of experimental adiposity considerable importance is attached to the onset of hyperphagia. This may be regarded as the result of the fact that the destruction of these nuclei releases the function of the ventrolaterally situated nerve formations, composing an important section of the food center, from the regulating (inhibitory) control [3, 6, 7]. A decrease in the mobility of the animals is of definite importance.

An increase in the respiratory coefficient above unity, observed in rats with hypothalamic adiposity after taking food or administration of glucose, demonstrated the intensification of the conversion of carbohydrates into lipids. Similar values of the respiratory coefficient were observed in rats without lesions of the hypothalamus, if by means of suitable training the animal was made to eat the whole of its day's ration in a short period. From this fact it has been suggested [6, 9, 10] that the increase in the respiratory quotient in "hypothalamic" rats is not the result of a primary disturbance of metabolism, but a secondary phenomenon due to hyperphagia.

We can hardly accept the view that hyperphagia is the principal factor concerned in the pathogenesis of hypothalamic adiposity. The adiposity persists in animals for a long time after the infliction of injury on the hypothalamic region, when the hyperphagia, which is well marked during the first few days and weeks after injury, is considerably weakened. The disturbance of the activity of the hypothalamic nerve formations is bound to influence the trophic processes associated with lipid metabolism. Diencephalic adiposity in man, of which experimental hypothalamic adiposity is a reproduction, is accompanied by no means invariably by hyperphagia.

It was therefore considered necessary to study the state of the basal metabolism and the value of the respiratory quotient in experimental hypothalamic adiposity in connection with the quantity of food eaten, and also the change in these indices in the obese animals during fasting and in response to the injection of glucose and amino acids.

EXPERIMENTAL METHOD

Experimental adiposity was induced in rats by bilateral electrolytic destruction of the region of the median eminence of the hypothalamus at the site of the ventro- and dorsomedial nuclei. The destruction was carried out by means of a stereotaxic apparatus devised by Belenev and Kabak [1]. Rats weighing 170-230 g were anesthetized with nembutal, and through an opening in the parietal bone an electrode (the anode) was introduced, the angled tip of which was situated approximately 1.8-2.0 mm posterior to the bregma, 0.5-0.6 mm lateral to the midline and 0.4 mm from the base of the skull. The cathode was connected by a wet contact to the animal's tail. A current of 2 ma was passed for 5-30 seconds (for a detailed description of the method see [1]). After

TABLE 1

Gas Exchange in Rats with Hypothalamic Adiposity

Rat No.	Date of injury	Initial wt. (in g)	Date of investigation (1959)	Wt. at the time of investigation (in g)	O_2 consumption (in 1 hr)		Excretion of CO_2 (in 1 hr)		Respiratory quotient
					absolute (liters)	per cm^2 of body surface (in ml)	absolute (liters)	per cm^2 of body surface (in ml)	
Control group – 10 rats (mean figures)		—	—	208	0.37	1.16	0.35	1.10	0.94
79 ♀	Jan. 20, 1959	182	Mar. 28, April 7	312—322	0.45	1.05	0.47	1.10	1.04
6 ♀	Dec. 17, 1958	280	April 1, May 13	340—386	0.62	1.28	0.62	1.28	1.0
15 ♂	Feb. 20, 1959	205	July 24, Aug. 31 Nov. 21	482—497 546	0.53 0.43	0.92 0.70	0.60 0.63	1.04 1.03	1.13 1.46
16 ♂	Feb. 20, 1959	211	July 23 Aug. 1 Aug. 15 Aug. 18	531 528 540 533	0.37 0.45 0.54 0.56	0.61 0.76 0.89 0.93	0.48 0.45 0.70 0.70	0.80 0.76 1.16 1.17	1.29 1.0 1.3 1.25
46 ♂	March 20, 1959	220	July 22, Aug. 17 Aug. 18, Aug. 24 Nov. 16, Nov. 20	686—700 703—680 646—654	0.55 0.62 0.59	0.77 0.87 0.86	0.60 0.58 0.73	0.84 0.81 1.06	1.09 0.93 1.24
24 ♀	June 27, 1958	170	Mar. 14, Mar. 23 Mar. 23, April 8	436—406 406—461	0.48 0.55	0.96 1.01	0.52 0.69	1.03 1.27	1.08 1.25
4 ♀	June 30, 1958	165	Mar. 13 Apr. 19	570 606	0.57 0.54	0.91 0.83	0.68 0.72	1.08 1.10	1.19 1.33
1 ♀	May 28, 1958	177	Feb. 28, Mar. 20	725—784	0.57 (0.51—0.63)	0.73	0.73 (0.68—0.78)	0.94	1.28 (1.25—1.36)

the operation the animals were kept for 1-2 days in separate cages; they were given food and water next morning. The rats developed a considerable hyperphagia very quickly after the operation, although its appearance during the first few days after the operation did not, in our observation, demonstrate the inevitable development of adiposity.

Investigation of the gas exchange for a period of one hour by the closed chamber method in an apparatus for small animals (Shaternikov's type, as modified by Isichenko [2]) was carried out 3-11 months after operation. The weight of the rats at this period was considerably above normal, and in one female (No. 1) it reached 784 g. At the end of the investigation the animals were sacrificed and serial histological sections of the hypothalamus were made (fixation with formalin, stained with thionin). We studied every tenth section, cut to a thickness of 10 μ. In all the adipose rats investigated we found bilateral lesions of the hypothalamus with total or partial destruction of the region of the ventro- and dorsomedial nuclei. In determining the site of the lesions we used the pictures from Szentagotai's atlas.

EXPERIMENTAL RESULTS

It will be seen from the figures in Table 1 that the absolute quantities of O_2 absorbed and CO_2 eliminated by the adipose rats were higher, but when calculated per cm^2 body surface (according to the formula: $S = 9.1\ W^{2/3}$, where S is the surface area of the body in cm^2 and W the body weight in g), lower than in the control animals of normal weight. The change in the respiratory quotient is characteristic: in the rats with only slight adiposity (Nos. 79, 6) it was equal or very close to unity; the result was the same in animals with well developed adiposity at those periods when weight was not increased or when it was decreased (rats Nos. 46, 24). At those periods when increase in weight was taking place the respiratory quotient was always greater than unity. In this respect rat No. 1, with well marked and increasing adiposity (see figure) is very demonstrative. At autopsy of this animal the region of damage to the hypothalamus was found to be more extensive than in the other rats (from the middle of the hypothalamus forward, including the anterior part of the ventro- and dorso-premamillary nuclei).

Change in weight in experimental hypothalamic adiposity in rats. On the right – control. On the left – experimental animal (initial weight 177 g, injured on May 29, 1958; weight on February 27, 1959 – 738 g).

It may be concluded from the results obtained that in animals with slight or moderate adiposity there is a preferential utilization of carbohydrates and, at the same time, economy in the utilization of fat. In severe adiposity, in the period of increase in weight, the respiratory quotient greater than unity testifies to the activation of the processes of conversion of carbohydrates into lipids. The same result was obtained during an investigation of the gas exchange in mice with experimental adiposity caused by aurothioglucose [4].

It must be emphasized that in rats in the stage of development of a relatively stable adiposity, with a respiratory quotient greater than unity, no hyperphagia was observed. In rat No. 16, for instance, the body weight remained unchanged for a period of seven days (526-528 g), and the quantity of edible standard diet taken in the 24 hours was on the average 31 g. In the same experimental conditions, in rat No. 15 (weight 490-500 g)

TABLE 2

Change in Gas Exchange in Control Rats and in Rats with Hypothalamic Adiposity during Fasting and Subsequent Feeding

Rat No.	Experimental conditions	Wt. of rat (in g)	Change in weight (in %)	O_2 consumption (in liters per hr)	O_2 elim. (in liters per hr)	Respiratory quotient
	Control					
	Feeding	306	—	0.55	0.50	0.91
	Fasting 24 hr	284	—7.1	0.58	0.49	0.84
	Fasting 48 hr	275	—10.1	0.68	0.55	0.81
	Feeding	290	+5.4	0.57	0.57	1.0
	Experiment					
15 ♂	Feeding	497	—	0.53	0.60	1.13
	Fasting 24 hr	485	—2.4	0.54	0.57	1.05
	Fasting 48 hr	472	—5.03	0.51	0.54	1.06
	Feeding 24 hr	484	+2.5	0.46	0.61	1.32
	Feeding 48 hr	490	+3.7	0.50	0.55	1.1
1 ♀	Feeding	772	—	0.58	0.80	1.38
	Fasting 24 hr	733	—5.05	0.73	0.92	1.26
	Fasting 48 hr	708	—8.3	0.76	0.93	1.22
	Feeding 24 hr	739	+4.4	0.47	0.80	1.7
16 ♂	Feeding	533	—	0.56	0.70	1.25
	Fasting 24 hr	524	—1.7	0.56	0.64	1.14
	Fasting 48 hr	509	—4.5	0.57	0.62	1.09
	Fasting 3 days	496	—7.1	0.60	0.64	1.06
	Feeding 24 hr	498	—0.4	0.55	0.59	1.07

the daily food intake was 30 g, and in rat No. 4 (weight 658-665 g) the daily food intake was 28.5 g. In the control group of rats (weight 219-225 g) the mean quantity of edible food taken in the 24 hours varied from 28 to 30 g. This suggests that in the stable stage of adiposity hyperphagia is not a factor maintaining the superfluous weight; the reason why it persists is evidently the excessive conversion of carbohydrates into lipids, since the respiratory quotient in these adipose rats was greater than unity, whereas in the control (non-adipose) rats it was less than unity.

The change in body weight of the adipose rats during fasting, as an index of the mobilization of fat, and also the changes in the value of the respiratory quotient in the period of fasting and during the subsequent reversion to normal feeding, are also of interest. In the rats with hypothalamic adiposity, the decrease in weight during fasting for 48 hours was less marked, when expressed in percent, than in the control group (Table 2). This may serve as an indirect index of the inhibition of mobilization of fat in the adipose animals. In the adipose rats with a respiratory quotient greater than unity, the value of the latter diminished during fasting without, however, falling below 1. This fact shows that even in the absence of intake of carbohydrates into the body, the conversion of endogenous carbohydrates into lipids takes place in the adipose animals.

Attention is drawn to the considerable increase in the respiratory quotient when the rats resume normal feeding after preliminary fasting (rats Nos. 15 and 1), if at the same time they increase in weight. When on resuming normal feeding their weight does not increase (rat No. 16), no increase in the respiratory quotient takes place. This variant of the experiments thus also confirms the fact that excessive conversion of carbohydrates into lipids is a factor in the gain in weight during hypothalamic adiposity.

The subcutaneous injection of glucose (0.3 ml of a 40% solution per 100 g body weight) into rats of the control group of normal weight leads in the course of one hour to an increase in the respiratory quotient (Table 3), and in some experiments its value is greater than unity. In adipose rats the injection of the same dose of

TABLE 3

Gas Exchange in Control Rats and in Rats with Hypothalamic Adiposity before and after Subcutaneous Injection of Glucose

Rat No.	Date of infliction of lesion	Date of experiment (1959)	Wt. of rat (in g)	Before injection of glucose			1 hr after injection of glucose				Notes
				O_2 consumption (in liters per hr)	elimination of CO_2 (in liters per hr)	respiratory quotient	dose of glucose (in ml 40% solution per 100 g body weight)	O_2 consumption (in liters per hr)	elimination of CO_2 (in liters per hr)	respiratory quotient	
Control (5 rats, mean figures)											
			200	0.36	0.34	0.94	0.3	0.32	0.34	1.06	
Experiment											
79	Jan. 20, 1959	Mar. 28	312	0.43	0.43	1.0	0.3	0.36	0.43	1.2	
24	June 27, 1958	Mar. 25	440	0.55	0.60	1.09	0.3	0.51	0.60	1.18	
1	May 28, 1958	Feb. 28	784	0.57	0.73	1.28	0.3	0.48	0.78	1.6	
15	Feb. 20, 1959	Aug. 18	492	0.55	0.56	1.02	0.6	0.59	0.61	1.03	Determination after 2 hours
		Aug. 25	510	0.59	0.56	0.95	0.3	0.52	0.55	1.06	
16	Feb. 20, 1959	July 23	531	0.39	0.51	1.3	0.3	0.38	0.51	1.3	
		Aug. 15	540	0.55	0.71	1.3	0.6	0.46	0.64	1.5	
4	June 30, 1958	Mar. 21	595	0.52	0.62	1.2	0.3	0.52	0.63	1.21	Determination after 1 hour
		May 19	606	0.54	0.76	1.4	0.6	0.59	0.75	1.27	
								0.46	0.75	1.63	Determination after 2 hours
46	Mar. 20, 1959	July 22	686	0.48	0.50	1.04	0.3	0.45	0.50	1.1	

TABLE 4

Absorption of Oxygen in Control Rats and in Rats with Hypothalamic Adiposity before and after Injection of 0.3 ml of 5% Cystein Solution per 100 g Body Weight

Rat No.	Date of infliction of lesion	Date of expt. (1959)	Wt. of rat (in g)	Absorption of O_2 (in liters/hr)	
				before injection	after injection
Control group (8 rats, mean figures)			220	0.42	0.50
79	Jan. 20, 1959	Apr. 7	320	0.48	0.57
15	Feb. 20, 1959	July 28	473	0.45	0.45
16	Feb. 20, 1959	Aug. 1	530	0.45	0.45
4	June 30, 1959	April 6	606	0.68	0.70
46	Mar. 20, 1959	July 27	670	0.46	0.43
1	May 28, 1959	April 8	714	0.56	0.56

glucose per 100 g body weight may be accompanied by a fairly well marked increase in the respiratory quotient (see Table 3, rats Nos. 79 and 24 – period of gain in weight, rat No. 1 – well marked adiposity); in other cases – an increase in the respiratory quotient which may be detected during the injection of a large dose of glucose (rat No. 16) or two hours after the injection (rats Nos. 4 and 15). In one rat (No. 46) with well marked adiposity the respiratory quotient was unchanged. These results show that in the stable stage of adiposity, glucose when injected parenterally is either not utilized (the absorption of O_2 and elimination of CO_2 are unchanged) or is partially converted into lipids (the respiratory quotient is greater than unity and the O_2 consumption is decreased).

In rats of normal weight the subcutaneous injection of the amino acid cystein (0.3 ml of a 5% solution per 100 g body weight) causes a significant increase in O_2 consumption in the course of one hour after injection (specific dynamic action). The same effect is observed in rat No. 79 in the initial period of increase in body weight, when it has not reached a high value (Table 4). In all the four remaining rats investigated with marked adiposity 4-11 months after injury to the region of the hypothalamus, no absorption of O_2 took place after the injection of cystein, i.e., the specific dynamic action of the amino acid was absent. The same result was observed by one of us (S. M. Leites) in mice with adiposity due to aurothioglucose.

It may be concluded from the findings as a whole that in rats with experimental hypothalamic adiposity the O_2 consumption in absolute figures is increased, but when calculated in terms of cm^2 body surface it is decreased. In the period of gain in weight the respiratory quotient is greater than unity; this is also observed in some animals after injection of glucose. This shows that the deposition of fat in hypothalamic adiposity is associated with an intensification of the conversion of carbohydrates into lipids, and in adipose rats this activation may take place also without hyperphagia. In severe hypothalamic adiposity the injection of cystein has no specific dynamic action, in contrast to its effect in animals of normal weight.

SUMMARY

In rats with experimental hypothalamic adiposity absolute O_2 consumption increases, but declines if taken as the rate per 1 cm^2 of the body surface. In the period of rising weight gain the respiratory quotient

exceeds 1; the same is observed in a number of animals after subcutaneous glucose injection. This indicates that deposition of fat in hypothalamic adiposity is connected with augmented conversion of carbohydrates into fats; this process may occur in adipose rats even without hyperphagia. Cystein administration does not exert any specific dynamic action in marked hypothalamic adiposity.

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