Insulin: its relationship to the central nervous system and to the control of food intake and body weight[1-3]

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ABSTRACT This article describes the close relationship among the hormone insulin, the central nervous system, and the regulation of food intake and body adiposity. The initial section documents the control of insulin output from the pancreas by the central nervous system, and a later section describes the relationship of insulin levels in the blood to the degree of adiposity. Another section documents the ability of insulin to gain access to the brain and to elicit responses there. Finally, the behavioral effects of insulin added to the brain, and especially its ability to reduce food intake and body weight, is discussed. The implications to obesity are stressed throughout. *Am J Clin Nutr* 1985;42:1063-1071.

KEY WORDS Insulin, adiposity, food intake, vagus nerve, cerebrospinal fluid, central nervous system

Introduction

The peptide hormone insulin, which is synthesized and secreted from the B cells of the endocrine pancreas, is a major controller of the level of glucose and other fuels in the blood. It causes adipose tissue and muscle to increase the efficiency of glucose uptake from the extracellular fluid and to store it for future use while simultaneously reducing hepatic glucose production. The importance of insulin in the control of blood glucose is such that if insulin secretion is compromised even slightly, there is a tendency for glucose levels to rise in the blood. Such hyperglycemia is a key part of the syndrome of diabetes mellitus.

Because of the importance of insulin in glucose regulation, and the realization that glucose is an essential stimulant of insulin secretion, in the first 50 yr after its discovery much of the research on insulin was focused on two aspects: *a*) mechanisms of action of insulin on insulin-requiring tissues; and *b*) mechanisms of action of glucose on insulin secretion. Many excellent reviews of these topics are available (eg, 1, 2).

The one major exception to the importance of insulin to glucose utilization was the nervous system. It was discovered that the brain does not require insulin in order to remove glucose from the surrounding extracellular fluid, and this insulin independence was found to be coupled with a large obligatory glucose requirement by the brain. The brain is thus one of the few organs which must use considerable glucose for fuel. (Organs such as muscle can use alternative fuels, especially fatty acids.) Such a system ensures that during a fast, when insulin and glucose levels in the blood are relatively low, the glucose which is present will be utilized mainly by the brain since in the absence of insulin, the rest of the body uses less glucose. After a meal, both insulin and

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glucose rise in the blood and insulin-sensitive tissues metabolize extra glucose. Therefore, the traditional view was that glucose is the major stimulant of insulin secretion, that insulin in turn is required for the major peripheral tissues to utilize glucose, and that the brain is independent of this system. This was in keeping with the concept that the hormone insulin, being a peptide, was not thought to cross the blood–brain barrier and gain access to neurons.

The possibility now exists, however, that there may also be a tight (though still largely unexplored) interrelationship among glucose, insulin, and the brain. Obviously the brain requires glucose and lack of availability of this substrate will be deleterious. Conversely, circumstantial evidence indicates that hyperglycemia adversely affects the brain. The interesting point to mention is that there are data suggesting that when glucose availability to the brain is ample (eg, periods of hyperglycemia), a brain-originating, vagus-nerve mediated series of processes comes into play that rapidly normalize hyperglycemia. When glucose availability to the brain becomes inadequate (eg, during periods of hypoglycemia or prolonged fasting), brain-originating, splanchnic-nerve mediated events are activated that tend to elevate glycemia and/or to alter the metabolic state such that the glucose which is present will be utilized mainly by the brain at the expense of the rest of the body (see 3, 4).

In the early literature, the only demonstrated link between insulin and the brain was the finding that when insulin is administered peripherally, eating is stimulated (5, 6). However, the overeating was attributed to the hypoglycemia elicited by the insulin since the simultaneous administration of glucose with the insulin prevented this behavior (7), and since the administration of other drugs which interfere with glucose utilization by the body also cause eating (8).

In the late sixties, evidence began accumulating that suggested that the autonomic nervous system can influence insulin secretion, and that certain cells in the brain are specifically and directly responsive to insulin. Such research challenged the traditional view and paved the way for considerable new and innovative research on the interrelationships among insulin, the nervous system and behavior. This early work has been reviewed elsewhere (3, 9). The purpose of the present paper is to summarize some of the new information in this area and to highlight the possible role of insulin in the control of food intake and the pathophysiology of obesity.

There are several avenues through which the CNS can influence insulin secretion. These include direct neural input to the islets of Langerhans via the sympathetic and parasympathetic branches of the autonomic nervous system, the possible secretion of hormones or other factors by the brain-pituitary system which act directly at the pancreas, and alteration of other hormonal systems throughout the body which secondarily influence glucose levels and/or insulin secretion. In turn, both glucose and insulin are thought to provide information to the CNS, and this feedback helps control the fluxes of fuels in the body as well as the size of the adipose mass. The following section summarizes the influence of the CNS upon the secretion of insulin and includes discussion of how malfunction of this system might exist in obesity or disorders of food intake.

The influence of the brain upon insulin secretion

The islets of Langerhans receive a rich supply of autonomic nerve fibers, including sympathetic axons from the splanchnic/coeliac trunk and parasympathetic axons of the vagal system. The latter synapse with parasympathetic postganglionic neurons located near or within the islet themselves. The efferent nerves make junctional contact with islet secretory cells, including the insulin-secreting B-cells, and the secretory cells are in turn electrically coupled by means of gap junctions. Activation of selected individual cells within an islet by the nervous system is thus able to be dispersed rapidly throughout that islet. There are also numerous sensory or afferent fibers in the pancreatic nerves, the function of which is largely unknown. Reviews can be found in refs 3, 9, 10.

The nerves to the islet have been traced back to the CNS, with most work having been done on the vagal system. Vagal fibers to the pancreas originate in several nuclei of the lower brain stem, and a polysynaptic pathway in-

terconnects these nuclei with several hypothalamic and other forebrain areas as well as with sympathetic areas of the brain. Several recent reviews of this neuroanatomical network exist (11–13).

Many neurotransmitters have been identified within axon terminals in the islets, including the sympathetic transmitter norepinephrine (NE), the parasympathetic transmitter acetylcholine (ACh) and several peptidergic transmitters. Pharmacologic experiments have revealed that ACh is stimulatory to insulin secretion and that catecholamines (including NE) are generally inhibitory to insulin secretion. The latter is complicated by the fact that stimulation of alpha-adrenergic receptors inhibits insulin secretion whereas stimulation of beta-adrenergic receptors enhances insulin secretion. The net effect of autonomic stimulation of the islets therefore depends upon the specific ratio of various transmitters released and upon their relative postsynaptic effects. The prevailing glucose level is also a factor determining neuroendocrine effects on the islet. While many neuropeptides can influence the islet, the physiologic role of peptidergic transmitters is uncertain (see 3, 10, 14).

Stimulation of the parasympathetic nervous system, or increased brain-initiated parasympathetic activity, increases insulin secretion. This is true of electrical stimulation of the pancreatic nerve (under appropriate blockade of the sympathetic neurons) (15, 16), the vagus nerve (17, 18), the dorsal motor nucleus of the vagus in the brainstem (19), or various hypothalamic nuclei (20, 21). An analogous situation exists when studying genetically obese or preobese animals since their exaggerated insulin secretion appears to be mediated by the vagus nerve; ie, it can be partly or completely inhibited by atropine (22). Animals with lesions of the ventromedial hypothalamic area are obese and hyperinsulinemic, effects which are also related to vagal hyperactivity (3, 23).

Electrical stimulation of the sympathetic nerves typically decreases insulin secretion although the response is variable and depends upon several factors including the duration of the stimulation and prevailing blood glucose levels (see 3, 9–11). In keeping with this is the observation that in some models of experimental obesity, the reported decrease of sympathetic activity is partly responsible for hyperinsulinemia by reducing tonic inhibitory effects on insulin secretion (24).

Therefore, a complex system exists for direct neural alteration of insulin secretion from the pancreas. In addition, recent evidence suggests that the hypothalamus contains factors which can directly stimulate insulin release from the pancreas. One such factor, thought to be a small peptide, has been isolated from the ventrolateral and ventromedial hypothalamic regions (25, 26) as well as from the blood (27). When injected intravenously into rats or administered to isolated rat pancreases in vitro, it stimulates insulin secretion. Although there is evidence that this factor is secreted from cells within the hypothalamus (28), its precise physiologic role remains to be elucidated.

In addition to these relatively direct neural influences over insulin secretion, the CNS also influences the secretion of several other hormones known to be important regulators of blood glucose and of insulin secretion. These include hormones of the pituitary and adrenal glands. Finally, there is also direct neural control of glucose-regulating enzymes in the liver (3, 29).

The afferent link of the neuro-pancreatic axis is less-well characterized and understood. Sensory endings are thought to exist within the islets and spontaneous activity has been recorded in branches of the vagus from the pancreas when the nerve was cut proximally (30). More recently, changes of vagal autonomic activity have been elicited by administration of glucose by various routes (31, 32: Sauter JF & Jeanrenaud B, unpublished). It is probable that information regarding glucose levels (as well as many other metabolically relevant parameters) reaches the CNS from several abdominal sites including the gut and the liver in addition to the pancreas. There are also specific insulin and glucose receptors within the CNS, and information from glucose sensitive tissues all over the body (including the taste buds of the tongue) probably converges within the brain stem.

The regulation of adiposity

Adiposity, or the total amount of fat in the body, behaves as if it were regulated (see 33–

35). The arguments in support of this contention have been detailed elsewhere and can be summarized here:

1) In adult animals, the amount of fat tends to remain relatively stable over time. This occurs in spite of wide fluctuations of food availability, food intake, and exercise. The fact that there are slow changes of body fat with age in some species (eg, male rats have a steady increase of fat as they get older) does not negate the concept of regulation. Rather it shows the influence of preprogrammed trajectories of adiposity within species or individuals. It is also the case that prolonged changes of average food palatability, or stressors, or forced feeding patterns, may alter the amount of fat defended (36). The important point is that when environmental conditions are relatively stable, adiposity tends to remain constant.

2) Animals and people defend their level of adiposity. This is true of obese animals and people as well as those with normal levels of body fat. What is different in obese individuals is the level of fat which is defended, not the ability to regulate it. A good example of the regulatory process is the common dieting experience of humans. Millions of people routinely try to lose weight by restricting their caloric intake but with variable success. In practice, most people can lose weight for short intervals. However, over time, weight tends to creep back to predieting levels such that the great majority of dieters eventually regain all of their lost weight. This may mean that although weight loss is feasible for the obese, underlying defects that include, among others, alterations of the interrelationships among glucose, insulin, and the brain, may become increasingly important as weight is lost and may ultimately prevent actual normalization of body weight. The system is symmetrical, although the symmetry does not imply the absence of underlying defects in obese subjects; rather, in such individuals the symmetry is indeed observable, but at higher absolute values. If normal animals or people are induced to eat excess food and put on weight, they undereat and lose weight when the experiment is ended. **Figure 1** depicts some of these processes.

3) Alteration of weight by direct manipulation of fat levels is soon reversed. If adipose

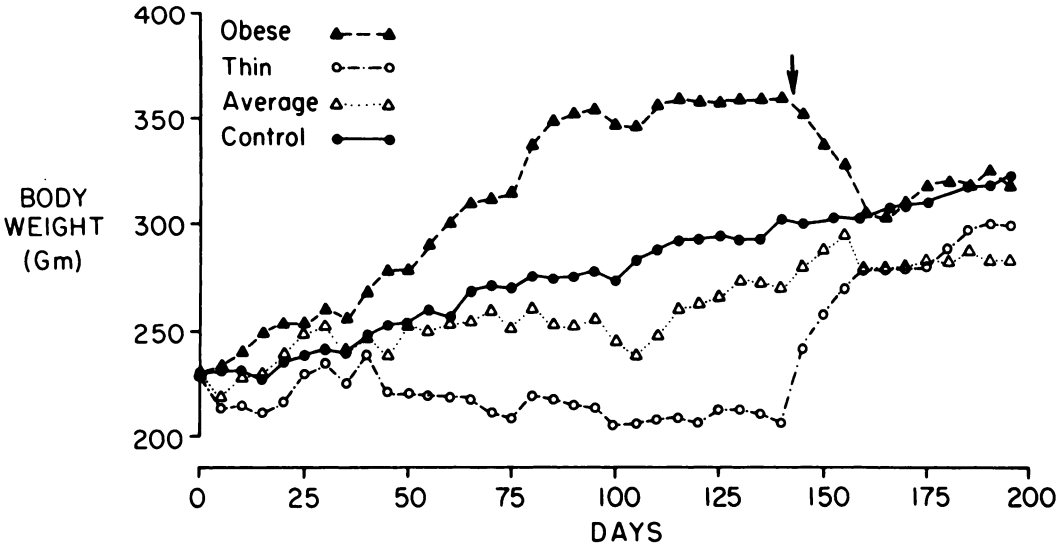

FIG 1. Mean body weight (in g) of four groups of rats over a 190-day period. Control rats received ad lib food (rat chow pellets, Ralston Purina Co, St Louis, MO) throughout. Rats in the other three groups were given different amounts of the same diet (a slurry of ground chow, corn oil, and sucrose) to bring their weights above the controls (Obese group), below the controls (Thin group) or at about the same average weight as the controls (Average group). The diet was given to all rats in these three groups by gavage three times a day. At the time indicated by the arrow, the gavage-feeding was stopped and all animals had ad lib chow for the remainder of the experiment. The weights of rats in all groups then converged with that of the control animals. The data are taken from Reference 36.

tissue is surgically removed (lipectomy), and if the animal has an adequate diet, it overeats and replaces exactly the mass of fat which was taken. If excess fat is surgically added to an animal, its own fat beds are reduced such that total fat is constant.

4) Although changes of food intake are the primary means of controlling adiposity, when this behavior is prevented by fixing food intake, animals appear to be able to regulate metabolic efficiency to control their adiposity.

The existence of a precise regulation of adiposity is often interpreted as inferring that attempts at controlling adiposity are futile. Quite to the contrary, the existence of a negative feedback control system implies that the system is susceptible to external influences and advantage might be made of the rigor of the system. It is the case that the tighter and more complex a system, the more prone it may become to abnormal regulation. The existence of a negative feedback system for adiposity implies the existence of some signal proportional to adiposity which can influence food intake. If such signal(s) were known and could be altered therapeutically, adiposity might be more easily controlled. The next section reviews the information suggesting that insulin might be one such signal.

The relationship between insulin and adiposity

Basal insulin is defined as the amount of insulin measurable in the blood in the absence of exogenous influences such as stressors or food. It is generally estimated after an overnight fast in humans when the person is relaxed and not exercising. Basal insulin is directly correlated with adiposity, such that fatter people or animals have higher basal insulin and leaner people or animals lower basal insulin, suggesting the existence of a direct functional interrelationship between fat cell mass and the endocrine pancreas. This robust relationship is also found when one's adiposity is changed. If one loses weight, basal insulin is reduced proportionally; and if one gains weight, basal insulin is increased (see 37). It is probably also the case that the total amount of insulin secreted throughout the day is directly related to adiposity, but such measurements are difficult (1).

The amount of insulin in the blood might therefore be considered a useful index for adiposity, and to the extent that the brain integrates information as to adiposity, blood insulin should be a possible candidate for the messenger. The problem with this simple schema is that insulin secretion and therefore the level of insulin in the blood is altered by most activities. Insulin is increased during and after meals and is decreased during times of stress or exercise. Spontaneous or random samples of insulin in the blood may therefore be poor correlates of adiposity but good correlates of fuel needs at that time. For this reason, blood insulin was not thought to be an adequate adiposity-related signal to the brain (38, 39).

However, it is known that insulin from the blood can penetrate into the cerebrospinal fluid (CSF) at a slow rate, and that the levels within the CSF are an integral over time of the levels in the blood (40). CSF insulin levels change relatively slowly and are thus a more stable parameter than plasma insulin levels. CSF insulin is therefore a potential candidate for the messenger signifying adiposity to the brain. In support of this concept, it has recently been found that genetically obese rats have significantly higher amounts of insulin in their CSF than do their lean littermates (41). Similarly, obese humans reportedly have higher levels of CSF insulin than lean controls, and the levels decrease with weight loss (42). Small increases of CSF insulin have also been observed after meals in rats and baboons (41, 43). Therefore, insulin is present in the CSF and the level there reflects changes in the blood and is increased in obesity.

Insulin receptors in the brain

For insulin to be a viable candidate as an adiposity signal to the brain, the brain must be able to detect its presence as well as any change in its levels. Numerous laboratories have now documented the presence of specific insulin receptors in the brain and many of these are located in sites known to be involved in metabolic control (44, 45). Of particular importance to this discussion, insulin uptake by the hypothalamus has been shown after insulin was added into the CSF of rats (46). Further, the labeled insulin is found in different

sites than when insulin is given into the carotid arteries. Therefore, insulin within the CSF may have access to brain receptors not directly accessible to plasma insulin. Such a system would allow for one population of insulin receptors (those sampling the blood) to be involved with the regulation of glucose and fuel needs of the body while a second, quite distinct population of brain insulin receptors (those sampling the CSF) would be directly or indirectly involved with the regulation of adiposity (see 47).

Functional insulin receptors in the brain have been inferred from electrophysiologic studies. Areas of the hypothalamus known to have a role in the control of food intake and body weight contain neurons whose electrical activity is altered by the direct iontophoretic application of insulin. Further, the response of these cells is modified by the simultaneous presence of glucose and peptide hormones which influence food intake (see reviews in 11, 48). Functional insulin receptors have also been inferred from physiological experiments. Specifically, the infusion of insulin into the carotid arteries or directly into the CSF results in vagally mediated changes of insulin secretion from the pancreas (49, 50) and glucose output from the liver (51).

Therefore, the brain has receptors specific for insulin and several reflexes triggered by changes of central insulin are known to exist. Since many of the receptors are located in anatomical areas where lesions or electrical stimulation alter food intake and body weight, one can postulate that insulin acting at the brain might also play a role in these behaviors.

Central insulin and food intake

Therefore, insulin secretion from the pancreas is correlated with adiposity, and some of this insulin gets into the CSF where it has access to specific receptors that may have specific though diverse final function(s) or output(s). If some of these functions related to insulin are an indicator of adiposity, it ought to be possible to interfere with the normal feedback process by manipulating CSF insulin levels. The hypothesis would be that an experimental elevation of CSF insulin would be interpreted by the brain to indicate that the animal is fatter than it actually is; conversely, the experimental lowering of CSF insulin from its normal level would be indicative of a lower level of adiposity. When CSF insulin is increased, the animal should decrease food intake and lose weight over time; when CSF insulin is decreased, the animal should eat more food and increase its weight over time (39, 47).

This hypothesis was tested in baboons by chronically infusing synthetic CSF at a slow rate into the lateral ventricles of their brains (52). When insulin was added to the infused fluid for periods of 2 to 3 wk, there was a dose-dependent decrease of food intake and body weight. The highest dose tested (100 μU/kg/day) reduced food intake by close to 75% at its maximum point, yet did not alter plasma insulin or glucose levels. Isomolar infusions into the CSF of glucagon, another pancreatic peptide, had no effect on any of these parameters. Similar results have been obtained in rats when the insulin was infused into the third ventricle by means of osmotic minipumps (53), and when insulin was infused for several days directly into the ventral hypothalamus (54). In every instance, the slow infusion of insulin into the CSF or directly into the hypothalamus caused a reduction of food intake and of body weight. Strubbe and Mein administered antibodies to insulin directly into the ventral hypothalamus (55). As a result, the rats ate more food than on control days. Those authors did not administer the antibodies chronically to ascertain the effect upon body weight.

Therefore, changes of insulin directly within the brain result in predictable changes of food intake and body weight. Since insulin enters the CSF from the blood, it should also be the case that a slow chronic infusion of insulin into the blood should ultimately reduce feeding and weight. Such experiments are confounded by the peripheral actions of insulin. As discussed above, peripherally administered insulin reduces plasma glucose and this effect is sufficient to stimulate increased eating. If plasma insulin could be chronically elevated without creating hypoglycemia, eating might be suppressed. This has in fact been shown in several ways. VanderWeele and his colleagues infused small amounts of insulin subcutaneously into rats via osmotic minipumps (56). The smallest doses of insulin had no effect at all; slightly larger doses, which raised plasma

insulin without creating hypoglycemia, reduced food intake and body weight; and larger doses of insulin, which caused hypoglycemia, increased food intake. Nicolaidis and Rowland infused glucose intravenously for long intervals in rats (57). The addition of a small amount of insulin to the infused glucose caused a greater reduction of food intake than the glucose alone. There was no hypoglycemia due to the presence of high levels of glucose. Therefore, if insulin is increased selectively within the brain, or else is increased in the blood and hypoglycemia is prevented, food intake and ultimately body weight are reduced.

Such a model assumes that insulin, as an indicator of adiposity, is but one of many stimuli influencing how much food is eaten. If an error were to occur in the feedback loop, there should be predictable consequences. The Zucker (fatty) rat is an example of an animal which might have a primary defect in this system. In these animals, obesity is transmitted as a homozygous recessive trait. These animals have an abnormal relationship between the brain and the pancreas. Prior to weaning, when obesity is not yet manifest, preobese Zucker rats secrete excess insulin in response to glucose or arginine challenges (22). Further, this response is normalized with the addition of atropine, a cholinergic blocking drug. Similarly, the isolated pancreases of adult obese Zucker rats secrete excess insulin to these same challenges which is also normalized with atropine (22). Obese Zucker rats also have a deficit in the cephalic phase of insulin secretion (Ionescu E & Jeanrenaud B, unpublished observation). When given either saccharin or glucose orally, they secrete less insulin (on a percentage basis) than their lean controls and (when the glucose is ingested) become more hyperglycemic. Cephalic insulin secretion is known to utilize the vagus nerve (58, 59). Finally, although somewhat controversial (60), there is evidence that vagotomy prevents the further weight gain of adult obese Zucker rats (61).

Insulin is found in the brain of rats in small quantities, and certain areas have slightly more insulin than other areas (see 62, 63). These areas include the hypothalamus and olfactory bulb. Obese Zucker rats have very low, almost undetectable amounts of insulin in the brain (64) although they have relatively high levels of insulin in the CSF (41) as well as high plasma insulin levels. This suggests that insulin within either the plasma or the CSF might not gain easy access to the brain in these animals. Consistent with this, the infusion of insulin directly into the CSF of obese Zucker rats has no effect on food intake whereas the infusion of the same amount of insulin into the CSF of their lean littermates causes a significant reduction of food intake and body weight (65). Failure to transport sufficient insulin to critical brain sites and/or absent or functionally deficient brain insulin receptors may lead to the false perception of leanness in these animals and contribute to their overeating and obesity.

Summary

This chapter has described an important relationship between the brain and the hormone insulin. Receiving information related to fuel needs throughout the body, the CNS has the ability to alter profoundly the secretion of insulin, as well as many other metabolic parameters including feeding. Insulin in turn feeds back to the brain to regulate food intake and adiposity to complete the feedback loop.

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