THE ISLET APPARATUS OF THE PANCREAS IN RATS WITH "HYPOTHALAMIC" OBESITY

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The study of the state of the endocrine apparatus in obesity caused by injury to the hypothalamus is by no means complete. In such cases the islets of Langerhans (IL) in the pancreas are of particular interest as an important link in the regulation of lipid and carbohydrate metabolism.

S. M. Leites and A. M. Agaletskaya [2] have reported that in persons with certain forms of obesity, in the initial, progressive stage hyperfunction of the IL may be present, giving way to hypofunction as the obesity changes into a stable form. S. M. Leites [3,4] cites the results of his own investigations and data from the literature, which suggest that hyperfunction of the IL has an important role in the pathogenesis of obesity. We were therefore skeptical of reports that no changes were present in the IL of rats with obesity caused by injury to the hypothalamus [5,6,7]. Long [8] observed glycosuria in obese rats, in contrast to normal rats, only after partial pancreatectomy. He regarded this as a manifestation of the greater lability of the IL in the obese animals.

TABLE 1. Mean Size of Nuclei of the β-Cells of the Pancreas (limits of variation are given in parentheses)

Group of rats	No. of animals	Body weight (g)	Size of nuclei (μ^2)
Control	8	200-300	21.68 ± 0.09 (20.26 ± 0.43–23.47 ± 0.33)
Experimental	11	300-400	26.61 ± 0.12 (22.17 ± 0.22–29.03 ± 0.41)
	9	400-500	28.34 ± 0.62 (24.07 ± 0.39–41.16 ± 3.0)
	6	More than 500	29.59 ± 0.2 (26.41 ± 0.31–31.97 ± 0.37)

Changes in the IL have been described in mice, but in other types of obesity. Hausberger and Ramsay [7], for instance, studied mice developing obesity as a result of grafting of a tumor secreting adrenocorticotropic hormone, and found enlargement of the IL with the appearance of cavities and newly formed β-cells, together with the degranulation of the β-cells to a degree corresponding to the degree of obesity. Mayer [9] described hypertrophy of the IL in mice with hereditary hyperglycemia. According to Mayer and co-workers [10], the level of the blood sugar is elevated in mice with hereditary obesity, but lies within normal limits in obesity caused by administration of aurothioglucose or by injury to the hypothalamus.

EXPERIMENTAL METHOD

Obesity was produced in female albino rats weighing 170-230 g by means of a bilateral electrolytic injury in the region of the ventromedial nuclei of the hypothalamus. The operation was performed by means of a stereotaxic apparatus constructed in our laboratory [1]. The rats remained under observation for 1-12 months after the operation.

Pieces were excised from the tail of the pancreas, in the region of the central artery, for histological examination.

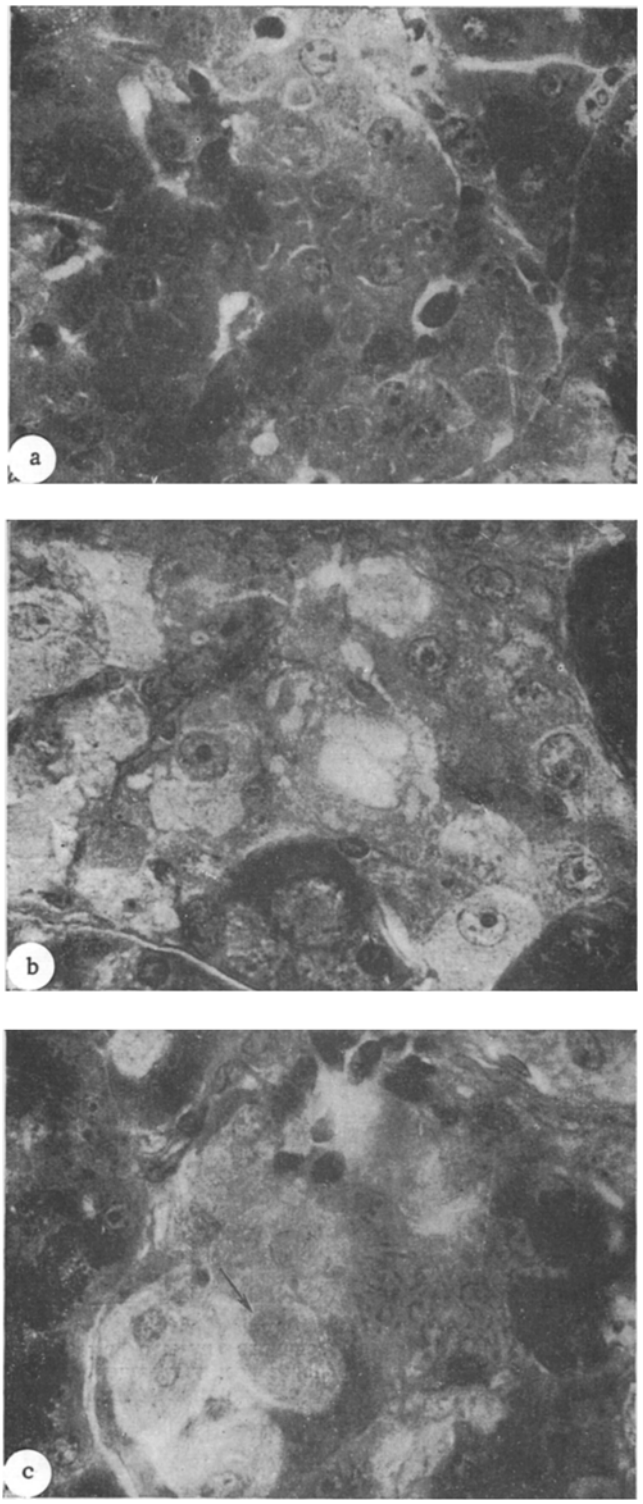

Fig. 1. β-Cells of the islets of Langerhans in the pancreas in rats. a) Normal; b) developing obesity; hypertrophy of the β-cells and of their nuclei and nucleoli is readily seen; in the center are destroyed β-cells; c) developing obesity; the arrow points to cells of transitional type. Azan — Mallory's stain. Magnification: eyepiece 15×; objective 50×.

TABLE 2. Duration of the Process of Obesity and Size of the Nuclei of the β-Cells

Time after operation	No. of animals	Size of nuclei (μ^2)
Control	8	21.68 ± 0.09
3 weeks	3	32.42 ± 0.12
1-3 months	5	27.98 ± 0.14
4-6 months	7	29.25 ± 0.29
7-9 months	6	28.51 ± 0.24
10-12 months	4	27.10 ± 0.15

The tissue was fixed by Helly's method and embedded in paraffin wax. Sections were cut to a thickness of 3μ and stained by Mallory's method, as modified by Heidenhain (azan). The nuclei of the β-cells were measured in two diameters (in microns) by means of an ocular micrometer. In each animal 100 nuclei in different islets were measured. The size of the nuclei was expressed conventionally as the product of the two diameters.

The blood sugar was determined by the Hagedorn-Jensen method. Food was withheld for 18 h before the experiment. Sugar was given by mouth in a dose of 3 g per kg body weight, and blood samples were taken in parallel series before, and 30 min and 1, 2, and 3 h after administration of glucose.

EXPERIMENTAL RESULTS

Definite changes were observed in the microstructure of the IL, associated with obesity. Most of the obese rats showed a considerable increase in the number and size of their IL. In some, but not all, rats, giant islets were found, several times larger than normal. Their β-cells were frequently hypertrophied and were distinguished by the clear demarcation of their outlines and by a varied degree of degranulation of their cytoplasm (Fig. 1a, b). In all but one of the obese rats, the nuclei of the β-cells were enlarged, and in the sections they frequently appeared less intensively stained ("light") than in the controls. A "light" nucleus of this sort was evidence of degenerative changes in the β-cells. In some specimens these cells had disintegrated, and empty spaces appeared where they had been (see Fig. 1b). Conversion of acinar cells into islet cells was observed, cells of a transitional type being found both in the immediate vicinity of the islets and in more distant parts of the pancreas (Fig. 1c). The sections showed many newly formed islets, often consisting of 3-5 cells. With the exception of these cells of transitional type, the acinar tissue, and also the α-cells of the IL, were unchanged.

The nuclei of the β-cells were measured in 8 control and 26 experimental rats, divided conventionally into 3 groups according to their degree of obesity (Table 1).

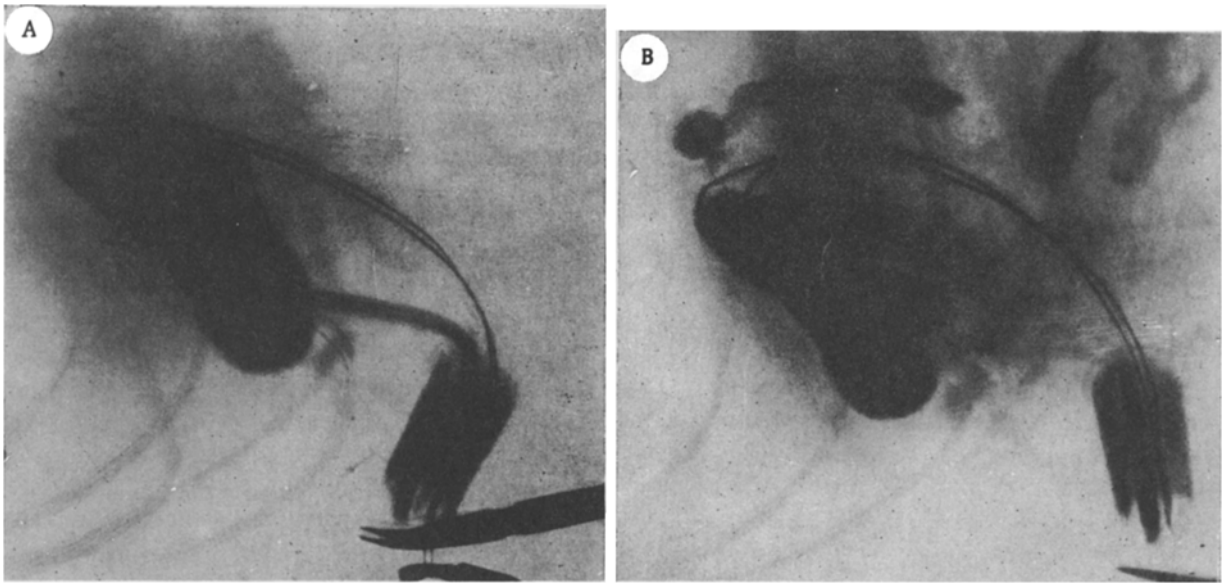

Fig. 2. Roentgenogram of the gall bladder with the obturator in situ (A) and immediately after its removal (B). The gall bladder is filled with 40% sergosin (abrodil) solution.

TABLE 3. Blood Sugar of Control and Experimental Rats at Different Times after Sugar Intake (as percentages of the initial level)

Group of rats	Rat No.	Fasting blood sugar (mg%)	Time after sugar intake				Size of nuclei of β-cells (in μ^2)
			30 min	1 h	2 h	3 h	
Control	1	120	123	121	124	110	
	2	106	138	131	111	102	20.26 ± 0.43
	5	124	117	106	104	92	
	8	127	115	121	100	99	
	9	119	120	126	–	110	20.88 ± 0.32
	7	106	123	119	101	115	23.47 ± 0.33
	10	104	141	134	115	101	
Experimental	24	102	121	116	135	116	27.22 ± 0.18
	38	102	116	112	147	142	25.26 ± 0.31
	50	116	156	149	104	–	26.42 ± 0.28
	56	110	120	121	128	112	
	1	91	141	125	173	163	38.36 ± 0.50
	3	64	278	268	278	337	31.97 ± 0.37
	8	92	129	121	119	119	
	13	101	130	125	112	101	

It is clear from Table 1 that as the body weight increased (reflecting to some extent the degree and duration of the obesity), so also did the size of the nuclei of the cells that were examined. The relationship between the size of the nuclei of the β-cells and the duration of obesity is shown in Table 2.

It will be clear from Table 2 that three weeks after the operation the mean size of the nuclei of the β-cells differed to a statistically significant degree from the mean size in the controls. Between 1 and 3, and between 4 and 6 months after the operation, a further successive increase in the mean size of the nuclei of the β-cells took place, and this also was statistically significant. Subsequently, no further increase in the size of the nuclei took place.

A sugar tolerance test was carried out on eight obese and seven control rats, and the blood sugar concentration determined (Table 3). The results given in Table 3 show that the control animals developed hyperglycemia after the

administration of sugar, but 3 h later the blood sugar in four rats had fallen approximately to the initial level, or even lower.

The initial blood sugar level in the obese rats was within normal limits or lower. In rats Nos. 1 and 3, the blood sugar 3 h after administration of sugar remained significantly higher than normal. It is interesting to note that these two rats were distinguished by the largest size of the nuclei of the β-cells. An unusual reaction to administration of sugar was observed in rat No. 38, in which the blood sugar level rose significantly only 2 h after the sugar was given, while the raised level was maintained during the third hour.

In eight experimental rats the blood sugar was determined without a preliminary period of fasting. In four of these rats the sugar concentration was increased, and in two of these rats the increase was such (to 164 and 241 mg%) that it could be regarded as frank hyperglycemia.

Our results showing significant changes in the microstructure of the pancreas in rats with "hypothalamic" obesity were in marked contrast to the results obtained by other workers [5, 6, 7, 10]. The increase in the size and number of the IL, associated with the new formation, hypertrophy, and enlargement of the nuclei of the β-cells, were evidence of stimulation of the endocrine function of the pancreas in rats with "hypothalamic" obesity. At the same time, degenerative changes were observed in the insular apparatus in certain animals, and we regarded these as indicating some degree of exhaustion.

The fact that among the rats with "hypothalamic" obesity we found animals with frank hyperglycemia or, judging from their sugar curves, animals in a diabetoid state (with latent diabetes) agrees with our suggestion that the insular apparatus of these rats may become exhausted as a result of physiological overstrain.

The changes in the insular apparatus of rats with "hypothalamic" obesity, as described above, and the discovery of hyperglycemia and latent diabetes in several such animals are not, in our opinion, a causative link (or, at least, not only that) in the process of hyperphagia and obesity, but are probably a secondary reaction. We base this opinion on the fact that changes in the IL are observed and intensified over a considerable period of time (weeks or months), whereas hyperphagia and obesity are observed soon after injury to the hypothalamus.

SUMMARY

The state of islets of Langerhans was investigated in 26 female rats with obesity developed after a bilateral electrolytic lesion of the hypothalamus.

In adipose rats an enlargement of the size of islets and of their number occurred at the expense of hypertrophy, hyperplasia, and β-cell neoformation. The size of the β-cell nucleus was enlarged, this being related to some extent to the degree and duration of the obesity process. In many obese rats degranulation of the β-cell cytoplasm was observed, whereas, in some animals, there were degenerative changes in these cells and even complete disintegration of some of them.

These data give ground to suppose that in obese rats the functional activity of β-cells of the islets is increased, which may lead to their exhaustion as a result of overexertion. This is in accordance with the presence among the obese rats of animals with distinct hyperglycemia and latent diabetes.

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