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Brain insulin and feeding: a bi-directional communication

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Abstract

Insulin and specific insulin receptors are found widely distributed in the central nervous system (CNS) networks related in particular to energy homeostasis. This review highlights the complex regulatory loop between dietary nutrients, brain insulin and feeding. It is well documented that brain insulin has a negative, anorexigenic effect on food intake. At present, a specific role for brain insulin on cognitive functions related to feeding is emerging. The balance between orexigenic and anorexigenic pathways in the hypothalamus is crucial for the maintenance of energy homeostasis in animals and humans. The ingestion of nutrients triggers neurochemical events that signal nutrient and energy availability in the CNS, down regulate stimulators, activate anorexigenic factors, including brain insulin, and result in reduced eating. The effects of insulin in the CNS are under a multilevel control of food-intake peripherally and in the CNS, via the metabolic, endocrine and neural modifications induced by nutrients. Single meals as well as glucose and serotonin are able to regulate insulin release directly in the hypothalamus and may be of importance for its biological effects. Central mechanisms operating in glucose-induced insulin release show some analogy with the mechanisms operating in the pancreas. Leptin and melanocortins, peptides that down regulate food intake and are largely affected by nutrients, are highly interactive with insulin in the CNS probably via the neurotransmitter serotonin. In the hypothalamus, insulin and leptin share a common signaling pathway involved in food intake, namely the insulin receptor substrate, phosphatidylinositol 3-kinase pathway. Over or under-feeding, unbalanced single meals or diets, in particular diets enriched in fat, modify the amount of insulin actively transported into the brain, the release of brain insulin, the expression of insulin messenger RNA and potentially disrupt insulin signaling in the CNS. This impairment may result in disorders related to feeding behavior and energy homeostasis leading to profound dysregulations, obesity or diabetes.

Keywords: Insulin; 5-HT (5-hydroxytryptamine, serotonin); Glucose; Nutrient; Hypothalamus; Hippocampus; Energy homeostasis; Feeding; Cognition; Regulatory peptide; Phosphatidylinositol-3 kinase

1. Introduction

Vital physiological processes, energy homeostasis, reproduction and cognition are regulated in the central nervous system by an interplay of key signaling molecules in interconnected neuronal networks. One concept currently emerging is that brain insulin plays a pivotal role in these functions. An impairment in the brain insulin availability or signaling results or contributes to such serious problems as: obesity, diabetes and mental or reproductive disorders. The concept that the development of diabetes mellitus is due solely to malfunctions at the level of beta cell, muscle and liver has to be reconsidered in the light of new evidence supporting the importance of the brain.

In this article we will review current understanding of brain insulin in two areas: firstly in the cellular and molecular mechanisms involved in the biological effects of insulin in the brain, particularly in relation to food intake, a fundamental aspect of energy homeostasis and secondly, in the regulation of brain insulin by information generated by nutrients (Fig. 1).

2. Regulation of food intake by brain insulin

The importance of insulin in normal brain functioning has been studied far less than its role in the periphery. While important issues remain unresolved, there is however increasing evidence that insulin possesses numerous metabolic, neurotrophic, neuromodulatory and neuroendocrine central biological effects (Barbaccia et al., 1982; Boyd et al., 1986; Duarte et al., 2003; Gispen and Biessels, 2000;

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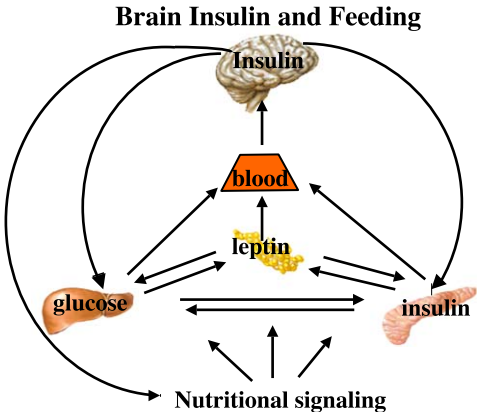

Fig. 1. Nutritional metabolic and endocrine signals reaching the brain, trigger the neurochemical cascade of events that control energy expenditure, ingestive and appetite behaviors, and maintain energy homeostasis. Brain insulin is implicated in those functions.

Jonas et al., 1997; Recio-Pinto et al., 1984; Snyder and Kim, 1980; Wan et al., 1997). Insulin acts as a mediator in the communication between the peripheral endocrine system and the brain via various steps of the neuroendocrine axis (Unger and Betz, 1998). The pleiotropic nature of the action of insulin in the central nervous system has been the subject of numerous reviews (Bruning et al., 2000; Gerozissis, 2003; Niswender and Schwartz, 2003; Park, 2001; Porte et al., 2002; Schulingkamp et al., 2000; Schwartz et al., 1992a; Woods et al., 1998, 2000; Wozniak et al., 1993; Zhao and Alkon, 2001).

2.1. Role of insulin in energy homeostasis

Despite the variations in physical activity, and in the composition and amount of food ingested daily, energy intake (in the form of food) largely matches energy expenditure (in the form of cellular metabolism and exercise) over time, through a regulatory process known as energy homeostasis. The central control of energy balance and the adjustment of both food intake and energy expenditure in response to a wide range of environmental factors and metabolic and hormonal signals occurs mainly in the hypothalamus. Insulin has a role as a marker of energy stores, an adiposity signal and a mediator of energy balance, and is one of numerous neuromodulators of energy homeostasis (Beck, 1999; Kalra et al., 1999; Kernie et al., 2000; Ludwig et al., 2001; Murakami et al., 2002; Neugebauer et al., 2003, Oomura and Kita, 1981; Rushing, 2003; Williams et al., 2001; Woods et al., 2000; Table 1). Insulin in the brain induces both short and long term effects on food intake regulation and body weight (Air et al., 2002a; Nicolaïdis, 1978; Woods et al., 1979). Intra-cerebroventricular or hypothalamic delivery of insulin inhibits food intake (anorexigenic effect) and produces a permanent loss of body weight (leptogenic action) in both rodents (McGowan et al., 1990; Nicolaïdis, 1978; Schwartz et al., 1992a) and primates (Woods et al., 1979). Injection of insulin antibodies into the ventromedial hypothalamus of rats increases food intake and results in body weight gain (McGowan et al., 1990; Strubbe and Mein, 1977), and antisense oligodeoxynucleotides directed against insulin receptor precursor protein in the third cerebral ventricle, dramatically decrease insulin receptors in the medial portion of the arcuate nucleus and induce hyperphagia and insulin resistance in rats. Additionally, mice with a genetic deletion of neuronal insulin receptors are hyperphagic and obese (Air et al., 2002c; Obici et al., 2002b). Absolute insulin deficiency is accompanied by pronounced and sustained "diabetic hyperphagia" (Sipols et al., 1995). Additional experimental support for a long-term action of insulin on energy homeostasis in the central nervous system comes from loss-of-function studies. Mice with neuron-specific insulin receptor "knockout" show an increase in food intake and body weight, and also a defect in the central nervous control of reproduction (Bruning et al., 2000). It is interesting to note that normal reproductive functioning necessitates the maintenance of energy stores within discrete limits. When energy stores are reduced, in particular in pre-or peri-pubertal animals, the priority for the organism is survival. Thus the activity of the reproductive axis is reduced, and appetite is stimulated. However, low fertility capacity is also observed in obese subjects. The role of brain insulin in reproduction is closely related to its importance in energy homeostasis.

2.2. Cognitive functions and feeding

The survival of an animal depends largely on how efficiently it can regulate its supply and use of metabolic fuels and essential nutrients. Food intake regulation depends

Table 1
Positive and negative regulators of energy balance acting in the central nervous system[a]

Orexigenic	Anorexigenic
	Insulin
AgRP	Amylin
β-Endorphin	Angiotensin II
Dynorphin A	α-MSH
GABA	BBS
Galanin	BDNF
Ghrelin	CART
MCH	CRH
Norepinephrine	Dopamine
NPY	Enterostatin
Orexins	GLP-1
	Leptin
	Peptide YY
	Serotonin

α-MSH = alpha-melanocyte stimulating hormone, AgRP = Agouti related protein, BBS = Bombesin, BDNF = Brain-derived neurotrophic factor, CART = Cocaïne and amphetamine related transcripts, CRH = Corticotropin releasing hormone, GLP-1 = Glucagon-like peptide 1, MCH = Melanin concentrating hormone, NPY = Neuropeptide Y.

[a] Kalra et al., 1999; Kernie et al., 2000; Ludwig et al., 2001; Murakami et al., 2002; Neary et al., 2003; Neugebauer et al., 2003; Rushing, 2003; Williams et al., 2001; Woods et al., 2000.

on the ability of the animal to encode and retain in its memory a variety of information about its experiences with food. The brain is efficient at controlling the provision of what is needed. Animals initiate meals even if ample energy is readily available. They learn associations based upon the caloric content of the food they receive and based upon the caloric and nutrient content of previously consumed foods. The decision to eat or not to eat, and the selection of food are based on learning to anticipate the post-ingestive consequences of food intake. The hippocampus is involved with either the detection or the utilization of hunger/satiety signals and the specific memories and learning related to food intake (Tracy et al., 2001; Woods et al., 2000). When animals are habitually fed at the same time each day, in expectation of the meal they synthesize and secrete hormones and neurotransmitters, including insulin, that are important regulators of food intake (Orosco et al., 1995; Yoshihara et al., 1996). We have proposed that brain insulin is a potential neuromodulator involved in cognitive processes related to feeding (Gerozissis et al., 2001; Gerozissis, 2003). Evidence for this is now briefly summarized.

Since the mid 1990s, data have accumulated on the involvement of brain insulin in cognitive processes, and at present it is generally accepted that insulin is involved in brain cognitive functions and dysfunctions (Craft et al., 1998, 1999; Gasparini et al., 2002; Henneberg and Hoyer, 1995; Hoyer, 2002a,b; Park, 2001; Park et al., 2000; Watson and Craft, 2003; Wickelgren, 1998; Zhao et al., 1999; Zhao and Alkon, 2001).

Using an in vivo microdialysis technique, cerebral insulin levels have been measured in rats habituated to a specific feeding time. During the 30-min period that precedes meal time extra cellular insulin levels in the hypothalamus are increased. This anticipatory hypothalamic insulin increase is unrelated to any visual, olfactory, aural or other sensory signal that could induce a Pavlovian conditioning and occurs even when the meal is not presented at all. The anticipatory increase in hypothalamic insulin is proportional to the number of repeated scheduled meals as if a specific learning or memory related to food had been established. If the meal is not presented at the expected time, hypothalamic insulin concentration is even greater. Peripheral insulin levels, estimated simultaneously, were found to be largely unaffected (Gerozissis et al., 2001, 2002; Orosco et al., 1995). Additional support for a role of insulin in brain cognitive functioning comes from further studies demonstrating a modification of brain insulin release and insulin messenger RNA expression, observed in animals absorbed a meal consisted exclusively of animal fat or in animals fed high fat diets (Gerozissis et al., 1997, 2001, 2002; Gerozissis, Cruciani et al., unpublished). In addition, in old rats in vivo, the extra cellular release of hypothalamic insulin and the postprandial hypothalamic insulin increase were completely altered (Gerozissis, 2003; Gerozissis et al., 2002). These observations should be set alongside with evidence that aging, or a high fat diet results in impaired cognitive function, reduce the transport of insulin in the brain or alter brain insulin signaling (Greenwood and Winocur, 2001; Kaiyala et al., 2000). In contrast, as will be discussed below, glucose, or meals rich in carbohydrates that increase release of hypothalamic insulin (Gerozissis et al., 1998, 2001), restore normal cognitive function in rats fed high fat diets (Greenwood and Winocur, 2001).

The hypothalamus has a crucial role on the origination and processing of feeding related stimuli, and the hippocampus is important for cognitive processes, including feeding-related cognition (Tataranni et al., 1999; Tracy et al., 2001). In addition, the hippocampus expresses insulin messenger RNA and has an abundance of insulin receptors capable of receiving signals from other brain regions that may be monitoring nutrient status (Schwartz et al., 1992a; Zhao and Alkon, 2001; Zhao et al., 1999). It is tempting to speculate that brain insulin is involved in the control of food-related cognitive functions. It seems likely that a number of other regulatory peptides involved in both eating behavior and cognitive functions, in particular leptin and galanin (Air et al., 2002b; Steiner et al., 2001) in interaction with brain insulin, might be involved in cognition related to feeding (Gerozissis, 2003). As we discuss below, signaling generated by the ingestion of nutrients can modulate brain insulin levels through glucose- and serotonin-mediated mechanisms, and thus information derived from nutritional behavior controls the effects of the peptide on cognitive functions related to feeding.

2.3. Mechanisms of action on feeding and energy balance

Growing evidence suggests that insulin interacts with both orexigenic and anorexigenic peptides in the brain in the control of feeding behavior, maintenance of body weight around a set point and energy homeostasis, which is essential for survival. Essential nutrients and metabolites participate actively, in a complex direct and indirect manner in this regulatory peptide interaction (Fig. 2).

Based on the important similarities between brain insulin and leptin action and on cross-talk between insulin and leptin signaling, recent studies suggest that convergent mechanisms mediate cellular responses to insulin and leptin in hypothalamic neurons (Carvalheira et al., 2001; Niswender and Schwartz, 2003; Niswender et al., 2003a; Obici et al., 2002c; Porte et al., 2002; Zhao et al., 2002a,b). The mechanisms that regulate the effects of insulin in the brain show similarities with peripheral insulin action even though there are differences between the characteristics of insulin receptors in neurons and the periphery (Heidenreich et al., 1983; Raizada et al., 1988; Le Roith et al., 1988; Schulingkamp et al., 2000; Unger and Betz, 1998; Wozniak et al., 1993). One of the intracellular signaling pathways of insulin that is well documented in peripheral tissues involves activation of the insulin receptor substrate (IRS)-phosphatidylinositol-3 kinase (PI3K) enzyme system (Saltiel and Kahn, 2001; Shepherd et al., 1998; see also this issue). A

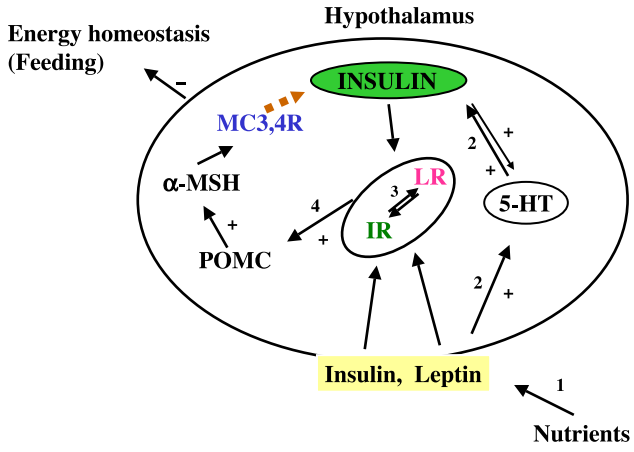

Fig. 2. Circulating insulin and leptin, among other metabolic factors and hormones regulated by food intake, reach the hypothalamus and activate the biochemical events that control energy homeostasis (1). The level of hypothalamic insulin depends on the amount of blood insulin transported in the brain and on insulin potentially originated from local sources. Hypothalamic insulin participates in the regulation of food intake and body weight as an inhibitory, anorexigenic and leptogenic signal, interacting with neurotransmitters and regulatory peptides. In this simplified diagram, only the interaction of insulin with some negative regulators of feeding behavior is summarized. Of particular interest is its potential interaction with leptin (2) via serotonin (5-HT), the cross-talk (3) of insulin receptors (IR) with leptin receptors (LR) and the activation of melanocortin pathway (4) by both insulin and leptin. MCR = melanocortin receptors, POMC = proopiomelanocortin, α-MSH = alpha-melanocyte stimulating hormone. Pathway depicted by broken arrows is speculative.

similar mechanism operates in insulin's action in the hypothalamus (Unger and Betz, 1998; Spanswick et al., 2000; Niswender et al., 2003a,b) and a similar pathway is also activated by leptin (Harvey et al., 2000; Niswender et al., 2003a; Porte et al., 2002; Spanswick et al., 1997; Szanto and Kahn, 2000; Zhao et al., 2002a,b; Fig. 3). This insulin receptor substrate-phosphatidylinositol-3 kinase pathway is implicated in food intake regulation in the hypothalamus and underlines the importance of insulin and leptin receptor cross-talk in the control of energy homeostasis (Carvalheira et al., 2001; Harvey et al., 1997, 2000; Niswender and Schwartz, 2003; Niswender et al., 2003a; Szanto and Kahn, 2000; Zhao et al., 2002a). Interestingly, insulin receptors, insulin receptor substrate, phosphatidylinositol-3 kinase and downstream proteins are present in the nervous system of evolutionary distant organisms such as *Drosophila melanogaster* and *Caenorhabditis elegans*, where they play an essential role in regulation of energy balance, reproduction and longevity via their action in the nervous system (Garofalo, 2002; Wolkow et al., 2000).

Insulin, along with other factors including leptin (inhibitory) and glucocorticoids (stimulatory), regulate the synthesis and release of the orexigenic neuropeptide Y (NPY) in the hypothalamus (Kalra et al., 1991; Schwartz et al., 1992b). The expression of neuropeptide Y in arcuate nucleus neurons is decreased after systemic or central administration of insulin and leptin, whereas neuropeptide Y neurons become overactive when the levels of these hormones fall during under-nutrition (Sipols et al., 1995; Schwartz et al., 1992b; Williams et al., 2001). Intracerebroventricularly injected neuropeptide Y influences glucose metabolism and insulin sensitivity (Marks and Waite, 1997). In addition, infusion of antisense oligodeoxynucleotide directed against insulin receptor precursor protein in the third cerebral ventricle, which induced hyperphagia and insulin resistance in rats, dramatically decreases insulin receptors in the medial portion of the arcuate nucleus, in neurons containing neuropeptide Y and Aguti related protein (AgRP) (Obici et al., 2001). These hypothalamic arcuate nucleus neurons also express proopiomelanocortin (POMC), are activated by insulin and leptin, and secrete α-melanocyte stimulating hormone (α-MSH). The NPY/AgRP neuron is unique in that neuropeptide Y release stimulates anabolic circuits, while Aguti related protein inhibits melanocortin signaling by antagonizing neuronal melanocortin receptors 3 and 4. Melanocortin receptor 4 subtype is particularly implicated in energy homeostasis. Serotonin and corticotropin releasing hormone as well are able to modulate the activity of this neuronal circuitry (Cone et al., 1996; Hillebrand et al., 2002; Huszar et al., 1997; for review, see MacNeil et al., 2002). Glucocorticoids have anabolic effects in the central nervous system, where they act to increase food intake (Dallman et al., 1995; Tempel et al., 1992). An interplay between glucocorticoids and insulin appears to be of importance in feeding and metabolic functions (Dallman et al., 1993; Strack et al., 1995). Glucocorticoids probably interact with insulin and leptin in the long-term regulation of

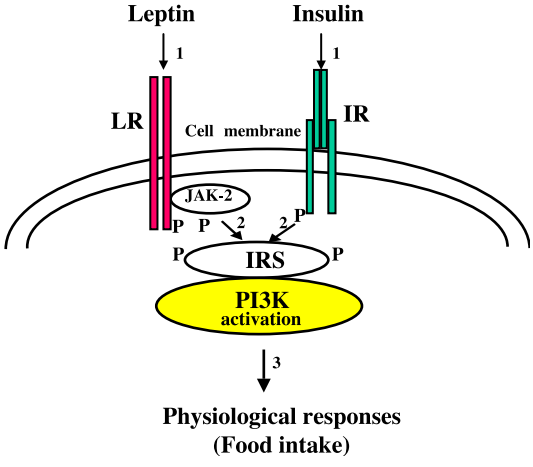

Fig. 3. Simplified diagram of the shared by insulin and leptin, common intracellular signaling pathway. Insulin binding to it's receptor (IR) (1) induces activation of an intrinsic tyrosine kinase resulting in receptor autophosphorylation and activates (2) insulin receptor substrate molecules (IRS) by tyrosine phosphorylation. Activated IRS molecules in turn activate a number of downstream targets, including phosphatidylinositol 3-kinase (PI3K). Activated PI3K phosphorylates phosphatidylinositol (4,5) bisphosphate (PIP2) to phosphatidylinositol (3,4,5) trisphosphate (PIP3). Leptin binding to its receptor (LR) (1) may also activate PI3K signaling, via JAK2 mediated phosph orylation of IRS proteins (2). Many of the physiological responses (3) to insulin and leptin action in the hypothalamus may be due to the utilization of this common signaling pathway.

energy intake and body adiposity. Removal of corticosterone by adrenalectomy increases sensitivity of insulin, delivered in the brain, in regulation of food intake, in a manner similar to that shown for leptin. In addition, chronic glucocorticoid administration appears to impair insulin transport to the central nervous system and to cause insulin receptor desensitization (Baura et al., 1996; Chavez et al., 1997; Giorgino et al., 1993).

3. Regulation of brain insulin

The source of insulin in the brain might be either peripheral or local in origin, or both (Baura et al., 1993; Devaskar et al., 1994; Gerozissis, 2003; Schechter and Abboud, 2001; Schechter et al., 1996; Woods et al., 2003; Young, 1986; Zhao et al., 2002b). The proposal that there are two sources of insulin in the brain fits with experimental data from numerous laboratories, and could explain the paradoxical observations and mismatches frequently reported between circulating and brain insulin profiles (Baskin et al., 1985; Gerozissis et al., 1993, 1997, 2001; Havrankova et al., 1979).

Brain insulin is subject to a multifactorial control exerted at various levels. It can be regulated both peripherally and in the central nervous system: biosynthesis and secretion in the pancreas along with transport in the brain, internalization, storage, stability and its potential local production and release in the central nervous system may be affected by numerous metabolites, circulating hormones, regulatory peptides and neurotransmitters (Fig. 2, Table 2). The biological effects of insulin depend on the availability of the hormone in the brain, its binding to specific receptors and the activation of its signaling pathways.

The molecular mechanisms involved in the production and secretion of insulin from beta cells have been intensively investigated and reviewed. In this review, however, we will focus on the release of insulin in the central nervous system. It is interesting to note some similarities between beta cells and neurons, particularly in relation to ATP-sensitive K^+ channel depolarization. Beta cells resemble neurons in that they are electrically excitable and respond to hormonal stimuli and glucose by depolarization and exocytosis, in a process that resembles neurotransmitter release from synaptic vessels. Enzymes involved in the synthesis of gamma-aminobutyric acid, the main inhibitory neurotransmitter in the brain for instance, are present in beta cells and it has been suggested that common signaling mechanisms occur in response to similar physiological responses (Obici et al., 2002c; Perry and Greig, 2002; Yang et al., 1999).

Depolarization of neuronal cells by potassium ions or veratridine in primary cultures of the brain of 1-day-old rats, caused a marked stimulation of insulin release. The immunoreactive peak obtained after high performance liquid chromatography (HPLC), commigrated with rat insulin I and II. The depolarization-induced release of insulin was inhibited by cycloheximide and was specific for neurons (Clarke et al., 1986; Wozniak et al., 1993). Similarly, insulin released from adult rat brain synaptosomes under depolarizing conditions depends on calcium influx, suggesting that insulin is stored in the adult rat brain in synaptic vesicles within nerve endings from which it can be mobilized by exocytosis in association to neural activity (Wei et al., 1990).

Table 2
Signals generated by nutrients can regulate the biological effects of insulin in the brain acting on multiple levels

Biosynthesis and secretion of insulin by beta cells
Transport in the brain
Local brain insulin production
Stores or release of insulin in the brain
Stability
Receptor characteristics, ligand-receptor binding and intracellular signaling

3.1. Nutritional signaling

The ingestion and processing of nutrients triggers neurochemical events that signal nutrient availability to the central nervous system, which in turn modulates appetite, further nutrient intake, and energy expenditure, and thus determines body weight and energy balance. Furthermore, recent reports claim that central administration of fatty acids may activate ATP-sensitive K^+ channels in a manner similar to insulin and leptin, directly signal the nutrient status to the hypothalamus and alter hepatic glucose production (Clement et al., 2002; Obici et al., 2002a). The hypothalamus is important in sensing and responding to changes in nutrients. Brain insulin is involved in the feedback loop between brain peptides and food intake. Circulating insulin concentrations are proportional to body fat content. However, their secretion and circulating levels are mainly influenced by recent energy intake and dietary macronutrient content (for review, see Havel, 2001). Food intake, fasting and refeeding, and the composition of the diet influence the rate of insulin entry in the brain. (Kaiyala et al., 2000; Strubbe et al., 1988; Woods et al., 2003).

Entry of serum insulin into the cerebrospinal fluid has been demonstrated in animals and humans (Schwartz et al., 1992a; Wallum et al., 1987). Meals increase the concentration of insulin in the cerebrospinal fluid and its release in the hypothalamus (Gerozissis et al., 1998; Orosco et al., 1995; Schwartz et al., 1992a). Fasting decreases extra cellular hypothalamic insulin concentrations, whereas the signals generated by the ingestion of macronutrients modify specifically the extra cellular hypothalamic insulin concentration, as has been shown in cerebral microdialysis studies in freely moving rats. Each macronutrient has a specific effect on hypothalamic insulin. Extra cellular hypothalamic insulin concentrations are increased in both balanced meals and after an exclusively carbohydrate meal, remain unchanged with a casein meal and are significantly reduced with a

saturated fat meal (Gerozissis et al., 1997, 1998; Orosco et al., 1995). This acute regulation of brain insulin by nutrients shows an anatomical specificity, since the modifications induced in the hypothalamus by a carbohydrate meal were not observed in the cerebellum (Gerozissis et al., 1998). The profile of circulating insulin differs from that of extra cellular hypothalamic insulin, in particular following a fat meal. As mentioned previously, effects of unbalanced diets on brain insulin were also observed. Rats fed high fat diets for seven days, show clear differences in the expression of messenger RNA encoding for insulin in the hypothalamus compared to animals fed a standard laboratory chow diet (Cruciani et al., unpublished). In addition, the glucose-induced insulin release in vitro by the hypothalamus was largely and specifically modified in rats fed these short-term high fat diets (Gerozissis et al., unpublished).

3.2. Local regulation

3.2.1. Glucose

What are the local factors that link the information generated by nutrients to brain insulin?

The determinant regulatory role of glucose on pancreatic insulin biosynthesis and secretion is a classic biochemical concept. The presence and action of glucose in the brain is extensively discussed in this issue. There is an increasing amount of evidence suggesting that insulin present in the central nervous system is a regulator of central glucose metabolism, similar to that observed in the periphery, even if it is considered that glycoregulation is not the main function of insulin in the brain (Alquier et al., 2003; Choeiri et al., 2002; Livingstone et al., 1995; Wozniak et al., 1993).

From the results of in vivo and in vitro studies, it appears that glucose is also involved directly in brain insulin regulation. A rapid non-genomic effect of glucose was shown on induced insulin release from brain synaptosomes (Santos et al., 1999). Glucose must be metabolized within the beta cell in order to stimulate insulin secretion (Ashcroft et al., 1984). The mechanism of action of glucose on brain insulin release is probably similar to the mechanism of glucose action in the pancreas. In fact, a glycolytic inhibitor blocks insulin release by glucose in synaptosomal preparations, suggesting the necessity of glucose metabolism for its action (Santos et al., 1999). In microdialysis studies, glucose administered in the median hypothalamus in freely moving rats, at a concentration that represents the semi-maximal effective dose for pancreatic insulin secretion, causes a rapid dramatic increase in extra cellular hypothalamic insulin concentrations. The same dose of glucose only slightly modifies cerebellar insulin levels, showing a specific area-dependent regulation of hypothalamic insulin release (Gerozissis et al., 2001). The mechanism of action of glucose in the central nervous system is local, as neither insulinemia nor glycemia are affected. Interestingly, glucose induces a modest, delayed, increase in hypothalamic serotonin release, suggesting that the effect of glucose on hypothalamic insulin is independent of the local serotonin-induced insulin release discussed below (Gerozissis et al., 2001). Since glucose supplied by feeding is transported actively to the brain (Livingstone et al., 1995; Vannucci, 1994; Vannucci et al., 1991), it is not surprising to observe a similar increase in the extra cellular brain insulin content in response to local glucose infusion and to a carbohydrate meal (Gerozissis et al., 1998, 2001). Consequently it is tempting to speculate that meals regulate hypothalamic insulin, at least in part, through brain glucose modifications. It is of interest to point out the bi-directional communication of brain insulin with energy sources, both endogenous (hepatic glucose), and exogenous (nutrients) (Gerozissis et al., 2001; Obici et al., 2002a; Fig. 1).

3.2.2. Serotonin

The monoamine serotonin is a neurotransmitter that inhibits food intake (Blundell, 1984; Leibowitz and Shor-Posner, 1986; Simansky, 1996). Specific macronutrients induce parallel modifications of extra cellular hypothalamic insulin and serotonin concentrations in rats (Orosco and Gerozissis, 2001; Orosco et al., 1999). Increased serotonin release in vivo in the median hypothalamic region increases hypothalamic insulin release rapidly, whereas tracked in parallel, neither insulinemia nor glycemia are affected (Orosco and Gerozissis, 2001; Orosco et al., 2000). Serotonin exerts a rapid local effect on insulin release, probably acting on an immediately available pool of the peptide in the hypothalamus. In the same in vivo studies, when insulin was infused in the median hypothalamic area, a delayed increase on serotonin release was observed, suggesting that the activation of hypothalamic insulin by the neurotransmitter is the primary event of the insulin-serotonin interaction. The insulin-serotonin interaction seems to be a link in a larger cascade of events in the complex regulatory loop between hypothalamic neuropeptides and nutritional behavior (Ahima et al., 2000; Finn et al., 2001; Gerozissis, 2003; Kalra et al., 1999; Fig. 2).

3.3. Hormones and regulatory peptides

We have mentioned above the effects of insulin on a wide range of hormones and regulatory peptides. Hormones and peptides such as leptin, corticosteroids, neuropeptide Y and galanin, which are implicated in energy homeostasis, can influence insulin release in the pancreas. We suggest that the same factors potentially regulate brain insulin. It is now clear that neuropeptides or hormones act through complex networks involving the main hypothalamic nuclei, participating in regulation of food intake (Kalra et al., 1999; MacNeil et al., 2002; Niswender and Schwartz, 2003). Nutritional signaling controls the transport, production, release or action of these same regulators of energy homeostasis, in the hypothalamus. The regulatory action of hypothalamic peptides is also sensitive to information transiting through the brain structures that are relays for cognitive

events (Beck, 1999; Berthoud, 1999). Insulin, in interaction with those regulatory peptides, can activate processes related to feeding behavior, learning and memory, is potentially involved in the communication within brain structures, in particular hippocampus–hypothalamus and may be involved in cognitive processes related to feeding.

3.3.1. Neuropeptides

Both orexigenic and anorexigenic neuropeptides could be involved in the regulation of insulin in the brain. We make the assumption that peptides regulating energy homeostasis that are subject to control by insulin in the central nervous system, might also exert a retrocontrol on brain insulin. The hypothalamic melanocortin system regulates the action of insulin in rats and decreases plasma insulin concentrations in mice (Benoit et al., 2002; MacNeil et al., 2002; Niswender and Schwartz, 2003; Obici et al., 2001). A recent report suggests that leptin decreases glucose-stimulated pancreatic insulin secretion via its action on central melanocortin receptors (Muzumdar et al., 2003). It seems plausible that the melanocortin system, in addition to its action, modulates brain insulin availability (Fig. 2). The hypothalamic melanocortin system is responsive to physiological inputs from peripheral signals originating from nutrients. Increased dietary fat for instance, attenuates the anorexic effects of a centrally delivered melanocortin receptor agonist (Clegg et al., 2003).

The orexigenic neuropeptide Y may also play a role in regulating brain insulin. An interplay was shown between galanin and leptin in the hypothalamic control of feeding *via* corticotropin releasing hormone and neuropeptide Y (Bergonzelli et al., 2001; Cheung et al., 2001). We speculate that the orexigenic peptide ghrelin that modulates the downstream molecules of insulin signaling in hepatoma cells and influences the release of various neuropeptides and neurotransmitters might also interact with insulin in the brain (Kojima et al., 1999; Murakami et al., 2002; Murata et al., 2002; Zigman and Elmquist, 2003).

3.3.2. Leptin

The cross-talk of insulin receptors and the receptors of the adipocyte hormone leptin in the hypothalamus and its importance in feeding behavior has already been discussed. A growing body of literature suggests that there are multiple possibilities for insulin and leptin interactions in the brain. They may interact directly or via other neuromodulators. As shown in Fig. 2, serotonin is a potential key mediator of these interactions. Leptin affects serotonin turnover and therefore it could regulate brain insulin availability (Calapai et al., 1999; Orosco et al., 2000). However it seems unlikely that leptin regulates the immediate postprandial hypothalamic insulin increase, since the plasma leptin response to a meal is delayed compared to both the postprandial plasma insulin and hypothalamic insulin responses (Dallongeville et al., 1998; Feurté et al., 2000; Romon et al., 1999). The possible action of leptin on insulin is more likely to be related to longer-term insulin responses to nutrient signaling, than to immediate postprandial changes. As has already been addressed, these complex insulin-leptin interactions via melanocortins in the brain seem of importance.

3.3.3. Glucocorticoids

Glucocorticoids generally produce metabolic effects antagonistic to those of insulin, induce carbohydrate intolerance and prolonged glucocorticoid excess can induce a state of diabetes in rodents, cats and dogs (for review, see Lenzen and Bailey, 1984). Glucocorticoids act on neuronal glucose utilization by inhibiting glucose transport and uptake into the brain. Furthermore, glucose utilization is enhanced after adrenalectomy (Kadekaro et al., 1998). Studies in our laboratory have shown that adrenalectomy blocks the serotonin release induced by food intake in the hypothalamus of adult rats. Therefore, glucocorticoids may have an effect on brain insulin, via both of the local regulators, glucose and serotonin (Gerozissis et al., unpublished). The potential effects of glucocorticoids on brain insulin could be a result of both peripheral and central action. In this latter case corticotropin releasing hormone could be involved (Kalra et al., 1999; Morley and Levine, 1982).

4. Impaired brain insulin signaling in metabolic and endocrine disorders

Altered brain insulin content and central insulin resistance have been observed in several disorders. A decrease in the ratio of cerebrospinal fluid (CSF) or brain to blood insulin has been reported in dysfunctions in both humans and animals. Hyperinsulinemic, genetically obese Zucker (fa-fa) rats have low levels of brain insulin (Baskin et al., 1985; Gerozissis et al., 1993). The combination of aging and obesity further reduces extra cellular hypothalamic insulin levels in rats in vivo (Gerozissis et al., 2001). Finally in humans, cerebrospinal fluid insulin levels decrease in Alzheimer's disease, whereas insulinemia increases (Craft et al., 1998).

Disturbances in brain insulin levels and signal transduction due to genetic or epigenetic factors are implicated also in dysfunctions related to reproduction. It has been suggested that the reduced neuronal signaling by both insulin and leptin observed in studies with neuron-specific insulin receptor "knockout" mice that have an hypothalamic impairment of reproduction similar to food deprived animals is involved in the reproductive disturbances as an adaptive response to starvation (Ahima et al., 2000; Bruning et al., 2000; Schwartz, 2000).

Brain insulin participates in both energy and glucose homeostasis. Dysregulation of insulin secretion and transport in the central nervous system along with insulin deficiency or resistance in the brain has been reported in relation to aging, obesity, diabetes and serious mental disorders in post mortem studies in humans and in animal

models in vitro and in vivo (Frolich et al., 1998; Gerozissis et al., 2001; Hoyer, 2002a,b; Niswender and Schwartz, 2003; Zaia and Piantanelli, 2000).

Diabetes and its treatment with insulin are likely to affect cerebral insulin levels and signaling. It is difficult however to separate the direct effects of alterations in energy homeostasis on the brain from the consequences of the accompanying alterations in peripheral and central glucose homeostasis, which themselves can affect the brain (Biessels et al., 2002; Gispen and Biessels, 2000).

Based on genetic studies, Bruning et al. suggested that insulin resistance in classical insulin target tissues, and non classical target tissues such as the beta cell and the brain, may act synergistically in the induction of obesity, insulin glucose intolerance and dyslipidemia, leading to the complex metabolic syndrome associated with type 2 diabetes mellitus (Bruning et al., 1998, 2000; Kulkarni et al., 1999; Porte et al., 1998). Obici et al. (2002a) have shown that the infusion of either insulin or a small-molecule insulin mimetic in the third cerebral ventricle suppresses glucose production independent of circulating levels of insulin and of other glucoregulatory hormones. These authors pointed out the importance of the action of brain insulin on glucose production, and suggested that hypothalamic insulin resistance can contribute to hyperglycemia in type 2 diabetes mellitus. Thus an intimate coupling of neuronal mechanisms regulating body weight and glucose metabolism is revealed. Defective signaling within key neuronal pathways, in particular impaired insulin and leptin signaling that serves to control both energy and glucose homeostasis, can be included among potential mechanisms linking obesity to type 2 diabetes (Porte et al., 1998; Schwartz, 2001). Additional loss-of-function studies are in favor of the hypothesis that impairment of the common part of the pathway shared by leptin and brain insulin signaling is involved in severe pathologies. The phenotype of a knock-out model lacking the insulin receptor substrate (IRS-2) is similar to models with neuron-specific deletion of either the leptin receptor or insulin receptor, characterized by increased food intake, body fat content and impaired hypothalamic control of reproduction (Burks et al., 2000). In dogs, obesity induced by high-fat diets is associated with reduced transport of insulin in the brain (Kaiyala et al., 2000). High fat diets result in peripheral insulin resistance through an impairment of the ability of insulin to activate the insulin receptor substrate-phosphatidylinositol 3-kinase pathway (Dresner et al., 1999; Griffin et al., 1999; Kim et al., 2001). Niswender and Schwartz (2003) speculate that a similar mechanism leading to combined insulin and leptin resistance during high fat feeding operates in the hypothalamus.

5. Conclusion

The bi-directional communication, determining the regulation of brain insulin by nutrients and its feedback effects on feeding behavior, involves several processes. In the complex loop between the periphery and the brain in the control of energy homeostasis, it is noteworthy to point out the multilevel and multifactorial interactions of nutritional signaling and insulin. Metabolic and endocrine factors, along with neural signals, control pancreatic insulin production and secretion and have a direct impact on circulating insulin levels and on the transport of blood insulin in the brain. Natural peripheral signals generated by nutrients, after a single meal or following specific diets, regulate hypothalamic insulin availability and activity. Nutrition-related information activates a chain of neurochemical events, and triggers interactions within brain structures implicated in feeding behavior and cognition. In this cascade of events, brain insulin, an anorexigenic and leptogenic peptide, has a pivotal role. Brain insulin has a potentially important, specific biological role on cognitive processes related to feeding. Thus, insulin present in the central nervous system, probably originating from both peripheral and local sources, in concert with other neurotransmitters and peptides—either orexigenic or anorexigenic, that are also strongly responsive to nutrients—contributes to the short term and long term regulation of functions critical for survival.

Disruption of physiological signaling leads, along with peripheral insulin resistance, to central insulin resistance that is responsible for severe metabolic and endocrine pathologies. In particular, under—or over—feeding, and unbalanced diets, disrupt peripheral and central insulin signaling, alter the transport, the release, and the action of insulin in the brain, dysregulate feeding behavior and energy homeostasis, contributing to several disorders including obesity and diabetes. A complete understanding of the molecular mechanisms involved in the information generated by food intake, controlling insulin in the central nervous system, will clarify an important aspect in the pathophysiology of energy homeostasis. This knowledge may translate into a development, along with new medication, of new preventive and therapeutic dietary strategies.

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