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Neuroendocrine Mechanisms Involved in Regulation of Body Weight, Food Intake and Metabolism

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STEFFENS, A. B., J. H. STRUBBE, B. BALKAN AND A. J. W. SCHEURINK. *Neuroendocrine mechanisms involved in regulation of body weight, food intake and metabolism.* NEUROSCI BIOBEHAV REV **14**(3) 305–313, 1990.—Body weight regulation is the result of food intake and energy expenditure. The central nervous system (CNS), and in particular, the hypothalamus, controls food intake as well as metabolism, the latter mainly by autonomic effects on the islet of Langerhans, hepatocytes and adipocytes. Body weight, more precisely body fat content, is probably controlled by a feedback mechanism in which insulin, released from the B cell of the islet of Langerhans, plays a key role. The islet of Langerhans is an intricate neuroendocrine unit in which the release of glucagon, insulin, and somatostatin from A, B, and D cells, respectively, is controlled by the CNS via a rich autonomic innervation. In addition, the endocrine cells of the pancreas influence each other by paracrine actions. The CNS control of the islets shapes the plasma insulin and blood glucose profiles during the circadian cycle and thereby regulates the nutrient flow to the different tissues in the body. Thus, the CNS structures involved in regulation of body weight and food intake control also metabolism. The mechanisms contributing to match food intake and the needs of metabolism are discussed.

Body weight regulation Food intake regulation Islet of Langerhans Sympathetic system
Parasympathetic system Metabolism Insulin Glucagon

BODY weight is the result of food intake and energy expenditure. In most adult animals and humans, body weight is maintained within narrow limits during long periods. Also body composition, i.e., the ratio between fat and fat free mass is kept nearly constant. To maintain body weight and body composition an accurate control of flow of nutrients to different tissues has to be achieved under all kinds of metabolic conditions. In this mini review we will present evidence that body weight and body composition are defended and that regulation of food intake may be considered a derivation of it.

In 1940, Hetherington and Ranson discovered that electrolytic lesioning of the ventromedial hypothalamic area (VMH) leads to hyperphagia and obesity (15). In 1951, Anand (3) reported that electrolytic lesioning of the lateral hypothalamic area resulted in a temporary aphagia and loss of body weight. Electrical stimulation of the VMH and LHA elicited the reverse reactions: suppression and an increase in food intake, respectively (4, 53, 57, 64). Initially, it was assumed that the observed hyperphagia and aphagia were major syndromes leading to obesity or a decline in body weight. However, our present view is that both lesioning and electrical stimulation of the VMH and LHA lead to a change in body weight setpoint, and consequently, to an adjustment in food intake. Evidence for this emerges from experiments with rats rendered obese by hyperphagia caused by electrical stimulation in the LHA (three times a day for 30 min continued during 3 weeks) (57,64). After termination of the stimulations, the rats returned to the same weight as control animals by diminution of spontaneous food intake (Fig. 1). Furthermore, Keesey (20) showed that VMH- and LHA-lesioned rats defend their altered body weight by adjustment of food intake. Most striking was the observation that LHA lesion in starved animals did not result in aphagia but in hyperphagia ultimately leading to the same body weight as in nonstarved animals with an LHA lesion (20).

The question arises as to which factor could be responsible for the defense of body weight. The pancreatic hormone insulin might be the major candidate. Insulin is the only true anabolic hormone. Partly in concert with other hormones, like growth hormone and thyroxine, insulin is capable to promote conversion of absorbed nutrients to fats in liver cells and adipocytes, to glycogen in liver and muscle cells, and to proteins in all body tissues. Insulin may serve as a marker for body weight since a correlation has been established between basal plasma insulin levels and the size of fat mass which is directly related to body weight (82,84). The scope of this review is to focus on 1) the mechanisms involved in insulin release, 2) the influences of the central nervous system (CNS) on circadian glucose and insulin profiles and 3) peripheral insulin in CNS regulation of body weight.

MECHANISMS INVOLVED IN THE REGULATION OF INSULIN RELEASE

Insulin release by the B cell of the islets of Langerhans is

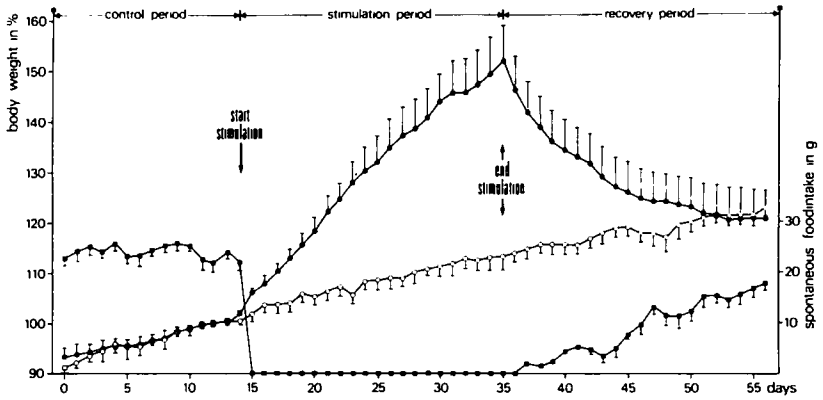

FIG. 1. Mean and SEM of body weight (●) and spontaneous daily food intake (■) of eight rats subjected from days 15 to 35 to three daily sessions of electrical LHA stimulation. For comparison mean body weight of four nonstimulated control rats (○) is added (57).

influenced by both humoral and neural factors. Elevated blood glucose levels (>100 mg/dl) is the main stimulus for insulin release. A linear increase in blood glucose causes an exponential increase in plasma insulin which flattens when blood glucose reaches a level of about 180 mg/dl (28). This levelling off is determined by the maximal secretory capacity of the B cells. Certain aminoacids, e.g., arginine and ornithine, can also trigger insulin release provided that basal blood glucose levels are present (31). Furthermore, gut hormones like cholecystokinin (CCK) and gastrin promote insulin release under physiological conditions (5,10).

Neural regulation of pancreatic outflow of insulin is achieved via a rich autonomic innervation of the endocrine pancreas (26). Both parasympathetic and the sympathetic nervous mechanisms affect hormone release from the islet of Langerhans with profound effects on metabolism. The first indication that the autonomic nervous system is involved in insulin output of the islets of Langerhans was provided by Kaneto, who demonstrated that electrical stimulation of vagal branches to the pancreas elicited insulin release (17). In addition, Porte reported that activation of α- and β-adrenoceptors on the B cells leads to, respectively, a suppression and stimulation of insulin release (37,38). Further investigations revealed that these adrenoceptors consisted of the α_2- and β_2-subtypes (22,46).

It is generally accepted that the islet of Langerhans functions as an intricate neuroendocrine unit in which nervous, neuroendocrine, and hormonal signals are interacting in the release of hormones. As a consequence, the release of insulin is strongly influenced by the other hormones of the endocrine pancreas by paracrine interactions (79). In particular, glucagon from the A cells and somatostatin from the D cells are involved. The D cells are strategically situated between A cells at the rim and the B cells in the center of the islets. The area between A and B cells receives the richest autonomic innervation (26). Glucagon release from the A cells is promoted both by vagal and sympathetic activity via muscarinic and adrenergic receptors (1, 18, 19, 42, 52). Somatostatin release by the D cells seems to be affected by sympathetic but not parasympathetic stimulation (41,74). Beta-adrenergic agonists elicit somatostatin release (2,43), whereas α-adrenergic agonists suppress somatostatin release (42). Sympathetic inhibition of somatostatin release might also be mediated via nonadrenergic mechanisms (2). Multiple paracrine interactions occur in the islet. A-cell stimulation resulting in glucagon release, affects both B and D cells leading to increased insulin and somatostatin output. Insulin released by the B cells inhibits glucagon output. Somatostatin suppresses glucagon and insulin release from the A and B cells (54, 78, 79). The effects of somatostatin are probably restricted to paracrine actions within the islets (72), whereas large amounts of insulin and glucagon are released into the portal circulation and exert their major effects initially on the liver and then on the other tissues of the body.

The secretion of insulin must be accurately controlled to ensure appropriate distribution of ingested substrates. Inadequate control of insulin release leads to abnormal body weight and body composition. For example, long-term administration of insulin resulted in hyperphagia and obesity (25,34). If hyperphagia and a change in body weight are prevented by strict pair feeding, long-term insulin treatment resulted in a shift in body composition i.e., increased body fat content and decreased fat free mass (77). Blood glucose levels must also be kept constant to guarantee an adequate glucose supply to the tissues. Hypoglycemia leads to severe impairment of cell function in glucose-dependent tissues (in particular the central nervous system). Hyperglycemia causes glycosylation of many cell membrane proteins (14), resulting in degenerations such as retinopathy and neuropathy as occurs in patients with long-standing diabetes. Since metabolism fluctuates considerably during the diurnal cycle (for example during sleep, food intake, and vigorous exercise), the neuroendocrine unit which constitutes the islets of Langerhans must be controlled in such a way that all tissues of the body receive the appropriate amount of nutrients.

The effects of glucose and autonomic nervous system on the hepatocyte and the adipocyte (the main storage tissues) and the pancreatic B cell are schematically presented in Fig. 2. The hepatocyte contributes to the maintenance of blood glucose homeostasis by storage and breakdown of liver glycogen. Liver glycogenesis is promoted by insulin and vagal stimulation which activate the liver glycogen synthetase (48,50). Liver glycogenolysis is activated by an α_1-adrenoceptor mechanism leading to an increase in intracellular Ca^{2+} concentration (50). These α_1-adrenoceptors are predominantly stimulated by sympathetic norepinephrine from splanchnic nerves to the liver (50). However, the mechanisms involved in the sympathetic activation of liver glycogenolysis are probably more complicated. Evidence for this emerges from experiments in which infusion of epinephrine caused a much higher rise in blood glucose than administration of equimolar quantities of norepinephrine (46,60), and from studies in which sympathetic activation of liver glycogenolysis occurred

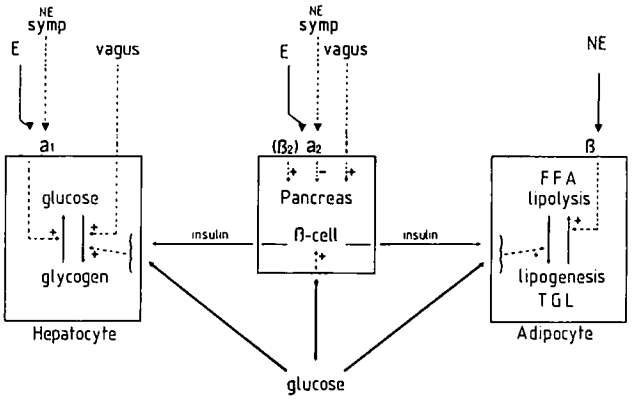

FIG. 2. Model showing influences of autonomic nervous system and circulating catecholamines on the hepatocyte, adipocyte and B cells of the islet of Langerhans. The effects of glucose on B cells and combined effects of glucose and insulin on glycogenesis and lipogenesis have been also indicated.

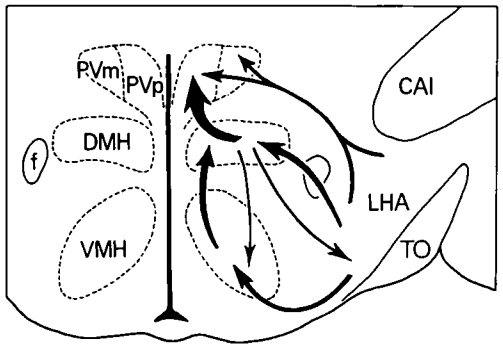

FIG. 3. Diagrammatic survey of the major connections between VMH, DMH, PVN and LHA. The thickness of the arrows is indicative for the relative density of the various projections. Note a predominant flow of connectivity to the parvocellular PVN (58).

through receptors other than the α_1-adrenoceptor (46,69). Glucagon is also a potent initiator of liver glycogenolysis by activating adenylcyclase. This is probably the main function of glucagon in physiological quantities (24). Although muscle cells contain large amounts of glycogen, they do not directly contribute to regulation of blood glucose, since this glycogen is only available for the muscle cells themselves. This is due to the absence of glucose phosphatase in muscle cells preventing the conversion of glucose 6-phosphate into glucose. The process of muscle glycogenolysis is started by the entry of Ca^{2+} in the cytosol due to the muscular contraction process. Cyclic AMP synthesis, elicited by activation of β_2-adrenoceptors in the muscle cell membrane, leads also to glycogenolysis. These β_2-adrenoceptors are activated by adrenal epinephrine.

White adipocytes do not receive direct autonomic innervation. However, lipolysis is increased during activation of the sympathetic nervous system via a hormonal effect of norepinephrine in the blood circulation (46). Circulating norepinephrine originates from terminals of the sympathetic nervous system by leakage from the synaptic cleft between nerve endings and effector cells, e.g., heart cells and smooth muscle cells in arterial walls (45). Norepinephrine stimulates an atypical β-adrenoceptor in the rat fat cell (87). Inhibitory α_2-adrenoceptors present in the human adipocyte seem to be absent in the rat adipocyte (21).

In summary, blood glucose homeostasis is accomplished by an intricate concerted action of the autonomic nervous system and the endocrine pancreas acting on storage and mobilization of energy substrates. Food intake continuously supplies the metabolic system with nutrients and has to be matched to the expenditure of energy substrates. Although conversion of ingested proteins, fats, and carbohydrates may occur, the intake of these macronutrients appears to be specifically regulated to a certain extent (75,85).

THE AUTONOMIC NERVOUS SYSTEM AND BLOOD GLUCOSE HOMEOSTASIS

During food ingestion plasma insulin increases before any rise in plasma levels of absorbed nutrients (39,62). This preabsorptive insulin response (PIR) forms a part of cephalic vagal reflex at the onset of a meal. The reflex arc consists of afferent nerves from the oral cavity to the CNS and efferent nerves from the CNS to the islets of Langerhans. Integration of the information takes place in the nucleus of the solitary tract and several parts in the hypothalamus (26,76). Electrolytic lesion of both the ventromedial hypothalamic area (VMH) and the paraventricular nucleus (PVN) led to an immediate increase in activity in vagal branches to the pancreas and suppression of activity in splanchnic branches (86). The reverse effect was observed after lesioning of the lateral hypothalamic area (LHA) (86). The PVN has direct and indirect connections with the intermediolateral column (IML) in the spinal cord (the motor area of the sympathetic system). The PVN also contains neurons projecting on the eminentia mediana and the neurohypophysis via which it may influence the release of corticotropin releasing hormone (CRH), oxytocin, and vasopressin. The LHA has direct and indirect projections on the dorsal motor nucleus of the vagus and also indirect projections on the IML. There are no projections from the LHA to VMH and vice versa. They communicate with each other via the dorsomedial hypothalamus (DMH) which has, however, a predominant flow of connectivity to the parvocellular PVN (58) (Fig. 3). The neuroanatomical data and the changes in pancreatic autonomic nerve activity found after lesioning of several hypothalamic areas indicate that the hardware for hypothalamical regulation of insulin release via autonomic outflow is available.

Changes in activity in the afferent or efferent limb of the vagal reflex arc involved in the PIR lead to alterations of the PIR (56,68). Figure 4 shows that interference in the afferent limb by intragastric versus oral food administration led to a suppression of the PIR. As a consequence, an exaggerated second tonic phase of insulin release occurred in the animals fed intragastrically. Elimination of the efferent limb to the islets of Langerhans was achieved by transplantation of neonatal pancreata under the kidney capsule of alloxan diabetic rats (Fig. 5). The denervated islets maintained basal plasma insulin and glucose levels. However, a PIR did not occur during food ingestion, and the insulin profile was comparable with that in the intragastrically fed rats. These data seemingly suggest that the PIR activates liver glycogen synthetase leading to immediate conversion of absorbed glucose into glycogen. As a consequence, less glucose leaks through the liver circulation into the general circulation resulting in higher blood sugar levels and enhanced stimulation of the B cells. However, this interpretation might be oversimplified, since also a preabsorptive glucagon response (PGR) occurs (13) which inhibits glycogen synthesis. Furthermore, it was reported that liver glycogen synthetase activation by insulin does not occur within 30 minutes (48). To investigate the possible role of PIR in activation of glycogen synthetase, insulin was intraportally infused at the onset of intragastric feeding to mimic the PIR. Figure 6 shows that

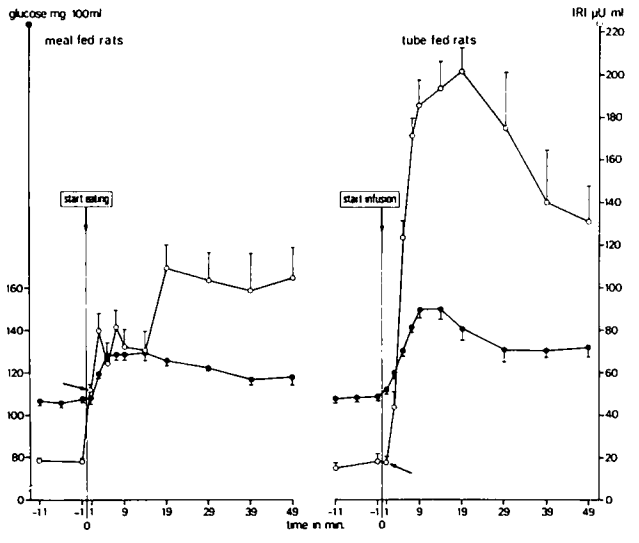

FIG. 4. Left: Blood glucose (●) and plasma insulin (○) levels during oral ingestion of carbohydrate rich fluid food. Start of eating at time zero. Right: Blood glucose (●) and plasma insulin (○) levels during intragastric infusion of carbohydrate rich fluid food. Entrance of fluid food into the stomach at time zero. Arrow indicates insulin level 1 min after start of ingestion of stomach infusion of food (56).

only a small decrement in blood glucose ensues with no changes in plasma insulin profiles. These results indicate that the PIR has only a small effect on liver glycogen synthesis. This suggests that during food intake activation of liver glycogen synthetase is achieved probably by a direct vagal stimulation of the liver. This is supported by findings of Shimazu, who showed that electrical stimulation of vagal branches to the liver elicited activation of glycogen synthetase within 5 min (49). However, this mechanism does not explain the higher increases in glucose and insulin during food ingestion in diabetic rats with transplanted islets (cf. Fig. 5), since a diminished activity in vagal branches to the liver is not likely in this condition. It might be that the reduced glycogen synthesis is due to higher glucagon output from the remaining parts of the alloxan-treated islets, since the A cells are not inhibited by a paracrine action of insulin (54,78).

Blood glucose homeostasis is also affected by activation of the sympathetic nervous system. Stimulation of splanchnic nerves to the liver elicits immediate activation of liver phosphorylase leading to glycogenolysis and increased glucose output (50). Electrical stimulation of splanchnic nerves to the pancreas causes diminished insulin output (29) and increased glucagon output (7) resulting in increased glycogenolysis. The suppression of insulin release is mediated by an α_2-adrenoceptor mechanism (37). This α_2-adrenergic inhibition overrules the β_2-adrenergic stimulation of insulin release (36,46). In addition, evidence is accumulating for peptidergic sympathetic inhibition of insulin release (1,2). The B cell is probably under continuous sympathetic α_2-adrenergic inhibition, since administration of the α-adrenoceptor antagonist phentolamine enhances basal levels of insulin and insulin release during food ingestion (Fig. 7).

CNS INFLUENCES ON AUTONOMIC OUTFLOW CONTROLLING BLOOD METABOLITE CONCENTRATIONS

As mentioned above, lesioning of several hypothalamic areas (LHA, VMH, and PVN) leads to immediate changes in pancreatic

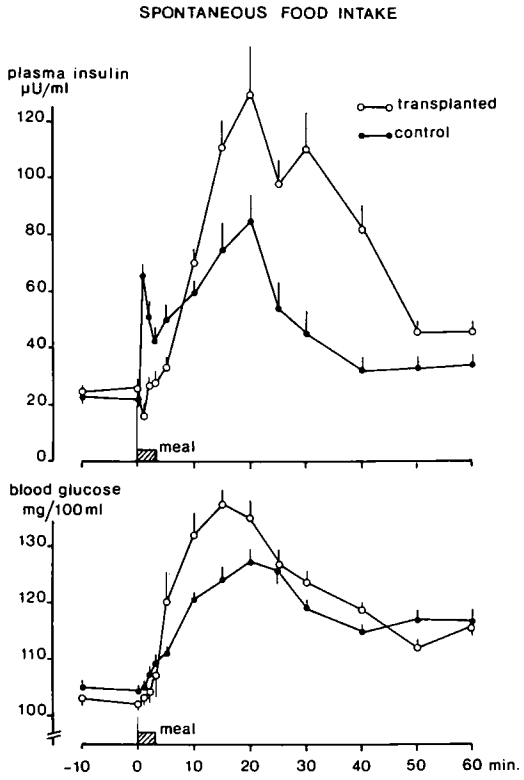

FIG. 5. Comparison of plasma insulin and blood glucose responses between control (●) and transplanted (○) rats (N = 6). The figure shows the effect of food intake in the fed state (68).

vagal and splanchnic nerve activity in anesthetized animals (86). Neurotransmitters and neuropeptides have been infused into several hypothalamic areas of unanesthetized, freely moving animals, and pronounced effects on food intake were found (23, 30, 51). Potentially, a large number of neurotransmitters and neuropeptides have to be taken into account since histochemical research showed

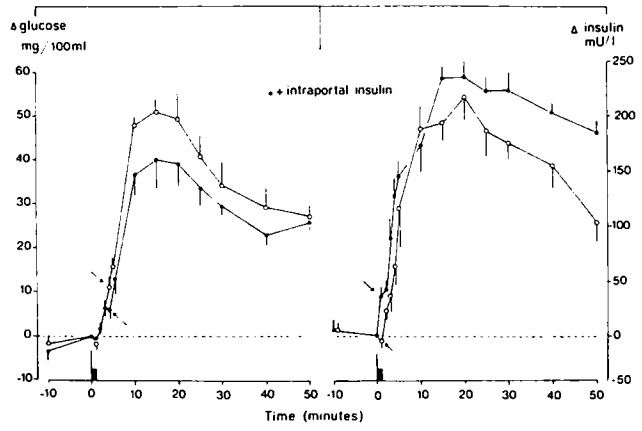

FIG. 6. Blood glucose (left) and plasma insulin levels (right) during intragastric infusion of carbohydrate rich fluid food. Start of infusion at time zero: (●) with intraportal insulin infusion (2.5 mU during 1 min starting at time zero). (○) with intraportal saline infusion.

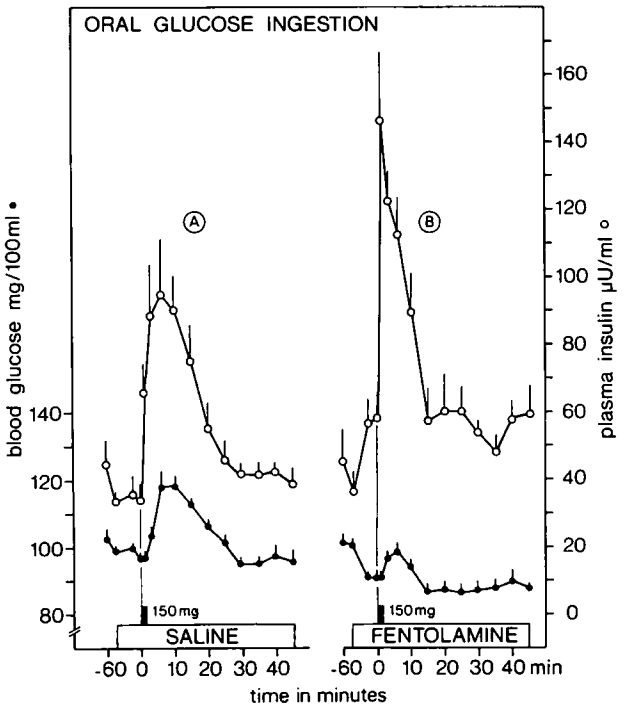

FIG. 7. Mean changes ± SEM of blood glucose (mg/dl) (●) and plasma insulin (µU/ml) (○) during ingestion of 150 mg glucose which was ingested during either intravenous saline infusion at a rate of 0.1 ml/min (left panel) or phentolamine infusion (10 µg/ml at a rate of 0.1 ml/min).

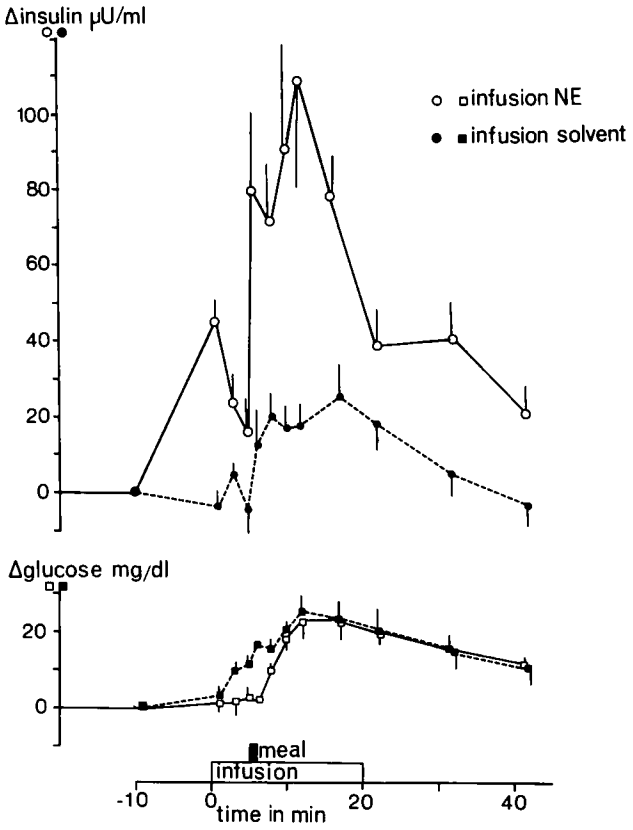

FIG. 8. Mean changes ± SEM of blood glucose (mg/dl) and plasma insulin (µU/ml) during ingestion of 135 mg glucose which was ingested during either buffer infusion at a rate of 0.25 µl/min during 20 min (●) or NE infusion into the LHA (12.5 ng/min at a rate of 0.25 µl/min) during 20 min (○) (61).

that the hypothalamus contain a great diversity of these substances (32). Push-pull perfusion and microdialysis experiments revealed that NE, dopamine, and serotonin levels changed in several hypothalamic areas during food intake (27, 47, 80). The hypothalamic neurotransmitters and neuropeptides involved in the regulation of food intake are also affecting peripheral energy homeostasis via autonomic pathways (50, 60, 61, 81). Infusion of NE into the VMH induced both glucagon and insulin release with a concomitant rise in blood glucose and plasma FFA (13, 49, 50). This rise in glucagon was probably caused by peptidergic mechanisms in the islet of Langerhans because atropinization and α- and β-adrenoceptor blockade did not suppress the response (8,13). Infusion of NE into the LHA elicited a vagally mediated increase in insulin release and a decrease in plasma FFA concentrations without changes in blood glucose (61). Ingestion of a glucose meal and an intravenous glucose tolerance test during infusion of NE into the LHA caused a much higher increase in plasma insulin than during infusion of solvent with no differences in blood glucose and plasma glucagon (61) (Fig. 8). This suggests that a noradrenergic mechanism in the LHA controls the setpoint to which the B cell of the islet of Langerhans releases insulin during a glucose load.

The rise in glucose after NE injection into the VMH was due to activation of liver phosphorylase followed by an enhanced glucose output from the liver (50). This effect on hepatic glucose production was independent of a concomitant change in islet of Langerhans activity. The effect was mediated by β-adrenoceptors in the VMH since it was blocked by prior administration of a β-adrenergic antagonist but not an α-adrenergic antagonist (50). Both α- and β-adrenoceptors in the VMH are involved in the exercise-induced rise in blood glucose via activation of both the outflow of E from the adrenal medulla as well as direct sympathetic activation of the liver (44,81). Microinjections of acetylcholine into the LHA elicit activation of liver glycogen synthetase via central as well as peripheral cholinergic mechanisms, since the effect was blocked by prior application of atropine into the LHA as well as by systemic injection of N-methylatropine, an anticholinergic drug which cannot cross the blood-brain barrier (50).

From these data, a picture emerges in which the hypothalamus is capable of exerting control on the islet of Langerhans, the adipocyte, and the hepatocyte. In particular, noradrenergic and cholinergic mechanisms in the hypothalamus seem to be important. Additional data in literature on neurotransmitters involved in the pathways between hypothalamus and dorsal motor nucleus of the vagus and intermediolateral column in the spinal cord are scanty. Furthermore, almost no data are available on neurotransmitters such as serotonin and neuropeptides such as NPY and galanin in the hypothalamus regarding regulation of metabolism. These factors might be particularly important in situations deviating from the basal metabolic circumstances, e.g., during food deprivation, unbalanced diet composition, and exercise.

CNS INVOLVEMENT IN CONTROL OF PLASMA GLUCOSE AND INSULIN PROFILES

Rats ingest most (about 80%) of their food during the night; their active period (65). Ingestion of a test meal after 3 hr of deprivation in the early night causes higher increases in blood

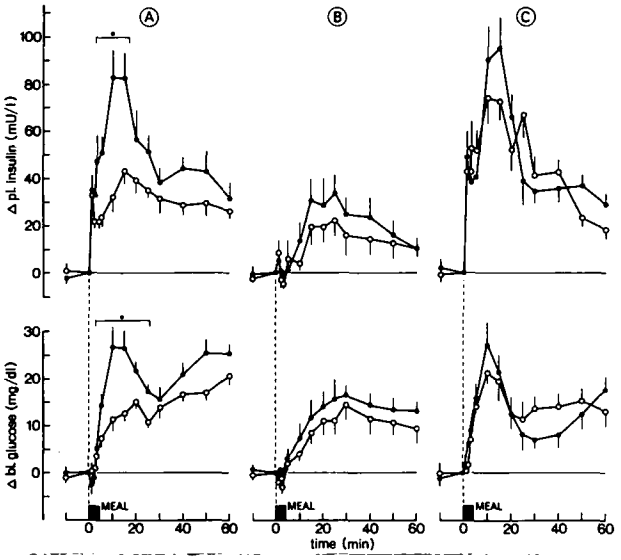

FIG. 9. Comparison of plasma insulin and blood glucose responses to food intake (mean ± SEM) between the light (○) and the dark phase (●). Control condition (A), after atropine administration (B) and SCN lesion (C). *Denotes a significant change ($p<0.05$) (67).

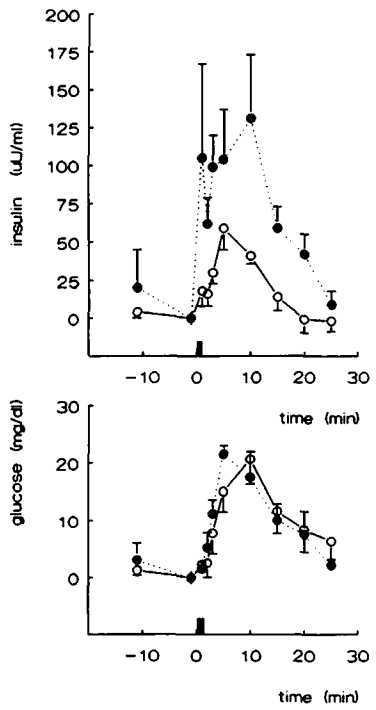

FIG. 10. Mean changes ± SEM of blood glucose (mg/dl) (bottom) and plasma insulin (μU/ml) (top) during an oral glucose tolerance test (1.5 ml of a 10% glucose solution) in pair-fed VMH-lesioned rats (●) and controls (○) in the fourth week after lesion.

glucose and plasma insulin than the responses in the same experiment during daytime (see Fig. 9A). Atropinization of the animal before ingestion of the test meal leads to a complete suppression of PIR and reduction of the size of nocturnal blood glucose and plasma insulin profiles to diurnal ones (see Fig. 9B). In contrast, lesioning of the suprachiasmatic nucleus (SCN) results in nocturnal profiles irrespective whether the test meal is ingested during nighttime or daytime (Fig. 9C) (67). These results suggest that the SCN controls vagal activity influencing circadian variations in blood glucose and plasma insulin profiles after food intake via either absorption from the intestinal tract, and/or activation of the B cell of the islet of Langerhans. The islet of Langerhans is also under continuous sympathetic control as appears from enhanced basal plasma insulin levels and increased PIR during food intake after α-adrenoceptor blockade (Fig. 7). Food ingestion by itself also leads to increased sympathetic activity reflected by elevated NE and E levels during a meal (63). These observations indicate that food ingestion is accompanied by simultaneous activation of the sympathetic and parasympathetic system (Fig. 2). The hypothalamus might control circadian insulin profiles by its effects on the autonomic nervous system. To investigate this, rats were accustomed to a fluid diet. Food was offered in 7 identical meals: one at the end of the light period and six during the night to mimic circadian-feeding behavior. Caloric content of liquid food was matched to normal daily intake. Animals were divided into two groups: one group received a small electrical lesion in the VMH with sham operated as control. The rats were followed during 4 weeks on a strict pair-feeding schedule. Carcass analysis showed that the VMH-lesioned rats had a higher body weight and fat content than controls which is in agreement with data in literature (12). This suggests that VMH lesion leads to a higher conversion of food into fats. Glucose responses during oral glucose tolerance tests (OGTT) were unaltered whereas basal and stimulated insulin concentrations gradually increased during successive OGTT's in the VMH-lesioned rats (Fig. 10). The exaggerated insulin release in the VMH-lesioned animals might be responsible for increased fat deposition, since insulin resistance after VMH lesion is secondary to hyperinsulinemia (35,40). The supra normal quantity of insulin enhances fat synthesis in fat cells and increases fat cell diameter, which leads consequently, to insulin resistance. The above data indicate that the VMH is involved in the control of the set point of the pancreatic B cell via autonomic pathways. It might be suggested that VMH lesion leads to an increased NE turnover in the LHA, since noradrenergic stimulation of the LHA leads to a shift of the set point of the B cell for glucose (Fig. 8). This hypothesis can be tested by microdialysis in the LHA in VMH-lesioned animals during food ingestion.

FEEDBACK FROM PERIPHERAL INSULIN TO THE CNS

From the data presented in previous sections, it is clear that the CNS exerts a powerful influence on the control of plasma insulin concentrations partly independent of blood glucose levels. The questions arise to what extent insulin in plasma exerts a feedback control on its own release via a central mechanism, and if central insulin is involved in the regulation of food intake. Insulin receptors are abundant in the brain (6), suggesting a role for central insulin. At present, evidence is accumulating that insulin acting on those receptors is of peripheral origin. First, circulating insulin penetrates into the CSF (59). Secondly, the brain does not synthesize insulin (6). Administration of insulin into the CNS affects peripheral metabolism. Injection of insulin into the cerebrospinal fluid (CSF) led to increased insulin release and hypoglycemia in the dog (11,73). Microinjection of insulin into the VMH of rats had comparable effects (16). Binding of insulin to insulin receptors in the brain vasculature affects blood glucose since injection of micro quantities of insulin into the carotid artery causes a drop in blood glucose (71). This was probably caused by a direct neural effect on the liver and not by an alteration of insulin release from the B cell (70).

A function for CNS insulin in the regulation of body weight and food intake is emerging from a number of studies. Infusion of insulin into the brain ventricular system of baboons (83) and rats (9) suppressed food intake and led to reduced body weight. Infusion of insulin antibodies into the VMH elicited feeding in rats (66). The evidence for a possible function of insulin receptors in the CNS in the regulation of food intake is strengthened by electrophysiological data. Electrophoretical administration of insulin and glucose in the VMH elicited an immediate increase of neural activity in that area (33). In addition, application of small amounts of insulin in the LHA increased neural activity in a dose-dependent way (33). These effects were not observed after administration of insulin and/or glucose into other brain areas studied. These data suggest that increased insulin and glucose levels in the VMH, which might occur after food ingestion, enhance neural activity in the VMH leading to satiety. The increased activity in LHA neurons after local insulin administration may be explained by the absence of glucose, since combined administration of glucose and insulin into the LHA did not elicit an increased neural activity (33). Thus, high insulin levels and low glucose availability in the LHA results in an increase in the activity of LHA neurons which should lead to food ingestion. This might occur when high doses of insulin are infused into the blood circulation (55). The high dose of insulin caused a slow decline in blood glucose concentrations. The animal started to eat every time when blood glucose levels dropped below approximately 50 mg/dl.

In conclusion, insulin receptors in the VMH and LHA are likely to be involved in the regulation of food intake and peripheral metabolism. The function of the insulin receptors in other parts of the CNS, e.g., the olfactory bulb, is not clear. Are they a part of other neural pathways than the described noradrenergic mechanisms in the hypothalamus, or do they play a role in the degradation of insulin in the brain? In addition, also serotonergic and dopaminergic mechanisms as well as many neuropeptides in both intra- and extra-hypothalamic networks contribute to regulation of food intake (23). The nonadrenergic networks might play a role in situations deviating from normal rest conditions with well-balanced carbohydrate rich laboratory food available ad lib. At present, these intriguing issues are under investigation in many laboratories and an answer to them, even a partial one, is beyond the scope of this mini review.

CONCLUDING REMARKS

The central nervous system, in particular the hypothalamus, controls diurnal plasma insulin and blood glucose profiles leading to an adequate distribution of nutrients. This control is exerted through autonomic nervous pathways. The hepatocyte, the adipocyte, as well as the islet of Langerhans serve as main targets. Muscle cells contribute only indirectly to plasma insulin and blood glucose homeostasis.

Hypothalamic areas involved in the control of blood glucose homeostasis are also involved in the regulation of body weight and food intake. The picture emerges that body weight setpoint is defended and that food intake regulation is merely a derivation of it. The control of body weight requires continuous matching of food intake and energy expenditure. Insulin might play a key role in the process.

Finally, knowledge concerning the role of the hypothalamus in the adaptation to varying situations with altered metabolic demands, e.g., exercise, fasting, unbalanced-feeding conditions, etc., is limited and awaits further investigations.

REFERENCES

1. Ahren, B.; Veith, R. C.; Taborsky, G. J., Jr. Sympathetic nerve stimulation versus pancreatic norepinephrine infusion in the dog: 1) Effects on basal release of insulin and glucagon. Endocrinology 123:323–331; 1987.
2. Ahren, B.; Veith, R. C.; Paquette, T. L.; Taborsky, G. J., Jr. Sympathetic nerve stimulation versus pancreatic norepinephrine infusion in the dog: 2) Effects on basal release of somatostatin and pancreatic polypeptide. Endocrinology 123:332–339; 1987.
3. Anand, B. K.; Brobeck, J. R. Hypothalamic control of food intake in rats and cats. Yale J. Biol. Med. 24:123–133; 1951.
4. Anand, B. K.; Dua, S. Feeding responses induced by electrical stimulation of the hypothalamus in the cat. Indian J. Med. Res. 43:113–122; 1955.
5. Balkan, B.; Steffens, A. B.; Strubbe, J. H.; Bruggink, J. E. Biphasic insulin secretion after intravenous but not after intraportal CCK-8 infusion in rats. Diabetes 39:in press; 1990.
6. Baskin, D. G.; Figlewicz, D. P.; Woods, S. C.; Porte, D., Jr.; Dorsa, D. M. Insulin in the brain. Annu. Rev. Physiol. 49:335–347; 1987.
7. Bloom, S. R.; Edwards, A. V. Certain pharmacological characteristics of the release of pancreatic glucagon in response to stimulation of the splanchnic nerves. J. Physiol. (Lond.) 280:25–35; 1978.
8. Bloom, S. R.; Edwards, A. V. Characteristics of the neuroendocrine responses to stimulation of the splanchnic nerves in bursts in the conscious calf. J. Physiol. (Lond.) 346:533–545; 1984.
9. Brief, D. J.; Davis, J. D. Reduction of food intake and body weight by chronic intraventricular insulin infusions. Brain Res. Bull. 12: 571–575; 1984.
10. Brown, J. C.; Otte, S. C. Gastrointestinal hormones and the control of insulin secretion. Diabetes 27:722–790; 1978.
11. Chen, M.; Woods, S. C.; Porte, D., Jr. Effect of cerebral intraventricular insulin on pancreatic insulin secretion in the dog. Diabetes 24:910–914; 1975.
12. Cox, J. E.; Powley, T. L. Intragastric pair feeding fails to prevent VMH obesity or hyperinsulinemia. Am. J. Physiol. 240:E566–E572; 1981.
13. De Jong, A.; Strubbe, J. H.; Steffens, A. B. Hypothalamic influence on insulin and glucagon release in the rat. Am. J. Physiol. 233: E380–E388; 1977.
14. Ditzel, J.; Nielsen, N. V.; Kjaergaard, J. J. Haemoglobin A1C and red cell oxygen release in relation to early retinal changes in newly discovered overt and chemical diabetes. Metabolism 28(Suppl. 1): 440–447; 1979.
15. Hetherington, A. W.; Ranson, S. W. Hypothalamic lesions and adiposity in the rat. Anat. Rec. 78:149–172; 1940.
16. Iguchi, A.; Burleson, P. D.; Szabo, A. J. Decrease in plasma glucose concentration after microinjection of insulin into the VMN. Am. J. Physiol. 240:E95–E100; 1981.
17. Kaneto, A.; Kosaka, K.; Nakao, K. Effects of stimulation of the vagus nerve on insulin secretion. Endocrinology 80:530–536; 1967.
18. Kaneto, A.; Miki, E.; Kosaka, K. Effects of vagal stimulation on glucagon and insulin secretion. Endocrinology 95:1005–1010; 1974.
19. Kaneto, A.; Miki, E.; Kosaka, K. Effect of β- and β_2-adrenoceptor stimulants infused intrapancreatically on glucagon and insulin secretion. Endocrinology 97:1166–1173; 1975.
20. Keesey, R. E.; Boyle, P. C.; Kemnitz, J. W.; Mitchel, J. S. The role of the lateral hypothalamus in determining body weight set points. In: Novin, D.; Wyrwicka, W.; Bray, G., eds. Hunger: Basic mechanisms and clinical implications. New York: Raven Press; 1976:243–253.
21. Lafontan, M.; Berlan, M.; Carpene, C. Fat cell receptors: inter- and intraspecific differences and hormone regulation. Int. J. Obes. 9: 117–128; 1985.
22. Langer, J.; Parten, U.; Zielman, S. Effects of α-adrenoceptor antagonists on clonidine-induced inhibition of insulin secretion by isolated pancreatic islets. Br. J. Pharmacol. 79:415–420; 1983.

23. Leibowitz, S. F. Brain monoamines and peptides: role in the control of eating behavior. Fed. Proc. 45:1396–1403; 1986.
24. Liljenquist, J. E.; Müller, G. L.; Cherrington, A. D.; Keller, U.; Chiasson, J. L.; Perry, J. M.; Lacy, W. W.; Rabinowitz, D. Evidence for an important role of glucagon in the regulation of hepatic glucose production in normal man. J. Clin. Invest. 59:369–374; 1977.
25. Lotter, E. C.; Woods, S. C. Injection of insulin and changes of body weight. Physiol. Behav. 18:293–297; 1977.
26. Luiten, P. G. M.; ter Horst, G. J.; Steffens, A. B. The hypothalamus, intrinsic connections and outflow pathways to the endocrine system in relation to the control of feeding and metabolism. Prog. Neurobiol. 28:1–54; 1987.
27. McCaleb, M. L.; Meyers, R. D.; Singer, G.; Willis, G. Hypothalamic norepinephrine in the rat during feeding and push-pull perfusion with glucose, 2-DG or insulin. Am. J. Physiol. 236:R312–R321; 1979.
28. Malaisse, W. J.; Malaisse-Lagae, F.; Wright, P. H.; Ashmore, J. Effects of adrenergic and cholinergic agents upon insulin secretion in vitro. Endocrinology 80:975–978; 1967.
29. Miller, R. E. Neural inhibition of insulin secretion from the isolated canine pancreas. Am. J. Physiol. 229:144–149; 1975.
30. Morley, J. E.; Levine, A. S.; Gosnell, B. A.; Mitchell, J. E.; Krahn, D. D.; Nizielski, S. E. Peptides and feeding. Peptides 6(Suppl. 2): 181–192; 1985.
31. Müller, W. H.; Faloona, G. R.; Unger, R. H. The effect of alanine on glucagon secretion. J. Clin. Invest. 50:2215–2218; 1971.
32. Nieuwenhuijs, R. Chemoarchitecture of the brain. Berlin: Springer Verlag; 1985.
33. Oomura, Y. Glucose as a regulator of neuronal activity. In: Szabo, A. J., ed. Advances in metabolic disorders. vol. 10 (CNS regulation of carbohydrate metabolism). New York: Academic Press; 1983:31–65.
34. Panksepp, J.; Pollack, J. A.; Kprost, K.; Meeker, R.; Ritter, M. Feeding in response to repeated protamin zinc insulin injections. Physiol. Behav. 14:487–493; 1975.
35. Penicaud, L.; Rohner-Jeanrenaud, F.; Jeanrenaud, B. In vivo metabolic changes as studied longitudinally after ventromedial hypothalamic lesions. Am. J. Physiol. 250:E662–E668; 1986.
36. Porte, D., Jr. Beta adrenergic stimulation of insulin release in man. Diabetes 16:150–155; 1967.
37. Porte, D., Jr. A receptor mechanism for the inhibition of insulin release by epinephrine in man. J. Clin. Invest. 46:86–94; 1967.
38. Porte, D., Jr.; Robertson, R. P. Regulation of insulin secretion by catecholamines, stress and the sympathetic nervous system. Fed. Proc. 32:1792–1796; 1973.
39. Rohner-Jeanrenaud, F.; Bobbioni, E.; Ionescu, E.; Sauter, J. F.; Jeanrenaud, B. Central nervous system regulation of insulin secretion. In: Szabo, A. J., ed. Advances in metabolic disorders. vol. 10 (CNS regulation of carbohydrate metabolism). New York: Academic Press; 1983:193–200.
40. Rohner, F.; Dufour, A. C.; Karakash, C.; Le Marchand, Y.; Ruf, K. B.; Jeanrenaud, B. Immediate effect of lesion of the ventromedial hypothalamic area upon glucose-induced insulin secretion in anaesthetized rats. Diabetologia 13:239–242; 1977.
41. Roy, M. W.; Lee, K. C.; Jones. M. S.; Miller, R. E. Neural control of pancreatic insulin and somatostatin secretion. Endocrinology 115: 770–775; 1984.
42. Samols, E.; Weir, G. C. Adrenergic modulation of pancreatic A, B, and D cells. α-Adrenergic suppression of β-adrenergic stimulation of somatostatin secretion, α-adrenergic stimulation of glucagon secretion in the perfused dog pancreas. J. Clin. Invest. 63:230–238; 1979.
43. Samols, E.; Stagner, J. I.; Weir, G. C. Autonomic function and control of pancreatic somatostatin. Diabetologia 20:388–390; 1981.
44. Scheurink, A. J. W.; Steffens, A. B.; Benthem, L. Central and peripheral adrenoceptors affect glucose, free fatty acids, and insulin in exercising rats. Am. J. Physiol. 255:R547–R556; 1988.
45. Scheurink, A. J. W.; Steffens, A. B.; Bouritius, H.; Dreteler, G.; Bruntink, R.; Remie, R.; Zaagsma, J. Adrenal and sympathetic catecholamines in exercising rats. Am. J. Physiol. 256:R155–R160; 1989.
46. Scheurink, A. J. W.; Steffens, A. B.; Bouritius, H.; Dreteler, G. H.; Bruntink, R.; Remie, R.; Zaagsma, J. Sympathoadrenal influence on glucose, FFA, and insulin levels in exercising rats. Am. J. Physiol. 256:R161–R168; 1989.
47. Schwartz, D. H.; McClane, S.; Hernandez, L.; Hoebel, G. B. Feeding increases extracellular serotonin in the lateral hypothalamus of the rat as measured by microdialysis. Brain Res. 482:261–270; 1989.
48. Shimazu, T. Regulation of glycogen metabolism in liver by the autonomic nervous system. V. Activation of glycogen synthetase by vagal stimulation. Biochim. Biophys. Acta 252:28–38; 1971.
49. Shimazu, T. Reciprocal innervation of the liver: its significance in metabolic control. In: Szabo, A. J., ed. Advances in metabolic disorders. vol. 10 (CNS regulation of carbohydrate metabolism). New York: Academic Press; 1983:355–384.
50. Shimazu, T. Neural control of intermediate metabolism. In: Lightman, S.; Everitt, B., eds. Neuroendocrinology. Oxford: Blackwell; 1986:304–339.
51. Shimazu, T.; Noma, M.; Saito, N. Chronic infusion of norepinephrine into the ventromedial hypothalamus induces obesity in rats. Brain Res. 369:215–223; 1986.
52. Skoglund, G.; Lundquist, I.; Ahren, B. α_1- and α_2-adrenoceptor activation increases plasma glucagon levels in the mouse. Eur. J. Pharmacol. 143:83–87; 1987.
53. Smith, O. A., Jr. Food intake and hypothalamic stimulation. In: Sheer, D. E., ed. Electrical stimulation of the brain. Austin: Univ. of Texas Press; 1961:3.
54. Stagner, J. I.; Samols, E.; Bonner-Weir, S. β-α-δ pancreatic islet cellular perfusion in dogs. Diabetes 37:1715–1721; 1988.
55. Steffens, A. B. The influence of insulin infusions on eating and blood glucose in the rat. Physiol. Behav. 5:823–828; 1969.
56. Steffens, A. B. The influence of the oral cavity on the release of insulin in the rat. Am. J. Physiol. 230:1411–1415; 1975.
57. Steffens, A. B. Influence of reversible obesity on eating behavior, blood glucose and insulin in the rat. Am. J. Physiol. 228:1738–1744; 1975.
58. Steffens, A. B.; Scheurink, A. J. W.; Luiten, P. G. M.; Bohus, B. Hypothalamic food intake regulating areas are involved in the homeostasis of blood glucose and plasma FFA levels. Physiol. Behav. 44:581–589; 1988.
59. Steffens, A. B.; Scheurink, A. J. W.; Porte, D., Jr.; Woods, S. C. Penetration of peripheral glucose and insulin into cerebrospinal fluid in rats. Am. J. Physiol. 255:R200–R204; 1988.
60. Steffens, A. B.; Damsma, G.; van der Gugten, J.; Luiten, P. G. M. Circulating free fatty acids, insulin, and glucose during chemical stimulation of the lateral and ventromedial areas of the hypothalamus in the rat. Am. J. Physiol. 247:E765–E771; 1984.
61. Steffens, A. B., Flik, G.; Kuipers, F.; Lotter, E. C.; Luiten, P. G. M. Hypothalamically-induced insulin release and its potentiation during oral and intravenous glucose loads. Brain Res. 301:351–361; 1984.
62. Steffens, A. B.; Strubbe, J. H. CNS regulation of glucagon secretion. In: Szabo, A. J., ed. Advances in metabolic disorders. vol. 10 (CNS regulation of carbohydrate metabolism). New York: Academic Press; 1983:221–257.
63. Steffens, A. B.; van der Gugten, J.; Godeke, J.; Luiten, P. G. M.; Strubbe, J. H. Meal-induced increases in parasympathetic and sympathetic activity elicit simultaneous rises in plasma insulin and free fatty acids. Physiol. Behav. 37:119–122; 1986.
64. Steinbaum, E. A.; Miller, N. E. Obesity from eating elicited by daily stimulation of hypothalamus. Am. J. Physiol. 208:1–5; 1965.
65. Strubbe, J. H.; Keijser, J.; Dijkstra, T.; Prins, A. J. A. Interaction between circadian and caloric control of feeding behavior in the rat. Physiol. Behav. 36:489–493; 1986.
66. Strubbe, J. H.; Mein, C. G. Increased feeding in response to bilateral injection of insulin antibodies in the VMH. Physiol. Behav. 19: 309–313; 1977.
67. Strubbe, J. H.; Prins, A. J. A.; Bruggink, J.; Steffens, A. B. Daily variation of food-induced changes in blood glucose and insulin in the rat and the control by the suprachiasmatic nucleus and the vagus nerve. J. Auton. Nerv. Syst. 20:113–119; 1987.
68. Strubbe, J. H.; van Wachem, P. Insulin secretion by the transplanted pancreas during food intake in fasted and fed rats. Diabetologia 20:228–236; 1981.
69. Studer, R. K.; Borke, A. B. Differences between male and female rats in the regulation of hepatic glycogenolysis. J. Biol. Chem. 257: 7987–7993; 1982.
70. Szabo, A. J.; Szabo, O. Influence of the insulin sensitive central nervous system glucoregulator receptor on hepatic metabolism. J.

Physiol. (Lond.) 253:121–133; 1975.
71. Szabo, O.; Szabo, A. J. Evidence for an insulin-sensitive receptor in the central nervous system. Am. J. Physiol. 223:1349–1353; 1972.
72. Taborsky, G. J., Jr. Evidence of a paracrine role for pancreatic somatostatin in vivo. Am. J. Physiol. 245:E598–E603; 1983.
73. Taborsky, G. J., Jr.; Bergman, R. N. Effect of insulin, glucose, and 2-deoxy-glucose infusion into the third cerebral ventricle of conscious dogs on plasma insulin, glucose, and free fatty acids. Diabetes 29:278–283; 1980.
74. Taborsky, G. J., Jr.; Ensinck, J. W. Contribution of the pancreas to circulating somatostatin-like immunoreactivity in the normal dog. J. Clin. Invest. 73:216–223; 1984.
75. Tempel, D. L.; Shor-Posner, G.; Dwyer, D.; Leibowitz, S. F. Nocturnal patterns of macro nutrient intake in freely feeding and food-deprived rats. Am. J. Physiol. 256:R541–R548; 1989.
76. Ter Horst, G. J.; de Boer, P.; Luiten, P. G. M.; van Willigen, J. D. Ascending projections from the solitary tract nucleus to the hypothalamus. A phaseolus vulgaris lectin tracing study in the rat. Neuroscience 31:785–797; 1989.
77. Torbay, N.; Bracco, E. F.; Geliebter, A.; Stewart, I. M.; Hashim, S. A. Insulin increases body fat despite control of food intake and physical activity. Am. J. Physiol. 248:R120–R124; 1985.
78. Unger, R. H.; Orci, L. Role of glucagon in diabetes. Arch. Intern. Med. 137:482–491; 1977.
79. Unger, R. H.; Dobbs, R. E.; Orci, L. Insulin, glucagon and somatostatin secretion in the regulation of metabolism. Annu. Rev. Physiol. 40:307–343; 1978.
80. Van der Gugten, J.; de Kloet, E. R.; Versteeg, D. H. G.; Slangen, J. Regional hypothalamic catecholamine metabolism and food intake regulation in the rat. Brain Res. 135:325–336; 1977.
81. Vissing, J.; Wallace, J. L.; Scheurink, A. J. W.; Galbo, H.; Steffens, A. B. Ventromedial hypothalamic regulation of hormonal and metabolic responses to exercise. Am. J. Physiol. 256:R1019–R1026; 1989.
82. Woods, S. C.; Decke, E.; Vaselli, J. R. Metabolic hormones and regulation of body weight. Psychol. Rev. 81:26–43; 1974.
83. Woods, S. C.; Lotter, E. C.; McKay, L. D.; Porte, D., Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. Nature 282:503–505; 1979.
84. Woods, S. C.; Porte, D., Jr.; Strubbe, J. H.; Steffens, A. B. The relationship among body fat, feeding, and insulin. In: Ritter, R. C.; Ritter, S.; Barnes, C. D., eds. Research topics in physiology: Feeding behavior: Neural and humoral controls. Orlando: Academic Press; 1986:315–327.
85. Wurtman, R. J.; Wurtman, J. J. Nutrients, neurotransmitter synthesis, and the control of food intake. In: Stunkard, A. J.; Stellar, E., eds. Eating and its disorders. New York: Raven Press; 1984:77–86.
86. Yoshimatsu, H.; Niijima, A.; Oomura, Y.; Yamabe, K.; Katafuchi, T. Effects of hypothalamic lesion on pancreatic autonomic nerve activity in the rat. Brain Res. 303:147–152; 1984.
87. Zaagsma, J.; de Vente, J.; Harms, H. H.; Jansen, J. D. The nature of adipocyte β-adrenoceptor(s). In: Szabadi, E.; Bradshaw, C. M.; Nahorski, S. R., eds. Pharmacology of adrenoceptors. New York: Macmillan Press; 1985.