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REVIEW

Avenues of Communication between the Brain and Tissues/Organs Involved in Energy Homeostasis

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Abstract. Obesity is a rapidly increasing public health concern worldwide as a major risk factor for numerous disorders, including diabetes, hypertension and heart disease. Despite remarkable advances in obesity research over the past 10 years, the molecular mechanisms underlying obesity are still not completely understood. To maintain systemic energy homeostasis, it is important that organs/tissues communicate metabolic information among each other. Obesity-related disorders can be thought of as resulting from dysregulation of this inter-tissue communication. This system has both afferent sensing components and efferent effecter limbs. The afferent signals consist of not only humoral factors, such as nutrients (glucose, fatty acids and amino acids) and adipocytokines (leptin, adiponectin and so on), but also autonomic afferent nerve systems. Both converge on brain centers, most importantly within the hypothalamus, where the signals are integrated, and the direction and magnitude of efferent responses are determined. The efferent elements of this physiological system include those regulating energy inputs and outputs, i.e. food intake and metabolic rates. In this review, we will summarize recent advances in research on metabolic information avenues to the brain, which are important for energy homeostasis.

Key words:

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THE worldwide prevalence of obesity, which is a major risk factor for numerous disorders, including diabetes, hypertension and heart disease, is increasing at an alarming rate, with major adverse consequences for human health [1]. Body weight is thought to be determined by the balance between energy intake and expenditure. However, alterations in daily food intake and physical activity do not rapidly affect body weight. Why is this? The most plausible explanation is the existence of systems which maintain energy homeostasis throughout the body. Energy homeostasis is maintained by multiple mechanisms that involve gathering information on the body's nutritional status and making appropriate behavioral and metabolic responses to changes in fuel availability. For such inter-organ/tissue communication, humoral factors, including insulin and adipocytokines, are known to be very important. In addition, we and other research groups have recently reported the autonomic nervous system to play an important role in conveying metabolic information. Using these systems, the brain obtains information on peripheral metabolic status and processes it to send signals which regulate metabolism in the periphery. In particular, the hypothalamus is a primary site of convergence and integration for redundant energy status signaling, which includes central and peripheral neural inputs as well as hormonal and nutritional factors. These pathways of inter-tissue communication are summarized in Fig. 1. Recent advances in this field are reviewed herein.

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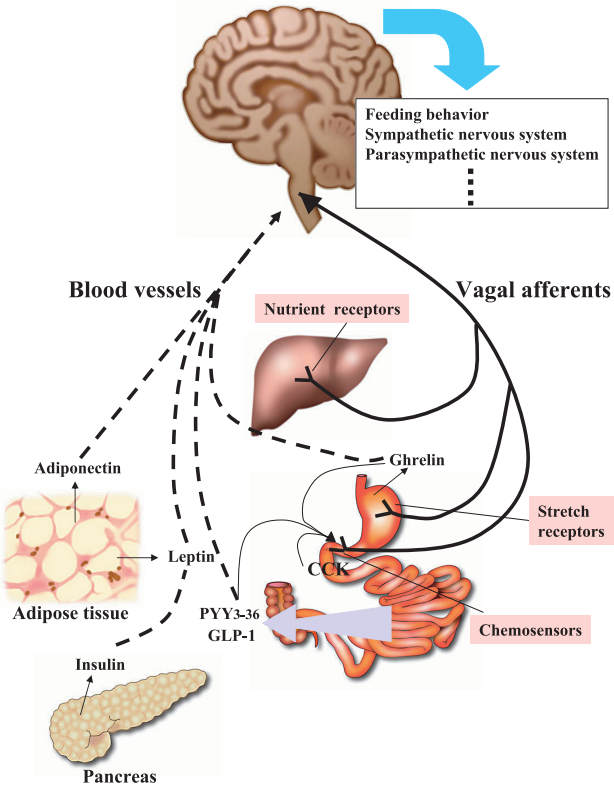

Fig. 1. Schematic presentation of inter-tissue communication (quoted from [31] with slight modification).

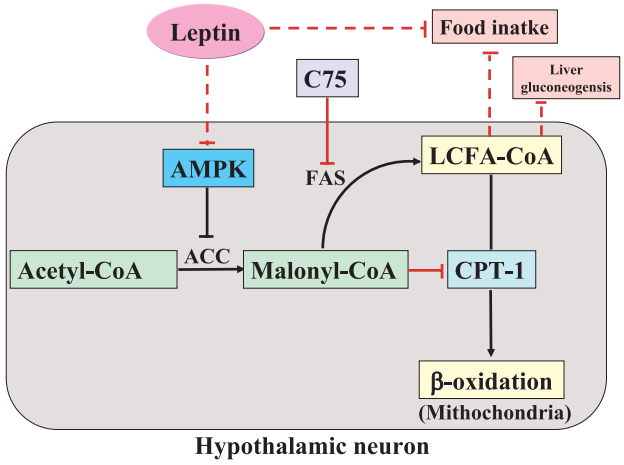

Fig. 2. Fatty acid metabolism, in the hypothalamic cells, which plays an important role in maintaining energy homeostasis (quoted from [65] with slight modification).

1. Brain inputs — humoral factors —

1) Nutrients

It is reasonable that essential nutrients, such as carbohydrates, lipids and proteins, mediate nutritional signals to the central nervous system by themselves. First, we will focus on the mechanism whereby these nutrients convey peripheral fuel status to the central nervous system.

a) Free fatty acids

The access of circulating free fatty acids to cerebrospinal fluids is generally proportional to the plasma fatty acid concentration [2, 3], indicating that the brain may acquire information regarding the peripheral metabolic state via cerebrospinal fatty acid levels. Fatty acid-sensitive neurons have been identified in the hypothalamus. For instance, an *in vitro* patch clamp study [4] showed that, among arcuate neurons, 13% of cells had increased electrical activity, while 6% had decreased activity when oleic acid was applied. Intracerebroventricular administration of oleic acid reportedly inhibits hepatic glucose production and food intake [5]. In addition, hypothalamic inhibition of carnitine:palmitoyl-CoA transferase-1 (CPT-1), an important mitochondrial enzyme that transfers long-chain fatty acyl-coenzyme A (LCFA-CoA) into mitochondria, decreases food intake and suppresses endogenous glucose production in the liver [6]. Furthermore, it was also reported that efferent vagal nerve signals from the brain to the liver are involved in hepatic gluconeogenesis in these experimental settings [7]. Hu *et al.* reported that central administration of C75, a potent inhibitor of fatty acid synthase (FAS), decreased food intake [8]. Since FAS inhibition increases malonyl-CoA and thus suppresses CPT1 activity, LCFA-CoA in hypothalamic neurons appears to be increased. Taken together, these results indicate that the cytosoplasmic LCFA-CoA concentration in hypothalamic neurons plays an important role in energy homeostasis (Fig. 2).

Leptin, an anorexigenic factor, reportedly decreases AMP-activated protein kinase (AMPK) activity in hypothalamic neurons [9], while ghrelin, an orexigenic factor, increases it [10]. AMPK is the downstream component of a kinase cascade that acts as a sensor of cellular energy charge, being activated by rising AMP coupled with falling ATP. AMPK phosphorylates and inhibits acetyl-CoA carboxylase (ACC), resulting in decreased malonyl-CoA levels. As malonyl-CoA inhibits CPT-1, AMPK activation decreases cytoplasmic LCFA-CoA levels. Thus, cytoplasmic LCFA-CoA in

hypothalamic neurons may be involved in appetite regulation by leptin and ghrelin.

b) Amino acids

Amino acids also seem to communicate energy status information from the periphery. Transport of amino acids across the blood-brain barrier has been demonstrated [11]. The levels of amino acids in cerebrospinal fluids are reflected by peripheral blood levels. Central administration of leucine increases hypothalamic mTOR (mammalian target of rapamysin) activity, and thereby decreases food intake and body weight [12]. mTOR is a highly conserved serine/threonine kinase, present in organisms from yeast to mammals, the activity of which is sensitive to levels of branched-chain amino acids, especially L-leucine [13, 14]. Thus, mTOR is known to be one of the energy sensors for amino acids conserved in throughout evolution in organisms and, in mammals, hypothalamic mTOR signaling appears to play an important role in regulating systemic energy metabolism. Leptin increases hypothalamic mTOR activity, and the inhibition of mTOR signaling blunts leptin's anorectic effect [12], although further studies are needed to clarify the role of mTOR in energy homeostasis.

c) Glucose

It is well known that increases in serum glucose affect glucose-sensing neurons in the hypothalamus, resulting in suppression of food intake and liver gluconeogenesis (glucostatic theory). Two populations of glucose-sensing neurons have been defined: those excited (in which electrical activity is increased; GE neurons) and those inhibited (decreased activity; GI neurons) as local glucose levels rise. Such neurons have mainly been characterized in the ventromedial hypothalamic nucleus (VMH) and the arcuate nucleus (ARC) [15]. Glucose sensing mechanisms in pancreatic β cells, which secrete insulin in response to rising blood glucose, have been well analyzed. The glucose sensor in pancreatic β cells involves mainly GLUT2, glucokinase and specific KATP channels. Analogously, glucose sensing mechanisms in glucose-responsive neurons have been proposed. Two recent studies found GLUT2 expression in the rat brain [16, 17]. In addition, glucokinase is expressed in the rat hypothalamus [18]. Expressions of both GLUT2 and glucokinase have also been demonstrated in the human hypothalamus [19]. Using calcium imaging and single cell RT-PCR in freshly dissociated neurons from the VMH, Kang *et al.* confirmed the presence of glucokinase and KATP channels in some glucosensitive neurons [20]. KATP channel activity represents a key step in the electrical activity of GE neurons in the ARC and VMH in response to glucose concentration changes [21].

2) Insulin

Insulin is a product of pancreatic β cells and is the master metabolic switch between the fed and fasted states, mediating metabolic fuel disposition and use. Therefore, it has been proposed that insulin itself might be the fuel status signal to the brain, but the precise mechanisms have long been unclear. The activation of insulin signaling in the ARC, in the absence of elevated systemic insulin, is sufficient to decrease food intake and blood glucose levels via substantial inhibition of endogenous glucose production (EGP) [22, 23]. A recent study revealed the central effects of insulin on the suppression of EGP to be mediated by the insulin receptor-insulin receptor substrate 2 (IRS2)-phosphatidylinositol 3OH kinase (PI3K) pathway, resulting in KATP channel activation in the ARC [24]. Inoue *et al.* reported that centrally administered insulin induces IL-6 production in the liver, followed by STAT3 activation, resulting in suppression of hepatic EGP [25]. The activation of insulin receptors in the brain, in particular the ARC of the hypothalamus, plays an important role in the regulation of glucose homeostasis and food intake.

3) Adipocytokines

a) Leptin

Leptin is produced mainly in adipocytes in proportion to fat stores; adequate leptin levels communicate the repletion of body energy stores to the central nervous system in order to suppress food intake and permit energy expenditure [26]. Leptin binds to leptin receptors (Ob-Rb) in the hypothalamus, resulting in activation of the JAK/STAT pathway [27, 28] and the IRS2/PI3K pathway [29]. In addition, Minokoshi *et al.* recently reported that leptin suppressed hypothalamic AMPK activity, leading to food intake suppression [9]. As stated above, leptin also activates mTOR signaling in the hypothalamus. Thus, leptin signaling involves at least four pathways, JAK/STAT, IRS2/PI3K, AMPK and mTOR. Complicated interactions

may exist among these four pathways.

In most individuals with ordinary obesity, circulating leptin levels are elevated, but the body does not adequately respond to this increased leptin with reduced food intake. This under-responsiveness to leptin in most forms of obesity has given rise to the idea that obesity is associated with, or even caused by, a state of relative leptin resistance similar to insulin resistance. The mechanisms underlying leptin resistance remain a matter of debate. From the therapeutic point of view, the mechanism underlying leptin resistance is an important issue which awaits clarification.

b) Adiponectin

There is a recent report [30] suggesting adiponectin to have central effects on energy metabolism. Intravenous administration of adiponectin increased the level in cerebrospinal fluid. In addition, central adiponectin administration increased systemic energy expenditure and reduced body weight, followed by decreased blood glucose and serum lipid levels. Detailed studies are needed to clarify the roles of adiponectin in communicating the peripheral metabolic state to the central nervous system.

2. Brain inputs — afferent nerve signals —

1) Innervation

a) Intra-abdominal innervation without white adipose tissues

First, the innervation of intra-abdominal tissues requires explanation. For example, the gut is innervated by both splanchnic (sympathetic) and vagal (parasympathetic) nerves. Detailed fiber count studies have revealed that the abdominal vagal nerve is comprised of approximately 75% afferent fibers, the splanchnic nerve 50%. Afferent signals from the gut to the brain are carried in vagal and splanchnic nerve pathways. Vagal afferents respond to specific luminal chemical stimuli, physiological levels of distention or nutrients, whereas splanchnic afferents convey information regarding noxious stimuli [31]. On the other hand, intrapelvic organs, urogenital organs and so on, are innervated by a pelvic nervous plexus, which consists of both sympathetic and parasympathetic nerves.

b) Innervation of intra-abdominal adipose tissues

White adipose tissues are also innervated by both efferent and afferent nerve fibers. As for the efferent sympathetic fibers, numerous reports have described functions, including lipolysis or β oxidation [32–34]. On the other hand, a recent study demonstrated white adipose tissues to be innervated by efferent parasympathetic nerve fibers [35], although their physiological functions remain to be elucidated. There are only a few articles focusing on the functions of afferent nerve fibers from white adipose tissues. Niijima [36] and Tanida *et al.* [37] used electrical firing measurements to show that leptin induces functional activation of afferent nerve fibers from epididymal white adipose tissues. In a more recent study, afferent nerve innervation in epidydimal white adipose tissues was demonstrated anatomically [38]. In addition, we recently reported the functional significance of afferent nerve signals from intra-abdominal adipose tissues which modulate hypothalamic leptin sensitivity, as described in detail below [39].

2) Signals transmitted by afferent autonomic nerve fibers

a) Signals from the gut

It has been reported that afferent autonomic nerve fibers convey signals carrying information about energy homeostasis [40–43]. Physiological distention of the gut as well as cholecystokinin (CCK) [44], PYY3-36 [45] and glucagon-like peptide-1 (GLP-1) [46] stimulate afferent vagal nerve fibers, resulting in food intake suppression. In contrast, ghrelin enhances food intake via the afferent vagus [47]. CCK is produced by mucosal enteroendocrine cells of the duodenum and jejunum and is secreted in response to the presence of food within the gut lumen. Sulfated CCK, which preferentially binds to CCK1 receptors on vagal afferent neurons, sends satiety signals to the brain; hence, vagotomy inhibits the anorectic effect of CCK [44]. GLP-1 and PYY3-36 secretions from enteroendocrine L cells are triggered by luminal nutrients. The mechanisms by which sugars activate L cells involve the closure of ATP sensitive potassium channels, resulting in depolarization of the cells, via a mechanism analogous to insulin secretion from β cells [48, 49]. Koda *et al.* [45] showed that peripheral administration of PYY3-36 stimulates vagal afferent nerves via a Y2 receptor which is expressed at nerve terminals. Abdominal

vagotomy abolished the anorectic effect of PYY3-36. Similarly, the anorectic effects of peripheral GLP-1 administration were also abolished by vagotomy [46]. Thus, peripheral PYY3-36 and GLP-1 transmit satiety signals to the brain via the vagal afferent pathway. On the other hand, ghrelin is a peptide recently found to be produced in the stomach, which acts on a previously identified orphan receptor (growth hormone secretagogue receptor), activation of which in the hypothalamus causes growth hormone (GH) release from the pituitary gland [50]. Date *et al.* [47] reported blockade of the gastric vagal afferent to abolish ghrelin-induced feeding, GH secretion and the activations of NPY- and GHRH-producing neurons. The ghrelin receptor is also expressed in vagal afferent terminals, and ghrelin suppresses vagal afferent firing. Taken together, these findings indicate involvement of gastric vagal afferent in conveying signals regarding satiety as well as starvation from the gut to the brain.

b) Signals from the liver — Liver functions as an energy balance sensor —

(1) Hepatoportal glucose sensor

Nutrients absorbed from the gut enter the portal vein, and thereby reach the liver directly. Therefore, given its anatomical location, it seems reasonable that the liver functions as a glucose sensor. It has been demonstrated that signals regarding serum glucose levels from the so-called hepatoportal glucose sensor to the brain are carried along afferent vagal nerve pathways [40]. The hepatoportal glucose sensor, which is an as yet incompletely defined structure, is activated by a glucose gradient established between the portal vein and the periphery. Raising portal vein glucose levels leads to a decrease in vagal afferent discharges reaching the nuclei of solitary tract neurons, leading to activation of sympathetic efferents to the adrenal glands, liver, splanchnic bed and pancreas. Because all of these reflex efferent outputs are blocked by hepatic vagotomy, it appears that signals triggered by high levels of portal glucose are transmitted through vagal afferents [51, 52]. Burcelin *et al.* showed that the hepatoportal sensor requires the presence of GLUT2 but that hepatocytes are not involved in this sensing process [53], in agreement with previous studies showing this sensor to be located upstream from the hepatic hylus [54]. They also reported that GLP-1 signaling modulates hepatoportal glucose sensing [55], an observation compatible with the role of GLP-1 in regulating the firing activity of hepatic vagal afferents [56]. A similar role for GLP-1 in canine hepatoportal sensor function has also been reported [57].

On the other hand, sympathetic afferents mediate hypoglycemic signals. Reportedly, a counterregulatory response to moderate systemic hypoglycemia, *i.e.* sympathetic efferent activation, is attenuated by clamping the liver at euglycemic levels and is disrupted by interruption of sympathetic (but not vagal) afferents from the hepatic portal circulation [58, 59]. Collectively, these observations indicate that the afferent autonomic nervous system, including both vagal and sympathetic nerves, from the hepatoportal structure, plays important roles in conveying information regarding peripheral glucose levels to the brain.

(2) PPARγ (peroxisome proliferator-activated receptor γ)

Recently, in a number of studies, tissue-specific knockout mice have been found to exhibit unexpected phenotypes, suggesting the presence of as yet unknown cross-talk between organs/tissues. Therefore, unraveling the complexities of this inter-organ communication would be very important for elucidating the mechanisms underlying not only energy and glucose homeostasis but also the development of obesity-related diseases. However, using genetically engineered mice, it is somewhat difficult to demonstrate the underlying mechanisms, since a substantial number of compensatory mechanisms can modify metabolic phenotypes. Alternatively, using adenoviral gene transfer into an organ/tissue of an adult mouse model, we observed an example of such inter-tissue communication; dissipating excess energy in the liver affects insulin sensitivity in muscle and adipose tissues [60]. Therefore, we suspected that, if metabolism could be altered in just one organ, it would be easier to analyze acute metabolic effects in other remote tissues and, assuming intervention to be possible, it would give us an understanding of the mechanisms.

Mice with tissue-specific knockout of peroxisome proliferator-activated receptor γ (PPARγ) may provide an example of such inter-tissue communication. Notably, liver-specific disruption of PPARγ in ob/ob mice prevented hepatic steatosis, but increased peripheral adiposity and decreased insulin sensitivity in muscle and adipose tissue [61]. Hepatic expression of PPARγ, especially PPARγ2, is functionally enhanced in a number of obesity models [62, 63]. Therefore, to unravel the mechanism underlying this inter-organ/tissue com-

munication between the liver and peripheral tissues including muscle and fat, we overexpressed PPARγ2 in the livers of mice using adenoviral gene transfer.

Hepatic PPARγ2 expression acutely induced severe hepatic steatosis, while peripheral adiposity was markedly reduced due to enhanced lipolysis. Systemic metabolic rates were increased and, therefore, peripheral insulin sensitivity and glucose tolerance showed marked improvement. Thus, hepatic expression of PPARγ2 exerts not only local effects in the liver, but also remote effects in adipose tissues and the whole body. These remote effects were explained by increased sympathetic outflow into muscle and adipose tissues. Therefore, to examine the possibility that afferent nerves originating in the liver are involved in the observed effects on energy expenditure and peripheral adiposity through efferent sympathetic nerve activation, we interrupted liver-brain communication by performing selective hepatic branch vagotomy. This manipulation significantly reversed the both reduction in peripheral adiposity and the enhancement of energy expenditure. In addition, pharmacological deafferentation of the vagus blocked the hepatic PPARγ2 expression-induced decrease in white adipose tissue weights. These findings indicate that hepatic PPARγ2 expression and/or hepatic lipid accumulation stimulate afferent vagal nerve fibers, communicating metabolic information to the brain, leading to anti-obesity and anti-insulin-resistant effects in muscle and adipose tissue [64].

Fat storage in the liver changes dynamically according to the systemic energy balance and is associated with several features of the metabolic syndrome. Since hepatic PPARγ expression is physiologically associated with obesity, the liver may convey information regarding excess energy to the central nervous system via the afferent vagus. This neuronal system is likely to underlie chronic “adaptive thermogenesis”, resulting in protection against metabolic perturbation induced by excessive energy storage (Fig. 3). When the brain obtains information regarding excess energy storage mediated by leptin from adipose tissues and via the afferent vagus from the liver, the sympathetic nervous system is activated to enhance energy expenditure and lipolysis, thereby maintaining energy homeostasis.

c) Signals from adipose tissues

There are only a few reports focusing on afferent nerve signals from adipose tissue. According to these reports, activation of afferent nerves from intra-abdominal (epididymal) adipose tissue resulted in reflex signals being sent to white adipose tissues via efferent sympathetic nerve activation [36, 37]. However, the functional significance of these afferent signals was unclear. We demonstrated hypothalamic leptin sensitivity to be modulated through afferent nerves from epididymal fat [39].

Fat accumulation in intra-abdominal fat tissue plays a major role in development of the metabolic syndrome associated with insulin and leptin resistance. Leptin resistance is induced by excessive adiposity and, in turn, is an important mechanism underlying maintenance of the obese state. To determine whether a local reduction in the adiposity of intra-abdominal adipose tissue of diabetic mice with diet-induced obesity would reverse obesity-related metabolic disorders, in particular insensitivity to leptin and insulin, we attempted to express uncoupling protein-1 (UCP1), which functions to dissipate energy as heat. UCP1 was expressed in epididymal adipose tissue only at very low levels. Nevertheless, food intake declined in association with decreased serum leptin levels as well as downregulation of the orexigenic neuropeptide Y and upregulation of the anorexigenic precursour neuropeptide proopiomelanocortin, in the hypothalamus. The anorectic response to exogenous leptin was enhanced by adipose UCP1 expression. In addition, the hypophagia could not be duplicated in db/db mice with mutant leptin receptors. Collectively, these findings clearly show that very limited UCP1 expression in the intra-abdominal fat pad dramatically improves hypothalamic leptin resistance. Local dissection of nerves from the epididymal fat pad and pharmacological deafferentation blunted the anorectic effects of UCP1 expression in adipose tissue. Taken together, the results suggest afferent nerve signals originating in epididymal fat pads to modulate hypothalamic sensitivity to leptin (Fig. 4).

Adipose tissues were long regarded as a simply being passive fuel storage sites. However, the discovery of various adipocytokines, with leptin being the most important example, has raised adipose tissue to the status of a versatile endocrine gland. Recent studies including ours provide further evidence of the key role of adipose tissue as a base from which neuronal signals regulating feeding and fuel metabolism are sent. Furthermore, identification of the neurotransmitted

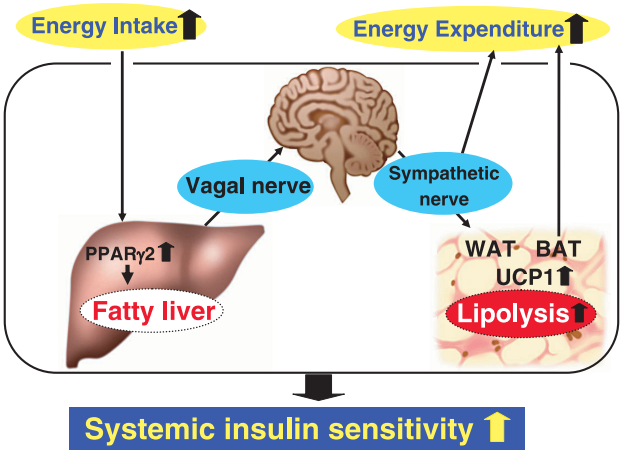

Fig. 3. Scheme of the neuronal pathway originating in the liver. Hepatic PPARγ expression associated with surplus energy results in increased energy expenditure, decreased peripheral adiposity and improved insulin sensitivity via the neuronal system consisting of afferent vagal and efferent sympathetic nerves.

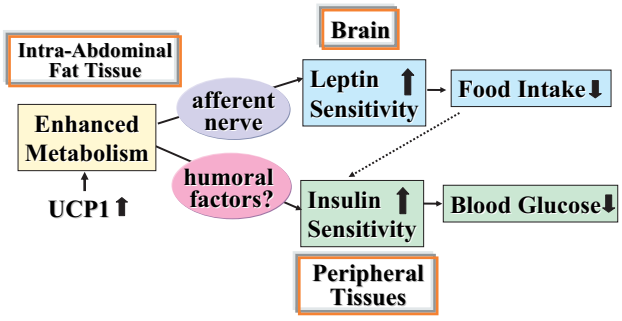

Fig. 4. The proposed mechanism whereby UCP1 expression in epididymal fat tissue decreases food intake and improves glucose tolerance (quoted from [39] with slight modification).

substance involved might lead to development of novel therapeutic strategies aimed at tackling the metabolic syndrome.

Conclusion

Metabolism does not go on independently in different organs/tissues, but rather in a coordinated and regulated manner throughout the body. Metabolic regulation coordinated among organs/tissues, which requires communication among these organs/tissues, appears to be essential for maintaining the homeostasis of systemic metabolism, in particular glucose and energy metabolism. In addition, disturbance of this coordinated control system may be implicated in the development of metabolic disorders, such as obesity, type 2 diabetes, hyperlipidemia and the metabolic syndrome.

Recent advances in this field revealed the complex and important roles of the central nervous system. The brain obtains a variety of metabolic information from peripheral organs/tissues through humoral and neuronal avenues. These inputs are likely to be integrated and processed in the brain, leading to the transmission of regulatory signals, which induce appropriate metabolic responses, throughout the body. Further elucidation of these regulatory systems, in much greater detail, may allow us to unravel the mechanisms underlying metabolic homeostasis and thereby to understand the metabolic disorders. Moreover, targeting of these neuronal pathways is a potential therapeutic strategy for the metabolic syndrome.

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