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Mini Review

Effect of glucose and fructose on food intake via malonyl-CoA signaling in the brain

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ABSTRACT

In the brain malonyl-CoA serves the important function of monitoring and modulating energy balance. Because of its central role in the metabolism of higher animals, glucose acts as the principal indicator of global energy status. Specialized neuronal nuclei within the hypothalamus sense blood glucose and signal higher brain centers to adjust feeding behavior and energy expenditure accordingly. As the level of glucose entering the brain rises, food intake is suppressed. Energy status information triggered by glucose is transmitted via hypothalamic signaling intermediaries, i.e. AMPK and malonyl-CoA, to the orexigenic/anorexigenic neuropeptide system that determines hunger and energy expenditure. The central metabolism of glucose by the glycolytic pathway generates ATP which produces a compensatory decrease in AMP level and AMPK activity. Since acetyl-CoA carboxylase (ACC) is a substrate of AMPK, lowering AMP increases the catalytic activity of ACC and thereby, the level of its reaction product, malonyl-CoA. Malonyl-CoA signals the anorexigenic–orexigenic neuropeptide system to suppress food intake. Unlike glucose, however, centrally metabolized fructose increases food intake. This paradox results because fructose bypasses the rate-limiting step of glycolysis and uses a rapid ATP-requiring reaction that abruptly depletes ATP and provokes a compensatory rise in AMP. Thus, fructose has the opposite effect of glucose on the AMPK/malonyl-CoA signaling system and thereby, feeding behavior. The fact that fructose metabolism by the brain increases food intake and obesity risk raises health concerns in view of the large and increasing per capita consumption of high fructose sweeteners, especially by youth.

Introduction

Energy balance is determined by caloric intake versus caloric expenditure. Complex control systems promote energy storage (primarily as adipose tissue fat) during periods of food surplus and mobilization of energy stores when food is scarce. These regulatory systems operate both locally within cells and between different body tissues and are mediated by circulating hormones and direct neural connection within and from the central nervous system (CNS) to peripheral tissues.

Glucose is metabolized by all mammalian cells especially erythrocytes and neurons of the CNS, which have an absolute requirement for glucose [1]. Because of its central role in metabolism and the need for glucose in all physiological states, blood glucose has evolved as the primary indicator of global energy status. Circulating glucose levels are rigorously maintained within narrow limits by insulin and glucagon – pancreatic hormones that regulate glucose uptake, storage and formation [2]. The inverse effects of insulin and glucagon on glucose metabolism ensure that glycogenesis and fat synthesis occur during periods of surplus, whereas hepatic glycogenolysis and gluconeogenesis occurs during periods of short supply. In this review we provide evidence that the CNS, notably the hypothalamus, monitors blood glucose and regulates energy intake and expenditure [3]. Unlike glucose, which suppresses food intake [5,6], fructose increases food intake when metabolized by the CNS [4,6]. Although glucose and fructose utilize the same signaling pathway to control food intake they act in an inverse manner and have reciprocal effects on the level of hypothalamic malonyl-CoA [5] (Fig. 1A and B). The malonyl-CoA signaling pathway that communicates this information to the orexigenic/anorexigenic neuropeptide system to regulate feeding behavior is detailed in the discussion that follows.

Hypothalamic malonyl-CoA and the control of food intake

Numerous lines of evidence have implicated malonyl-CoA as a key intermediate in the hypothalamic signal cascade that regulates energy balance in higher animals. The first evidence for the participation of malonyl-CoA was the finding that inhibitors of fatty acid synthase (FAS), an enzyme of the fatty acid synthetic pathway

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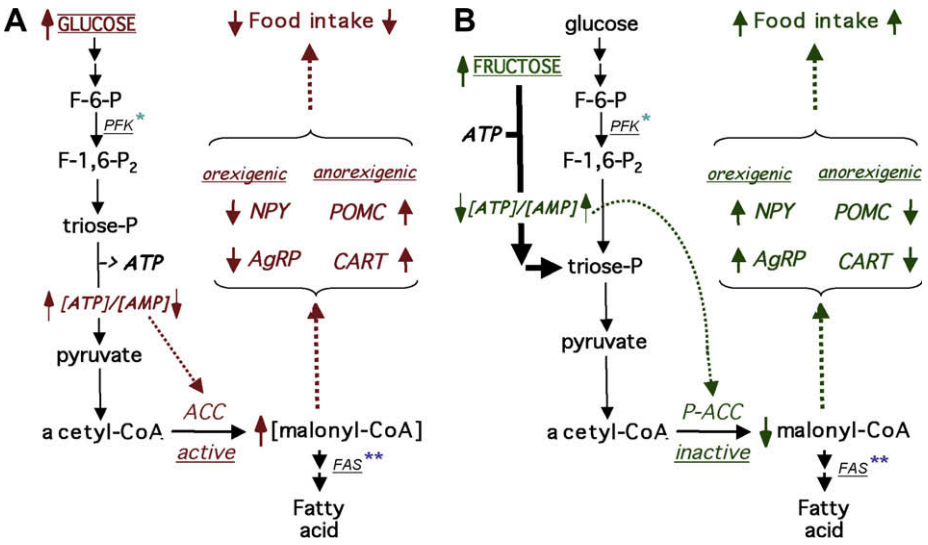


Fig. 1. Hypothalamic signaling pathways triggered by metabolism of (A) glucose and (B) fructose leading to inverse effects on food intake. *PFK** refers to phosphofructokinase and *FAS*** to fatty acid synthase.

(Fig. 1), suppress food intake [7]. Thus, FAS inhibitors, such as cerulenin,[1] a fungal antibiotic that binds covalently in the catalytic center of FAS, and its analogue, C75,[2] were found to decrease food intake. Inhibition of FAS would be expected to cause accumulation of its substrate, malonyl-CoA. This prediction was verified with the finding that administration of C75 by i.p. or i.c.v. injection rapidly (⩽5 min) increased the level of malonyl-CoA in the hypothalamus by 3- to 5-fold [8]. Importantly, this effect was reversed by inhibitors of ACC, which catalyzes the formation of malonyl-CoA from acetyl-CoA [8]. These findings identified hypothalamic malonyl-CoA as the probable cause of the anorexic effect of the FAS inhibitors. Later it was shown that the anorectic effect of FAS inhibitors is due to their ability to rapidly suppress expression of the key orexigenic neuropeptides, NPY and AgRP, and to increase the expression of the anorexigenic neuropeptides, α-MSH/POMC and CART in the hypothalamus [6]. These neuropeptides are secreted by neurons found in the medial and ventral regions of the hypothalamus, most notably the arcuate nucleus (Arc) [9]. Second-order neurons from the Arc project to higher brain centers where this information is processed and a behavioral response is formulated [3].

From the physiological perspective, the malonyl-CoA level in the hypothalamus correlates closely with nutritional state [6,8]. It is not surprising that this process evolved as a means of regulating energy homeostasis in the CNS, since fatty acid synthesis in other tissues, notably in the liver and adipose tissue, is a process that occurs primarily during energy surplus. Malonyl-CoA, the product of ACC (Fig. 1), is known to regulate energy metabolism in the liver through the inhibition of mitochondrial fatty acid oxidation [10]. While malonyl-CoA serves as the basic chain-elongating unit of fatty acid synthesis, it serves a signaling role as an allosteric inhibitor of CPT1, an outer mitochondrial membrane enzyme, by blocking entry of fatty acids into the mitochondrion for fatty acid oxidation [10].

When energy expenditure exceeds intake, as in the food-deprived state, the malonyl-CoA level in the hypothalamus is low, i.e. 0.1–0.2 μM [6,8]. When food intake is restored, the level rises 4- to 5-fold reaching 0.8–1.0 μM in the re-fed state [6,8]. Similar changes occur when a food-deprived animal is given glucose by i.p. or i.c.v. injection [6]. This rise is rapid, the response to re-feeding occurring in <1 h. These changes are followed immediately by changes in the expression of the orexigenic and anorexigenic neuropeptides that regulate feeding behavior [6] (Fig. 1A). In the food-deprived state NPY and AgRP are expressed at high levels, whereas POMC and CART are expressed at low levels [6]. Upon re-feeding this pattern immediately inverts. The changes in hypothalamic malonyl-CoA concentration also correlate closely with the hypothalamic expression of c-Fos, a documented indicator of neuronal activity [11]. Thus, FAS inhibitors prevent the normal activation of hypothalamic neurons that express orexigenic and anorexigenic neuropeptides. Following a 24-h fast neuronal activity, as indicated by increased c-Fos expression, is high in the Arc, VMN, and PVN, regions in the hypothalamus that control feeding behavior – increased expression of NPY and AgRP and decreased expression of POMC/αMSH and CART reflecting hunger. Upon resuming feeding c-Fos expression is rapidly suppressed leading to the inverse effects on the expression of NPY/AgRP and POMC/αMSH/CART that cause satiety [11].

Manipulation of hypothalamic malonyl-CoA level by other means, such as by gene knockout or virally directed gene expression has provided additional evidence that malonyl-CoA modulates feeding behavior. Genetic disruption of FAS gene expression in the hypothalamus increases malonyl-CoA and decreases body weight and adiposity – effects similar to those caused by FAS inhibitors. Crossing floxed FAS mice [12] with RIP-Cre mice which drives Cre expression, causes excision of the FAS gene both in the pancreas and the hypothalamus. While these mice do not manifest changes in pancreatic β-cell function, they exhibit a hypothalamic FAS knockout phenotype, i.e. decreased food intake, body weight gain and adiposity [12]. Consistent with disruption of expression of the hypothalamic FAS gene, malonyl-CoA concentration increases along with changes in expression of the orexigenic and anorexigenic neuropeptides that lead to suppression of food intake. These findings provide genetic validation of the malonyl-CoA hypothesis.

The perturbations described above give rise to an increased hypothalamic malonyl-CoA level that suppresses food intake. To assess the inverse effect, forced expression of cytosolic malonyl-CoA decarboxylase (cMCD) in the ventral hypothalamus was employed using viral expression vectors. This was accomplished by the introduction of viral vectors encoding cytosolic MCD into the ventral hypothalamus by bilateral stereotactic injection [13,14]. This region of the hypothalamus includes the Arc, which is a major

[1] 2,3-epoxy-4-oxo-7E, 10E-dodecadienamide.
[2] 3-carboxy-4-octyl-2-methylenebutyrolactone.

site for the regulation of feeding behavior. The effectiveness of an adenoviral-cMCD (Ad-cMCD) vector was first tested with several hypothalamic neuronal cell lines in which the concentration of malonyl-CoA was reduced by ~80% [13]. Expression of the viral cMCD vectors in the ventral hypothalamus induced increases in both food intake and body weight [13,14], and in longer-term experiments a marked increase in adiposity [14]. Moreover, introduction of the Ad-cMCD vector into the ventral hypothalamus dramatically increased food intake in mice given the FAS inhibitor, C75, by central administration [13]. Thus, i.c.v. injection of C75 increased hypothalamic malonyl-CoA and totally suppressed food intake, whereas Ad-cMCD completely prevented the C75-induced blockade of food intake. The fact that the anorexic effect of the FAS inhibitor was completely reversed, provides strong support for the view that hypothalamic malonyl-CoA acts as an indicator of energy status and participates in the regulation of feeding behavior. In addition, these results indicate that malonyl-CoA, rather than fatty acids, is the effector that regulates energy homeostasis. Inhibition of FAS leads to an increase in malonyl-CoA and a decrease in *de novo* synthesis of fatty acids, which leads to a lean phenotype. Not only does expression of MCD in the ventral hypothalamus lower both malonyl-CoA and *de novo* fatty acid synthesis, but it also leads to obesity. These findings rule out a primary role for fatty acids or fatty acyl-CoAs *per se* as endpoint effectors in the AMPK/malonyl-CoA signal system and validate malonyl-CoA as the key effector in this system.

Glucose sensing via the AMPK/malonyl-CoA signaling pathway produces satiety

It is well known that food deprivation leads to a decreased blood glucose level, a state in which the hypothalamic malonyl-CoA level is at a minimum [6,8]. Upon re-feeding or i.c.v. injection of glucose, hypothalamic malonyl-CoA increases dramatically [6]. Given that glucose is the primary physiological fuel for the brain [1] and is a precursor of cytoplasmic malonyl-CoA (see Fig. 1A), which suppresses food intake, the question is raised of whether there is a causal relationship between glucose supplied to the brain and hypothalamic malonyl-CoA. It was found that immediately following glucose infusion into the CNS of fasted mice malonyl-CoA level rises [6], orexigenic neuropeptide (NPY and AgRP) expression decreases and anorexigenic neuropeptide (αMSH and CART) expression increases in the hypothalamus [6] (Fig. 1A). Within 30 min after infusion, when the glucose-treated mice are given access to food, food intake is drastically reduced [6].

Glucose metabolism in the hypothalamus is known to rapidly activate neuronal firing [11], which is coupled to the inactivation of AMPK (Fig. 1A). Decreased AMPK activity allows the dephosphorylation and activation of ACC, increasing in the level of malonyl-CoA – its reaction product. It was established that AMPK and acetyl-CoA carboxylase (ACC) [6] respond to changes in blood glucose and function in transmitting the malonyl-CoA signal. Thus, increased glucose flux into the hypothalamus/CNS causes dephosphorylation and thereby, inactivation of AMPK, which leads to activation of ACC and an increase in the level of malonyl-CoA. As discussed above an increase in hypothalamic malonyl-CoA suppresses food intake and increases energy expenditure. The sequence of events in this signaling system (discussed in more detail below) (see (1) and Fig. 1A).

ATP is the primary energy currency used by cells to drive energy-requiring processes. At the cellular level AMPK serves as a sensor of 'energy charge', i.e. the ATP level of the cell. AMPK responds to fluctuations in the cellular levels of ATP through changes in the level AMP, an activator of AMPK whose concentration is inversely related to that of ATP [15]. The relationship of the levels of the adenine nucleotides is determined by the reaction catalyzed by adenylate kinase (AK), ubiquitous enzyme, illustrated (see (2) below):

$$\mathrm{ATP} + \mathrm{AMP} \underset{K_{eq}\simeq 1.0}{\overset{\mathrm{AK}}{\leftrightarrows}} \mathrm{ADP} + \mathrm{ADP} \tag{2}$$

Since total adenine nucleotide concentration is constant and the K_{eq} for the reaction is ~1.0, it follows that as the ATP level falls, the level of 5′-AMP rises. Thus, as the 'energy charge' of a cell decreases due to ATP depletion, AMPK, is activated. Many key regulatory enzymes of energy metabolism (e.g. ACC, glycogen synthase and hormones-sensitive lipase) are substrate targets of AMPK that undergo phosphorylation provoking either inhibition or activation depending on whether the enzyme is involved in energy storage or mobilization [15]. In general, pivotal enzymes that control biosynthetic pathways are inhibited by AMPK as the ATP level falls, while enzymes that control mobilization of energy reserves to replenish ATP are activated [15]. From a global perspective, whole body energy status is assessed by the rate of glucose metabolism in the CNS. This in turn is linked to the intra-neuronal AMPK system, which senses the 'energy charge' of key neurons within the Arc of the hypothalamus. As illustrated in (1) above glucose entering hypothalamic neurons is metabolized via the glycolytic pathway causing a rise in ATP level [6] and a fall in AMP level, which lowers phospho-AMPK and AMPK activity and thereby, phospho-ACC and ACC activity [6].

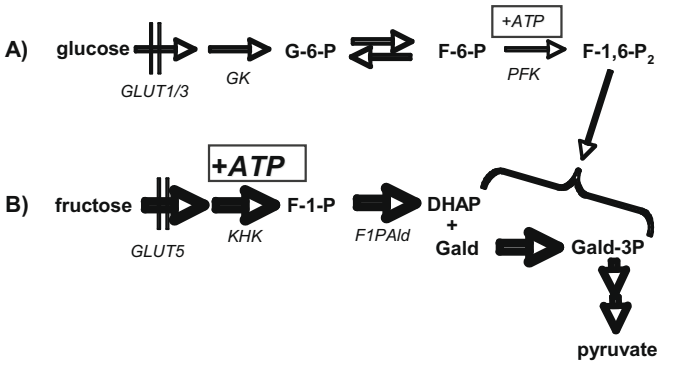
Recent evidence [4,6] indicates that changes in hypothalamic malonyl-CoA during feeding and fasting cycles are the result of changes in the phosphorylation state and activity of ACC that are mediated by AMPK. ACC is found in hypothalamic neurons [11] and is targeted for phosphorylation (thus, inhibition) by AMPK. Several lines of evidence indicate show that hypothalamic ACC and thereby malonyl-CoA concentration, are regulated by AMP: 1. Conditions that lead to the activation AMPK in neuronal cell culture [13] and in the hypothalamus [6] provoke phosphorylation/inactivation of ACC [6]; 2. Leptin, an anorexigenic hormone produced by adipocytes, suppresses AMPK activity in the hypothalamus including the Arc [6]. This action derepresses ACC and thereby increases malonyl-CoA [6]. 3. The central administration of 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), an AMPK activator, lowers hypothalamic malonyl-CoA and promotes food intake [13]. AICAR also activates the phosphorylation/inhibition of ACC and lowers malonyl-CoA concentration in a hypothalamic cell line in culture [13]. These findings indicate that during fasting the [AMP]/[ATP] ratio increases in neurons in critical hypothalamic nuclei, notably the Arc, causing phosphorylation/activation of AMPK, phosphorylation/inactivation of ACC, and a decreased malonyl-CoA level.

Fructose sensing via the AMPK/malonyl-CoA signaling pathway produces hunger

Although both glucose and fructose enter metabolism via the glycolytic pathway, the initial steps of fructose metabolism differ

$$\begin{array}{l}\text{Glucose -> } \Uparrow\text{[ATP] -> } \Downarrow\text{[AMP] -> dephos-AMPK -> dephos-ACC -> } \Uparrow\text{[malonyl-CoA]} \\ \qquad\qquad\qquad\qquad\qquad\quad \textit{(inactive)} \qquad\quad \textit{(active)} \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \downarrow \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \Downarrow\text{food intake}\end{array} \tag{1}$$

from those of glucose in certain tissues, most notably liver. Recent findings [4] show that these differences also occur in the central nervous system (CNS), notably the hypothalamus, where the initial steps of fructose metabolism utilize different enzymes than those for the initial steps of glucose metabolism. These differences allow fructose to bypass the rate-limiting regulatory step of glycolysis catalyzed by phosphofructokinase (PFK), which is used by glucose, but not fructose (see (3) and Fig. 1B).



(3)

Bypassing this glycolytic step allows fructose to be metabolized far more rapidly than glucose. Specifically, the initial steps of fructose metabolism are catalyzed by the cell-surface sugar transporter (GLUT3/5), 2-ketohexokinase and fructose-1-phosphate aldolase. These steps allow fructose to enter the glycolytic pathway at the triose phosphate level beyond the slow PFK-catalyzed step (see (3) and Fig. 1B). Since the action of 2-ketohexokinase on fructose rapidly consumes ATP, the entry of fructose into the hypothalamus produces a rapid depletion of ATP [4]. This decrease in ATP is accompanied by an increase in AMP which lowers ACC activity and malonyl-CoA concentration provoking increased food intake [4]. In contrast, the central administration of glucose leads to an increase in ATP concentration that initiates the cascade above to produce satiety. Thus, the downstream events in the signaling pathway triggered by fructose are the inverse of those provoked by glucose (see (4) below).

Fructose -> ⇓[ATP] -> ⇑[AMP] -> phos-AMPK *(active)* -> phos-ACC *(inactive)* -> ⇓[malonyl-CoA] → ⇑food intake (4)

Discussion

Over the past four decades life-styles have gravitated toward the excessive consumption of 'high energy' foods and sedentary behavior that has resulted in a high incidence of obesity and its pathological consequences [16]. This scenario has led to the increased occurrence of insulin resistance and Type 2 diabetes. At present, approximately thirty percent of adult Americans can be classified as obese [16]. Moreover, these changes now extend into the younger age group that is now experiencing a marked increase in the incidence of obesity and Type 2 Diabetes.

In this review we compared the effects of the metabolic and behavioral effects of centrally administered glucose and fructose. We report that centrally administered glucose leads to an increase in the hypothalamic ATP level and a concomitant decrease in AMP level, inactivation of AMPK, activation of ACC, increased malonyl-CoA which gives rise to a suppression of food intake (see (1) and Fig. 1A). The effects of centrally administered fructose were not only unexpected, but counterintuitive. Central fructose has the inverse effect of glucose on intermediates in the signal transmission pathway and leads to an increase in food intake. Thus, centrally administered fructose decreases hypothalamic ATP, increases AMP level, activates AMPK, inactivates ACC, decreases malonyl-CoA which promotes hunger and thereby, an increased of food intake (see (4) and Fig. 1B). The reasons for this inverse effect are twofold, 1. central fructose enters the glycolytic pathway at a point beyond that of glucose, thereby bypassing the rate-limiting regulatory step (i.e. catalyzed by PFK; Fig. 1A and B) in the pathway (see (3)), and 2. central fructose is rapidly phosphorylated by 2-ketohexokinase, an ATP requiring enzyme, which causes ATP depletion. This in turn, increases, rather than decreases, the level of AMP and malonyl-CoA giving rise to an increase of food intake.

Evidence presented here suggests that an excessively high fructose intake might suppress the hypothalamic malonyl-CoA signaling pathway and thereby exert an orexigenic effect. Obviously, this effect would depend on the ability of fructose to cross the blood–brain barrier or to enter the brain through circumventricular structures with weak blood–brain barriers, notably in the arcuate nucleus. Recent studies in the author's laboratory show that fructose administered systemically, i.e. by i.p. injection, rapidly (<10 min) reaches, enters and is metabolized in the brain as indicated by its rapid metabolism to lactate in the hypothalamus (unpublished results). Thus, it can be concluded that fructose circulating in the blood can cross the blood brain barrier and undergo metabolism in the hypothalamus.

The fact that central fructose stimulates food intake may be relevant to the increased use of high-fructose sweeteners, e.g. high-fructose corn syrup, in the American diet. The total per capita consumption of high fructose sweeteners is about 140 lbs per year, of which high fructose corn syrup 77 lbs per year. This is of particular concern among the younger members of the population who are the major consumers of high fructose-containing soft drinks. Paralleling the rise in consumption of high-fructose sweeteners are the increases in the obesity epidemic [16,17] and Type 2 diabetes in youth [17]. These correlations are consistent with animal and human studies which show that high-fructose diets promote insulin resistance, glucose intolerance, and increased rates of hepatic lipogenesis in laboratory animals [16].

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