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REVIEW ARTICLE

NEURAL REGULATION OF GLUCOSE HOMEOSTASIS

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Abstract : The regulation of blood glucose is generally stated to be under the control of the endocrine system. But the endocrine secretion is itself regulated by the central nervous system, especially the hypothalamus. The brain can sense the energy status of the body by using neural afferent signals and metabolic cues such as glucose. A variety of experimental evidences have been put forth to support the postulate that there are "glucoreceptors", sensitive to blood glucose and glucose utilisation, in the hypothalamus. Gastrointestinal afferents, which carry information about the energy intake, reach the hypothalamic regions and interact with the glucose sensitive mechanisms. Available evidence suggests that obesity and decreased body weight, resulting from lesions of the hypothalamic 'satiety' and 'feeding' centres respectively, are not only due to altered food intake, but also to derangement in glucose homeostasis. The medial preoptic area does the fine tuning of energy balance (regulation of food intake) in response to alterations in the temperature, locomotor activity and sleep wakefulness. Thus the hypothalamus regulates energy balance through its control of energy intake on the one hand, and its expenditure and storage on the other. Neuroendocrine system and autonomic nervous system deal with storage and expenditure of energy.

Key words : glucoreceptors satiety centre feeding centre endocrine food intake hypothalamus energy balance autonomic nervous system gastro intestinal afferents

INTRODUCTION

On the basis of simple logic, it was assumed that the glucose level in the blood is regulated by the brain, as glucose is very essential for the normal functioning of the nervous system. But the evidence in favour of this hypothesis came through several painstaking experiments (1–4). Furthermore, the blood sugar level was thought to be related to the feelings of hunger (5), though studies later showed a poor correlation between the two (6). Based on the fact that people with uncontrolled diabetes mellitus are usually polyphagic in spite of their high blood sugar level, Mayer suggested that it is the arteriovenous glucose difference which is related to the feeling of hunger (1–4). It therefore seemed logical to Mayer and his colleagues to

postulate that the 'satiety centres' in the hypothalamus, which serve to regulate feeding, may also serve as 'glucoreceptors.' (The concept of 'satiety' and 'feeding' centres will be discussed later in the section dealing with the hypothalamus). Injection of goldthioglucose, which destroyed the cells in the ventromedial nuclei of the hypothalamus, produced hyperphagia and obesity in the mouse (7–9). The work of Anand and his collaborators, provided experimental evidence for a hypothalamic glucoreceptor mechanism (10–13).

Maintenance of plasma glucose concentrations within a narrow range, despite wide fluctuations in the demand and supply, results from regulated release and removal of glucose from the circulation. On a moment-to-moment basis, these processes are controlled mainly by insulin and glucagon. Under stressful conditions (e.g. hypoglycemia, trauma, vigorous exercise), increased secretion of other hormones such as adrenaline, cortisol and growth hormone, and increased activity of the sympathetic nervous system, also come into play (14). Insulin secretion by pancreatic beta cells is modulated by several neural stimuli, although glucose is undoubtedly the major regulator (15). Neural regulation of glucose homeostasis takes place not only through the control of endocrine secretion by its autonomic innervation, but also through the regulation of food intake. Food intake is increased when the availability of cellular metabolic fuel is low (16). In fact glucose homeostasis is part of the energy balance regulation which is performed primarily by the brain in short, intermediate, and long cycles that are superimposed on each other. The brain can sense the energy status of the body by using its central and peripheral receptors, and by metabolic signals such as glucose, insulin, and leptin (17). It then initiates a wide variety of physiological and behavioural adjustments that are required to maintain caloric homeostasis.

Glucose monitoring system

The availability of glucose can be detected by the central and peripheral chemosensors. Glucose-sensitive neural elements exist in the hypothalamus, the brain stem and visceral organs such as liver and gastrointestinal tract. Glucose generally suppresses the glucose-sensitive cells in the liver, the brain stem and the lateral hypothalamic area (LHA), and is generally excitatory to the afferents from the small intestine and neurons in the ventromedial hypothalamic nucleus (VMH), and also glucoreceptors in the brain stem.

In starved animals, activity of satiety centre neurons in the hypothalamus is slower than that of feeding centre neurons. The frequency of action potentials from satiety centre neurons increased and that of feeding centre neurons decreased significantly after glucose infusion, while activity from these centres showed a reverse pattern of response after intravenous injection of insulin (13). Other hypothalamic and cortical neurons did not show any significant change. The change in spike activity of satiety and feeding centre neurons showed a good correlation with changes in the A-V glucose difference. As these changes were observed in deafferented animals, it was suggested that the hypothalamic neurons are influenced directly by changes in the level of glucose utilization in the central nervous system.

Intravenous injection of Fenfluramine, which produced anorexic behaviour and decrease in food intake in monkeys, resulted in slow wave electrical activity in the 'feeding centre.' The activity of the satiety centre changed to low voltage fast response, specially in starving animals. Arteriovenous glucose estimations suggest that the effects of Fenfluramine may be due to the increased level of glucose utilization in the body (18).

The neural network, which monitors the glucose, also analyses and integrates information about other metabolites including peptides in the blood and cerebrospinal fluid. This network regulates the peripheral metabolism and endocrine activity as well as feeding behaviour (19).

Brain regions regulating glucose homeostasis

Many areas in the brain have some role or the other to play in the regulation of energy balance. But the importance of hypothalamic mechanisms could be understood from the severe derangements in energy balance following production of tiny lesions in localised areas there. According to Brobeck, regulation of energy balance is probably based on feeding reflexes which are operating through the spinal cord and the brain stem (20). These reflexes are facilitated and inhibited by the feeding and satiety centres of the hypothalamus. These are further influenced by other regions of the brain like the limbic system in a discriminative manner, to provide a discriminative appetite (21). Neocortical regions may also produce modifications as a result of habit formation and conditioning (22).

Hypothalamus

Attention was focused on the hypothalamic mechanisms in the regulation of energy balance by Heterington and Ranson who produced obesity in rats by lesions confined to the VMH (23). Brobeck and his colleagues later showed that the hypothalamic obesity was due to hyperphagia (24). Investigations by Anand and Brobeck showed that the lesions in the LHA produced aphagia and adipsia while those in the ventromedial hypothalamus produced hyperphagia and obesity (25). They gave the name 'feeding centre' to the lateral mechanism, and 'satiety centre' to the ventromedial area. Later studies showed that the dorsomedial hypothalamus (DMN) is also important for the satiety mechanism.

Though the neurons of the middle region of the hypothalamus (VMH, DMN and LHA) are primarily involved in the regulation of food intake, the medial preoptic area is responsible for fine tuning of energy balance in response to alterations in the temperature, locomotor activity and sleep-wakefulness. The medial preoptic area lesions produce increase in locomotor activity, rectal temperature and awake period (26–30). Though there was no change in food intake, there was a reduction in the body weight of the rats after the lesion (29). There was no compensatory increase in energy intake (food intake), in spite of the increase in locomotor activity, rectal temperature and awake period. Therefore, after the lesion, the animals did not recognize low energy reserves, and so they did not bother to conserve energy. Thus, the medial preoptic area lesioned animals

had lost the mechanisms for the fine tuning of food intake regulation in response to the alteration in body homeostasis. The functional integrity of the medial preoptic area may be essential for the regulation of food intake in response to alterations in temperature, locomotor activity and sleep-wakefulness (29).

Bernardis and Bellinger (31), who reviewed the findings that have accumulated since the original description of the syndrome that follows destruction of the LHA, have concluded that several of these changes may be due to the reduced food intake, but others appear to be due to a "true" lesion effect, involving profound changes in glucose metabolism like glycolysis, glycogenesis and gluconeogenesis (31). According to them, the rats with LHA lesions regulates their body weight set point in a primary manner and not because of destruction of a 'feeding centre.' The lower body weight is not due to finickiness. In the early stages of the syndrome, catabolism and running activity are enhanced, and so is the activity of the sympathetic nervous system as shown by increased norepinephrine excretion that nomalizes one month later. Tissue preparations from the LHA promote glucose utilization and insulin release. Although it does not belong to the classical hypophyseotropic area of the hypothalamus, the LHA does affect neuroendocrine secretions.

In the first phase after VMH lesion, rats are hypersensitive and hyperresponsive to insulin. But in the later phase, when obesity is well established, VMH-lesioned rats become insulin resistant and display a decrease in sensitivity and responsiveness of liver and muscle tissues to the hormone (32). There is progressive development of insulin resistance in the muscles after the lesion of the VMH. Six weeks after the lesion, the muscles utilized less glucose than those of controls. Simultaneously, there is a transient insulin hypersensitivity in the white adipose tissue. In this tissue, glucose utilization was increased by two times in one week and returned to normal in six weeks. This, together with a hypersecretion of insulin, could contribute to the development of body fat mass by redirecting glucose towards the adipose tissue (32).

A significant decrease in blood glucose was observed following the VMH and the preoptic area stimulation. An opposite response was obtained from LHA and posterior hypothalamus (33). There was increase in immunoreactive insulin following LHA stimulation. An opposite response was obtained from the VMH. Thus, insulinogenic and insulinoprival responses were obtained from feeding and satiety centres, suggesting a significant role for these areas in insulin regulation (34). The growth hormone and cortisol release were facilitated by the stimulation of the LHA and the VMH. The endocrinal responses from preoptic area resembled those from the VMH. The posterior hypothalamus and mamillary body showed trends which were common to both the LHA and VMH (35).

Electrical stimulation of the VMH, in streptozotocin induced diabetic conscious male rhesus monkeys, significantly increased growth hormone, and decreased blood glucose. Serum insulin, free fatty acids, triglycerides and cortisol were largely

unaffected though in normal animals the insulin level was significantly decreased. Cortisol and free fatty acids increased significantly by the VMH stimulation. None of the biochemical parameters showed any significant change at any time following electrical stimulation of the parietal cortex. Thus the VMH stimulation did not alter the diabetic syndrome drastically. It also did not prevent the changes in metabolism seen after VMH stimulation (36).

Neuropeptide Y (NPY) neurons in the arcuate nucleus of the rodent hypothalamus may respond to reductions in the body energy stores. They may be involved in appropriate changes in energy homeostasis, namely food-intake and heat production by brown adipose tissue (37). Disordered regulation of NPY and monoamine metabolism within the VMH is a consistent finding in the brains of obese rodents. Genetically obese rodents show hyperactivity of the NPY neurons, and it may contribute to their hyperphagia, reduced energy expenditure and excessive weight gain. Injection of NPY into the brain sites of projection of the NPY neurons elicit food-taking behaviour. Animals that are threatened by energy deficits (e.g. through starvation or insulin-deficient diabetes) show increased activity of these neurons. The NPY neurons may be inhibited by insulin and leptin, which may both serve as signals of peripheral fat mass.

Hypothalamus has a rich innervation of monoaminergic and cholinergic fibres, and central monoamine neurotransmitters affect blood glucose homeostasis. Activation of central noradrenergic, histaminergic, serotonergic and cholinergic neurons rapidly increase hepatic glucose output by the sympathetic nervous system activation (38). The magnitude of epinephrine secretion is closely related to the magnitude of hyperglycemia. Neuropharmacological stimulation of central cholinergic muscarinic receptors, histaminergic H1 receptors, and serotonergic 5–HT2 receptors increases hypothalamic noradrenergic neuronal activity, which is associated with hyperglycemia. Local injection studies suggest the involvement of a central beta adrenergic mechanism in the neural control of glycemia in pigeons (39). The central monoaminergic neurons could be playing a homeostatic role in the regulation of hepatic glucose metabolism (38). In contrast, central GABA receptors play an inhibitory role in the regulation of hepatic glucose metabolism.

Brain stem regulation of glucose homeostasis

Alterations in feeding behaviour caused by ablation of the area postrema (AP) in rodents indicate the participation of this structure in the control of ingestion (40). Two types of glucose responsive neurons were identified in the AP: one is characterized by increasing the discharge rate in response to glucose (glucoreceptor type) and the other by decreasing the discharge rate (glucose sensitive type). These glucose responsive neurons may participate in glucose homeostasis.

The glucose responsive neurons exist within the caudal portion of the nucleus of the solitary tract (NTS), a relay station of the visceral afferents. Two types, similar to the AP, were also recognized. It is confirmed that hepatic glucose sensitive afferents

terminate on some of the glucose sensitive neurons. This convergence may serve as a fail-safe mechanism. In addition, the NTS involving complex neural networks of excitatory and inhibitory interneurons may be concerned with integration of information related to the regulation of glucose levels.

Some neurons within the dorsal motor nucleus of the vagus (DMV) were identified as the glucose responsive ones. Both types were found in this area also. It is confirmed by antidromic activation that these glucose responsive DMV neurons send their axons towards the stomach, intestine and pancreas. Some of the DMV neurons may subserve an enteroceptor function by themselves. They may also play a role in the brain stem neural control of glucose homeostasis as the fail-safe mechanism (40).

Regulation of glucose homeostasis by autonomic innervation

Parasympathetic stimulation via the vagus nerve increases insulin release, whereas sympathetic stimulation via the splanchnic nerve inhibits insulin release. Administration of epinephrine or norepinephrine systemically inhibits insulin release. This effect is mediated through alpha receptors. Agnosists which act on the beta adrenergic receptors stimulate the release of insulin, but the alpha effect of the naturally occurring catecholamines dominates under ordinary circumstances. The decrease in insulin release associated with stress (such as severe infections, exercise, or hypothermia) may be attributable in part to an increase in sympathetic discharge. Administration of phentolamine, an alpha adrenergic blocking agent, increases insulin release, suggesting that a tonic suppressive effect of the sympathetic nervous system is constantly operative.

Most of the regions of the central nervous system regulate insulin secretion via the hypothalamus and the autonomic nervous system (41–43). Stimulation or lesion of the hypothalamus induces various changes in the pancreatic autonomic nerve activity. The VMH, the DMN and the paraventricular nucleus have inhibitory effects on vagal nerve activity and excitatory effects on splanchnic nerve activity. The LHA is excitatory to the vagus nerve, and both excitatory and inhibitory to the splanchnic nerve (19, 44). While it is difficult to document and quantify, it is likely that the emotional state of the subject may importantly alter insulin release by way of the hypothalamus and its autonomic outflow tract. Fluorescent labelling studies in the rats have shown that the hypothalamic paraventricular neurons, projecting to sympathetic preganglionic cells which innervate the various organs involved in glucose metabolism, are mainly located in the dorsal part of the paraventricular hypothalamic nucleus (45).

Peripheral signals in the neurophysiological regulation of glucose homeostasis

The centres in the brain regulating glucose homeostasis are under the constant influence of humoral and neural factors. The level of available glucose in these regions is the major humoral factor. The various sensory afferents arising from the periphery, especially the gastrointestinal tract, constitute the important neural factor.

Gastrointestinal afferent signals: The details regarding the receptors sensitive to physico-chemical changes in the gastrointestinal tract have been reviewed by Paintal (46) and Sharma (47). Electrophysiological studies demonstrated the changes in the spontaneous electrical activity recorded from the hypothalamic feeding regions on stimulation of gastric afferents (22, 48). Herrin and Meek provided evidence suggestive of a possible role of intestinal afferents in the regulation of food intake by inhibiting feeding responses on distension of intestinal loop (49). In these studies, however, it was not clear whether the intestinal afferents produced these effects through their possible projection to feeding and satiety centres in the hypothalamus or through any other mechanism. Relationship of intestinal afferents to the hypothalamic mechanisms was shown by Kumar (50–52). They have shown that the impulses from the intestine project to the feeding areas of the hypothalamus and evoke potential changes there in a well defined pattern. Furthermore, these evoked responses are sensitive to the availability of glucose in the body (46). Thus, it has been possible to visualize the manner in which intestinal afferents may be modulating the activity of the hypothalamic feeding regions for the regulation of food intake.

The observations on the changes in evoked responses after administration of intravenous glucose and insulin provided further evidence in support of the role of these intestinal afferents in the regulation of the hypothalamic mechanism related to glucose homeostasis. There was an increased activation of the medial satiety area (VMH) and inhibition of the feeding area (LHA) on increasing the glucose availability in the body (51). Extra-hypothalamic regions did not show any specific change.

Insulin produced initial facilitation followed by inhibition in VMH. Since insulin initially increased the glucose availability in these areas, the initial facilitation was understandable. Subsequently, however, the effect was quite different. The responses from the LHA showed changes which were the reverse of what was shown by VMH (51, 53). These observations confirm the hypothesis proposed by Anand, Chhina and their colleagues who have shown regarding the rate sensitivity of medial satiety and lateral feeding mechanism to the availability of glucose (10–12, 18).

Administration of Fenfluramine (an appetite-depressing drug) produced an initial decrease and later potentiation of the evoked responses from LHA. The evoked response from VMH was also inhibited (51, 53). Thus, the Fenfluramine effect was rather paradoxical. It is likely that the drug may also have a generalised depressive effect on the brain.

Thus the information from the gastrointestinal tract not only reaches the hypothalamic energy regulating areas, but also produces specific types of excitation and inhibition in these regions. The neural elements responsible for the production of evoked responses in the hypothalamus are glucose sensitive and they are also influenced by the appetite depressing drugs.

Hepatic signals: There is ample evidence that the neural signals from hepatic

metabolic sensors can affect eating (54). Hepatic afferent nerves presumably represent glucosensors which contribute to the control of eating by monitoring their own glucose utilization. Yet, the nature of the putative sensors that respond to the oxidation of metabolites other than glucose had not been identified. ATP and sodium pump activity may link hepatic oxidative metabolism and membrane potential, because hepatic phosphate-trapping by 2, 5-anhydro-mannitol, and inhibition of sodium pump activity by ouabain is associated with a stimulation of eating. Hepatocyte membrane potential is also subject to changes in transmembranal potassium flow through volumetrically controlled membranal potassium channels. Yet it is not known as to whether the hepatocytes are linked to afferent nerves; if so, it is also unclear as to how the effects of glucagon and insulin fit into the hepatic metabolic control of eating. Glucagon appears to induce satiety through its actions in the liver, but the involved mechanism is still unclear. Recent studies suggest that insulin, which has mainly been explored as a centrally acting long-term satiety signal, has an immediate effect on meal size, but it is presently unknown whether a hepatic action of insulin is involved in this effect.

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