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OVERALL CHARACTERISTICS OF OBESITY SYNDROMES

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1. The evolutive aspect of the obesity syndromes

Although obesity syndromes have been extensively studied by clinicians and "basic" researchers as well, a general concept of the syndrome(s) is still very difficult to sort out. In animals, contradictory data were partly understood when it was found that obesity was an evolutive syndrome and that the early phase of obesity was quite different from the late (or later) one. The following sequence of events was eventually proposed: hyperinsulinemia + hyperphagia (or hyperphagia + hyperinsulinemia; or hyperinsulinemia alone due to some unknown overreactivity of the β -cells) would initially produce an over-stimulation of target tissues of insulin, carbohydrate tolerance being normal. Subsequently, (i.e. with time and increasing hyperinsulinemia) a decrease in the sensitivity of the target tissues of insulin would become apparent, leading to an insulin-resistant state that translated itself by the simultaneous presence of hyperglycemia and hyperinsulinemia together with abnormal tolerance to carbohydrates (1).

Several studies (2-7) made with experimentally- or genetically-produced animal obesities strongly suggested the following sequence of events:

* Invited speaker. This summary reflects the research work carried out by the investigators of this Laboratory. The references given are therefore almost exclusively those of this Laboratory, for which apologies are presented to other groups working in these fields.

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	<u>Early phase of obesity</u>	<u>Late phase of obesity</u>
1. Basal insulinemia	normal or moderately increased	increased
2. Stimulated insulinemia	moderately increased	markedly increased
3. Glycemia	normal or decreased	normal or increased
4. Glucose tol. test (GTT)	normal	usually abnormal
5. Blood sugar lowering capacity of exogenous insulin	normal	decreased or nil
6. Insulin receptor number at plasma membranes	normal	decreased
7. Adipose tissue lipogenesis	increased (basal) and insulin responsive	increased (basal) and insulin resistant
8. Liver lipogenesis	normal	increased
9. Muscle glucose metabolism	already insulin resistant	more insulin resistant
10. Body weight	increased	markedly increased

These data together supported the concept that obesity syndromes were indeed a pathology in which abnormalities did become more marked with the duration of the syndrome, the duration being accompanied by an increase in insulin secretion seen as an important pathological factor probably, however, with other as yet unidentified abnormalities.

2. The Central Nervous System (CNS) - endocrine pancreas axis

On the basis of many experiments carried out in a variety of obese insulin-resistant animal models, it appeared that hyperinsulinemia was, if not the earliest, at least one of the earliest abnormalities that could be detected, and that it could well be responsible for many of the pathological changes found in these animals (8).

The rationale for proposing the existence of a Central Nervous System (CNS) endocrine pancreas axis, an axis that could be abnormally regulated in animals, was as follows: a) in the inherited forms of obesity, several defects exist that can be attributed partly or completely to CNS dysfunctions: hyperphagia, infertility, alterations of concentration and/or localizations of brain hormones and neurotransmitters, abnormal body temperature regulation (1, 8); b) it was striking to observe that whether obesity was of genetic etiology or produced experimentally by hypothalamic lesions, the final respective syndromes and their respective evolution with time were analogous (4, 6); c) the existence of an altered neuroanatomical organization of the CNS of the genetic (ob/ob) obese mice was described (9, 10).

On the basis of the above-mentioned considerations, we favored the view that genetically obese animals might be defective in some CNS sites partly responsible for the regulation of adequate insulin secretion.

Due to this and as an initial step, we initiated experiments attempting, albeit often via invasive techniques, to suggest the existence of a relationship between the CNS and the endocrine pancreas in normal rats, with the aim of subsequently investigating this relationship in genetically obese rodents. For the sake of clarity, the summary of the data obtained will be summarized as two subheadings:

- a) the CNS-endocrine pancreas axis studied with non-invasive techniques
- b) the CNS-endocrine pancreas axis studied with invasive techniques

a) The CNS-endocrine pancreas axis studied with non-invasive techniques

A CNS-endocrine pancreas loop has been demonstrated to exist. This loop is triggered, among other factors, by the presence of food in the oral cavity (in our experimental design the trigger used was the artificial, metabolically inert sweetener, saccharin) and can be shown to promote, in unanesthetized normal rats, a rapid, transient insulin secretion that is unrelated to any changes in blood sugar levels (cephalic phase insulin secretion) (11). Of further importance was the demonstration that for cephalic phase insulin secretion to occur, the endocrine pancreas required an intact innervation, the presence of the vagus nerve in particular. Indeed, when the pancreas was severed from its normal innervation, the occurrence of cephalic phase insulin secretion was completely abolished (11). The cephalic phase insulin secretion is certainly a complex loop, the regulation of which is still poorly understood. However, it definitively requires a CNS integration since it is possible to suppress it by injecting procaine locally in the ventromedial hypothalamus (12).

Cephalic phase insulin secretion may only represent a tool for studying CNS-endocrine pancreas relationships. It may also have physiological and/or pathological implications. This view was supported by the following experiments. Identical normal rats of the same sex, age, basal insulinemia and body weight were tested for the amplitude of their cephalic phase insulin secretion. Under these conditions, the seemingly homogeneous group of rats was splitted in two sub-groups, i.e. high and low cephalic phase insulin responders (13). Subsequently, all rats were given a calorie rich diet, and their increases in body weight over the next following days were measured. Under these conditions, high cephalic insulin secretion responders gained almost twice as much body weight than the low responders. These findings support the concept of a causative relationship between the amplitude of orosensory-endocrine-metabolic reflexes, appetite, and the likelihood to develop obesity in the rat (13).

b) The CNS-endocrine pancreas axis studied with invasive techniques

In an initial series of experiments carried out with normal anesthetized rats, it was demonstrated that acute electrolytic lesions of the ventromedial hypothalamus (VMH) resulted in marked increases in glucose-induced insulin secretion (14). It was suggested that the VMH and/or related CNS sites normally exerted an inhibitory influence upon the secretory activity of the β -cells that was removed by such lesions. Subsequently, it was shown that the rapid, glucose-induced hyperinsulinemia that followed acute VMH lesions made in normal anesthetized rats, could be promptly and completely reversed to normal by superimposed acute vagotomy (15). This indicated that the normal inhibitory influence of the CNS on the secretory activity of the β -cells involved the autonomous nervous system, and that an acute lesion (e.g. by extrapolation, possibly a dysfunction of the CNS) of the VMH and related areas produced hyperinsulinemia via the vagus nerve.

The consequences of semi-chronic (7 days) lesions of the VMH upon the secretory activity of the endocrine pancreas were also studied. In these experiments, the increased food intake that usually follows VMH lesions was prevented by pair-feeding, using an automatic food distributor. Seven days after VMH lesions, pancreases were isolated and perfused. These investigations revealed changes not only in insulin secretion but in those of glucagon (16) and somatostatin as well (16, 17). More specifically, there was an increase (in pancreas from VMH-lesioned rats compared to controls) in insulin and glucagon secretion, together with a decrease in that of somatostatin. These abnormalities of the pancreases from VMH-lesioned rats were partly related to an increased cholinergic activity (presumably due to hyperactive intra-islets post-synaptic ganglion cells) since they could be reversed to normal by superimposed infusion of the cholinergic inhibitor, atropine. Such data further supported the concept, that emerged from the acute *in vivo* experiments mentioned above, of a link between CNS sites, the VMH in particular, the vagus nerve and the overall secretory activity of the endocrine pancreas. Other experiments stressed the role of the vagus nerve as an important link between the CNS and the endocrine pancreas. It had been reported by Powley et al. (18) that, when using anatomical tools such as the retrograde axonal transport of horseradish peroxidase (HRP) used as marker administered randomly into the whole pancreas, both nucleus ambiguus and the dorsal motor nucleus of the vagus nerve were stained, within the brain stem, with HRP. This suggested that these two loci could well be the source of vagal efferent fibers that would innervate the endocrine pancreas. To test this point, the brain stem was explored via discrete local, electrical stimulation of sites that would stimulate insulin secretion in normal anesthetized rats (19). It was found that unilateral stimulation of nucleus ambiguus indeed produced a rapid rise in plasma insulin levels, whereas stimulation of most of other brain stem regions (except the

dorsal motor nucleus of the vagus nerve that is currently being investigated) were silent in this respect. Insulin secretion produced by stimulation of the nucleus ambiguus was greatly decreased by bilateral cervical vagotomy or by pre-treatment of the animals with the cholinergic inhibitor, atropine (19). Thus, these two brain stem sites, the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve, appear to be the main source of vagal motor-neurons that facilitate insulin secretion (20).

The brain stem will certainly (of course with other CNS sites) prove to be submitted to a complex regulation from many different interrelated fibers and neurotransmitters. Thus, using an electrophysiological approach it could be shown that the nucleus of the tractus solitarius was not only one of the main relay site for afferences arising from the oropharynx (and therefore involved, in particular, in cephalic phase insulin secretion) but was under the control of higher structures such as the lateral hypothalamic area (21). It was also shown that the nucleus ambiguus, demonstrated to elicit insulin secretion upon its electrical stimulation, was under a tonic inhibition by γ -amino-butyric acid (GABA), a finding that may also have physiological and pathophysiological implications (Bereiter, Berthoud, Becker and Jeanrenaud, in preparation).

Most of the data summarized above indicate that the vagus nerve appears to be one of the major link between the CNS and the endocrine pancreas. However, the CNS might also regulate endocrine pancreas via humoral factors, as suggested below.

It was observed that bilateral electrical stimulation of the lateral hypothalamic area in anesthetized rats produced, under certain conditions, a prompt and marked (changes over baseline being around 8 ng/ml) rise in plasma insulin levels that was not related to changes in glycemia (21). However, such stimulation of insulin secretion was not changed by superimposed atropine administration, or bilateral acute vagotomy, or β -adrenergic blockade, or chordotomy. Thus, this lateral hypothalamic area-induced rise in insulin levels did not appear to be mediated by classical autonomic neural output pathways. Instead, these data suggested that insulin secretion had been promoted by the release of a humoral factor.

Before attempting to detect a humoral factor that would be released into the blood upon lateral hypothalamic stimulation (an impossible task before knowing the nature of such potential humoral factor), experiments were carried out by which extracts of the hypothalamus were tested for their insulin secretion promoting activity when administered to normal anesthetized recipient rats. Indeed, hypothalamic extracts (VLH, VMH) had the ability to stimulate insulin secretion *in vivo*, an effect that was not related to changes in glycemia (23). It was shown, in particular for extracts obtained from ventrolateral hypothalamus, that catecholamines, acetylcholine and enkephalins could be excluded as candidates in producing

insulin secretion. This was of importance as these neurotransmitters are present in the hypothalamus. When hypothalamic extracts were partially purified, their insulin-releasing activity was found to correspond to compounds of low molecular weight (3600 daltons or lower) which appeared to be polypeptidic in their nature (23). It is not possible as yet to assign a physiological role to the factor(s) found in the hypothalamus. It is of interest to mention, however, that preliminary data indicate that the insulin promoting activity of ventrolateral hypothalamus of genetically as well as experimentally produced (VMH lesions) obese rats is increased when compared to that of control animals (23).

Conclusions:

1. Obesity syndromes in rodents are a progressive pathology. During the initial phase of the disease, hyperinsulinemia is moderate but suffices to over-stimulate hepatic lipogenesis, therefore resulting in over-production of very low density lipoproteins, VLDL. It also suffices to over-stimulate lipogenesis and VLDL uptake by adipose tissue, hence obesity. During a later phase of obesity, a state of insulin resistance occurs that produces inappropriate glucose homeostasis. It is conceivable that such observations may partly apply to human obesity syndromes.
2. The etiology of hyperinsulinemia is unknown. It is suggested that a possible cause of some obesity syndromes might be a dysfunction of the modulation of the endocrine pancreas by the Central Nervous System.

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