Cell Metabolism
Perspective

A Balance of Lipid-Sensing Mechanisms in the Brain and Liver

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Recent work has cast a spotlight on the brain as a nutrient-sensing organ that regulates the body's metabolic processes. Here we discuss the physiological and molecular mechanisms of brain lipid sensing and compare these mechanisms to liver lipid sensing. A direct comparison between the lipid-sensing mechanisms in the brain and liver reveals similar biochemical/molecular but opposing physiological mechanisms in operation. We propose that an imbalance between the lipid-sensing mechanisms in the brain and liver may contribute to obesity-associated type 2 diabetes.

The incidence of obesity and diabetes has reached epidemic proportions, and many laboratories worldwide have dedicated major efforts and resources toward elucidating the potential mechanisms underlying the development of these diseases. Two critical features of obesity and diabetes are hyperphagia and hyperglycemia. The central nervous system (CNS) has been demonstrated to regulate food intake (Cota et al., 2006; Flier, 2004; Friedman, 2000; Kahn et al., 2005; Schwartz and Porte, 2005; Wolfgang and Lane, 2006). In addition, there is growing evidence indicating that the CNS (specifically the hypothalamus) senses hormones and nutrients to regulate glucose homeostasis (Bence et al., 2006; Coppari et al., 2005; Flier, 2004; Gelling et al., 2006; Inoue et al., 2006; Kievit et al., 2006; Lam et al., 2005a, 2005b, 2005c; Obici et al., 2002a, 2002b, 2003; Schwartz and Porte, 2005). This perspective focuses on the physiological and molecular mechanisms of glucose regulation by CNS lipid sensing and compares the associated sensing mechanisms to liver lipid sensing.

Brain/Liver Lipid Sensing and Liver Insulin Action

Intracerebroventricular (i.c.v.) administration of oleic acids (a type of long-chain fatty acid [LCFA]) for 6 hr was first demonstrated to lower plasma insulin and glucose levels under basal physiological conditions in rodents (Obici et al., 2002a). To assess whether the decline in blood glucose levels induced by i.c.v. oleic acids corresponded to a change in peripheral insulin action, the i.c.v. administration protocol was combined with a pancreatic (basal insulin) euglycemic clamp technique. Under these experimental conditions, i.c.v. oleic acid administration reduced hepatic glucose production (GP) (Obici et al., 2002a).

Carnitine palmitoyltransferase-1 (CPT-1) regulates the transportation of fatty acids into the mitochondria for β-oxidation. Chemical inhibition of CPT-1 in the mediobasal hypothalamus increases esterified LCFA (LCFA-CoA) (Obici et al., 2003). Elevation of hypothalamic LCFA-CoA levels (via CPT-1 inhibition) for 6 hr suppresses GP to an extent similar to short-term i.c.v. oleic acid administration (Obici et al., 2003). However, administration of ATP-sensitive potassium (K_{ATP}) channel blockers abolishes the suppressive effects of both i.c.v. oleic acid administration and hypothalamic CPT-1 inhibition (Obici et al., 2002a; Pocai et al., 2005b), while activation of central K_{ATP} channels alone (via hypothalamic diazoxide administration) suppresses GP (Pocai et al., 2005a). Taken together, these initial findings by Rossetti and colleagues suggest that short-term hypothalamic accumulation of LCFA-CoAs and the activation of K_{ATP} channels play an important role in CNS lipid sensing and subsequent suppression of GP.

By contrast, it has been demonstrated in rodents, dogs, and humans that short-term elevation of LCFAs in the blood induces liver insulin resistance. Specifically, intravenous (i.v.) lipid administration increases GP during hyperinsulinemic-euglycemic clamp conditions (Boden et al., 1994; Lam et al., 2002, 2003b; Lewis et al., 1997; Rebrin et al., 1996; Sindelar et al., 1997). The elevation of GP is associated with increased hepatic glycogenolysis (Boden et al., 2002). In parallel, transgenic mice with liver-specific overexpression of lipoprotein lipase (the rate-limiting enzyme in triglyceride hydrolysis, which releases free fatty acids [FFA] and glycerol) develop hepatic insulin resistance (Kim et al., 2001). These mice manifest defects in insulin activation of hepatic IRS-2-associated phosphatidylinositol 3-kinase (PI3K) activity. These data indicate direct impairment of liver insulin action by lipids.

One proposed molecular mechanism underlying these effects is the accumulation of LCFAs in liver cells, followed by conversion to and accumulation of LCFA-CoA as the active species. This model is supported by the observation that increases in hepatic LCFA-CoA and diacylglycerol (DAG, an esterification product of LCFA-CoA) induced by high-fat feeding or i.v. lipid infusion are associated with liver insulin resistance (Boden

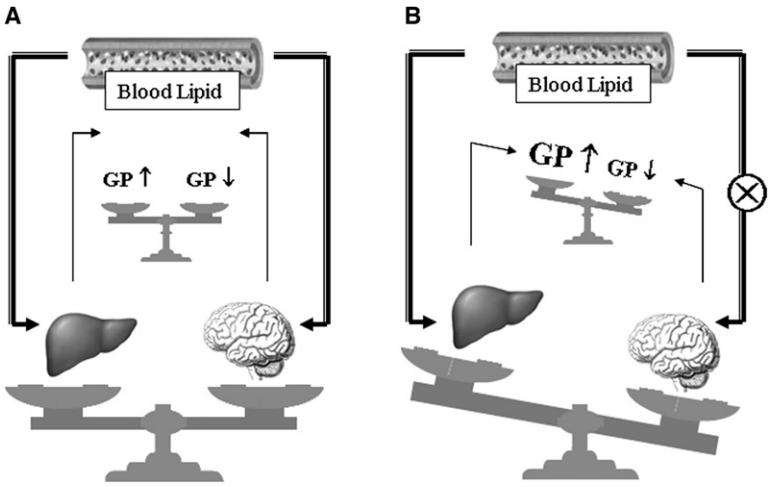

Figure 1. The Balance of Lipid-Sensing Mechanisms in the Brain and the Liver
(A) Lipid sensing in the brain reduces glucose production (GP). In contrast, lipid sensing in the liver reduces liver insulin action, thereby promoting GP. Under normal conditions, the opposing effects of lipid sensing in these two vital organs achieve a balance in GP regulation, contributing to plasma glucose homeostasis.
(B) The balance between lipid sensing in the brain and in the liver is disrupted in obesity-associated diabetes, leading to an elevation of GP.

et al., 2005; Samuel et al., 2004). Elevated levels of DAG and malonyl-CoA (an allosteric inhibitor of CPT-1) are also associated with glucose-induced liver insulin resistance (Kraegen et al., 2006). Since CPT-1 is responsible for β-oxidation in the transport of FFA into the mitochondria, inhibition of CPT-1 activity would result in the accumulation of LCFA-CoA (McGarry et al., 1977; Ruderman et al., 1999). Indeed, inhibition of liver CPT-1 with etomoxir induces liver insulin resistance (Dobbins et al., 2001). These data collectively indicate that short-term elevation of liver LCFA-CoA or LCFA-CoA-derived DAG increases GP under hyperinsulinemic-euglycemic clamp conditions.

In summary, short-term accumulation of LCFA-CoAs in the brain reduces GP, whereas short-term increases in liver LCFA-CoAs increase GP. The relative contributions of these two mechanisms to GP regulation is not known and may differ in various physiological and pathophysiological conditions. However, taken together, the data pose an interesting paradigm. We propose that the lipid-sensing mechanisms in both the brain and liver balance GP regulation and maintain plasma glucose homeostasis (Figure 1A). More importantly, diet-induced obesity impairs this balance and increases GP, progressively leading to type 2 diabetes (Figure 1B).

An Imbalance in Brain/Liver Lipid-Sensing Mechanisms in Experimental Models

Could the manipulation of lipid-sensing mechanisms in the brain and/or liver affect the balance of GP regulation and disrupt plasma glucose homeostasis? If so, what is the relative contribution of brain and liver lipid effects on GP and plasma glucose levels? To address these questions in vivo, we employ an experimental model in which short-term elevation of circulating LCFAs increases liver gluconeogenesis while inhibiting glycogenolysis. This balances GP regulation under basal insulin clamp conditions (Chen et al., 1999; Chu et al., 2002; Lam et al., 2005b). The first strategy abolishes the hypothalamic lipid-sensing mechanisms in this in vivo model and tests whether this disruption leads to an increase in GP. The experimental approach targets the prevention of either the accumulation of LCFA-CoAs or the activation of the K_{ATP} channels in the hypothalamus, since both have been demonstrated to play an important role in CNS lipid sensing (see above). It has been reported that circulating LCFAs cross the blood-brain barrier (Miller et al., 1987), and i.v. administration of LCFAs for 4 hr doubles hypothalamic LCFA-CoA levels (Lam et al., 2005b). When the hypothalamic LCFA esterification pathway is inhibited via administration of triacsin C (an inhibitor of acyl-CoA synthase), the ability of circulating LCFAs to increase hypothalamic LCFA-CoAs is negated (Lam et al., 2005b). This negation has also been observed in rats overexpressing hypothalamic malonyl-CoA decarboxylase (MCD) (He et al., 2006). More importantly, both of these approaches result in an increase in hepatic glycogenolysis and GP in response to i.v. lipid infusion (He et al., 2006; Lam et al., 2005b). Furthermore, central pharmacological blockade and genetic disruption of hypothalamic K_{ATP} channels markedly elevate hepatic glycogenolysis and GP in response to systemic lipid infusion (Lam et al., 2005b). Together, these initial findings show that disruption of hypothalamic lipid-sensing mechanisms leads to an imbalance of GP regulation.

Does the abolition of liver lipid-sensing mechanisms disrupt GP regulation in an opposing manner in order to lower GP? Unfortunately, no studies to date have addressed this working hypothesis in the hyperlipidemic basal insulin clamp model described above. However, other approaches to abolish liver lipid-sensing mechanisms have included lowering liver lipid (i.e., LCFA-CoA) accumulation or inhibiting subsequent causative insulin resistance mechanisms (i.e., protein kinase C [PKC] activation) under hyperlipidemic-hyperinsulinemic clamp conditions. For example, liver MCD overexpression results in decreased malonyl-CoA levels and increased lipid oxidation, which ameliorates high-fat-diet-induced liver insulin resistance (An et al., 2004). Antisense oligodeoxynucleotide inhibition of liver acetyl-CoA carboxylase, an enzyme that stimulates the production of malonyl-CoA from acetyl-CoA, lowers hepatic levels of malonyl-CoA, LCFA-CoA, and DAG in rats fed a high-fat diet. This also reverses diet-induced hepatic insulin resistance (Savage et al., 2006).

Table 1. Comparison of Brain and Liver Lipid-Sensing Mechanisms

	LCFA-CoA Level	GP
Free fatty acid influx		
Brain (Lam et al., 2005b; Obici et al., 2002a)	↑	↓
Liver (Kim et al., 2001)	↑	↑
CPT-1 inhibition		
Brain (Obici et al., 2003)	↑	↓
Liver (Dobbins et al., 2001)	↑	↑
MCD overexpression		
Brain (He et al., 2006)	↓	↑
Liver (An et al., 2004)	↓	↓

Increased abundance of LCFA-CoAs or LCFA-CoA-derived DAG induces hepatic insulin resistance. This is possibly through the activation of liver PKC (Boden et al., 2005; Lam et al., 2002; Samuel et al., 2004). Subsequent work has shown that lipid metabolites activate liver PKC (Boden et al., 2005; Chen et al., 2006; Collins et al., 2006; Lam et al., 2002; Samuel et al., 2004). Furthermore, activation of PKC (a serine/threonine kinase) can phosphorylate IRS-2, reducing the ability of IRS-2 to undergo tyrosine phosphorylation, which is in turn needed for the recruitment and activation of downstream signaling pathways in the liver (Samuel et al., 2004). This scenario would result in liver insulin resistance (Kido et al., 2000; Kubota et al., 2000; Withers et al., 1998). In fact, work from independent laboratories has demonstrated that lipid- or high-fat-diet-induced hepatic insulin resistance is associated with activation/membrane translocation of hepatic PKC-δ and -ε in vivo (Boden et al., 2005; Lam et al., 2002; Samuel et al., 2004). Moreover, antisense oligodeoxynucleotide downregulation of liver PKC-ε expression prevents diet-induced liver insulin resistance (Samuel et al., 2007). Taken together, these data show that a disruption of liver lipid-sensing mechanisms also leads to an imbalance in the regulation (in this case suppression) of GP under hyperinsulinemic clamp conditions.

We propose, however, that a pancreatic basal insulin (and not hyperinsulinemic) clamp condition is required to directly assess the balance and relative contributions of liver and brain lipid-sensing mechanisms. This is mainly because lipid-sensing mechanisms in the brain do not appear to inhibit GP during hyperinsulinemia. Circulating LCFAs increase GP under hyperinsulinemic (Boden et al., 1994; Lam et al., 2003a; Lewis et al., 1997; Rebrin et al., 1996; Sindelar et al., 1997) but not pancreatic (basal insulin) clamp conditions (Chen et al., 1999; Chu et al., 2002; Lam et al., 2005b). Interestingly, hypothalamic lipid-sensing mechanisms are impaired in diet-induced obesity, a condition that is also associated with hyperinsulinemia (see below) (Morgan et al., 2004). To directly assess the relative contribution that liver lipid-sensing mechanisms make to the regulation of GP, the underlying mechanisms responsible for lipid-induced liver gluconeogenesis will first need to be examined (Collins et al., 2006; Yoon et al., 2001). Although the mechanisms controlling lipid-induced liver gluconeogenesis remain unknown, short-term incubation of oleate has been found to activate PKC-δ in hepatocytes (Chen et al., 2006), and this hepatocyte PKC-δ activation has been reported to mediate lipid-induced gluconeogenesis (Collins et al., 2006). Thus, lowering liver LCFA-CoA accumulation (i.e., liver MCD overexpression or ACC downregulation) and inhibiting hepatic PKC activation under the hyperlipidemic pancreatic (basal insulin) clamp condition is a favored approach to selectively evaluate the relative contribution of liver versus brain lipid-sensing mechanisms.

The evaluation of the selective and relative contributions of lipid-sensing mechanisms in the brain and liver is therefore ideally performed under pancreatic (basal insulin) clamp conditions, which eliminate potential confounding effects of hyperinsulinemia in the brain. However, the basal insulin clamp experimental model would not be suitable for evaluating any potential regulatory effects of the CNS lipid-sensing mechanisms on the rate of insulin-stimulated peripheral glucose uptake. In addition, potential regulatory effects of CNS lipid-sensing mechanisms on insulin and glucagon secretion also cannot be assessed. This is because somatostatin is administered during the clamp studies in order to inhibit endogenous insulin and glucagon secretion. These clamp techniques, however, do enable selective evaluation of the ability of the lipid-sensing mechanisms to regulate body glucose metabolism independent of changes in circulating glucoregulatory hormones at basal levels. This is critical, given that insulin can independently signal the brain to regulate GP (Inoue et al., 2006; Obici et al., 2002b; Pocai et al., 2005a), although the central effect of insulin has recently been questioned (Edgerton et al., 2006).

Future studies are needed to address the selective and relative regulation of GP and plasma glucose levels by lipid-sensing mechanisms in the basal (unclamped) conditions as well. Preliminary findings indicate that hypothalamic nutrient-sensing mechanisms appear to regulate plasma glucose levels under basal (unclamped) conditions since direct administration of either oleic acid or glucose into the hypothalamus lowers plasma glucose levels (Lam et al., 2005a; Obici et al., 2002a). This glucose-lowering effect by the brain is retained for at least 4 hr in response to the central administration protocol and is associated with changes in the plasma level of glucoregulatory hormones. These data indicate that the potential regulation of insulin and glucagon secretion by the CNS could play a role in regulating GP and maintaining glucose homeostasis. Future experiments designed to address these issues are needed.

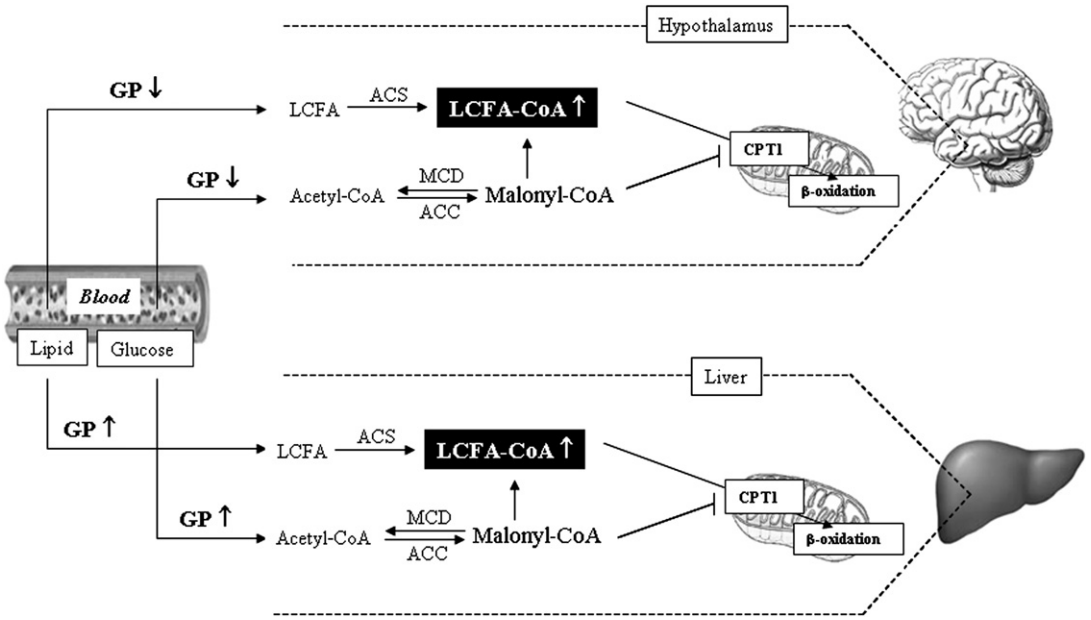

Figure 2. Mechanisms of Lipid and Glucose Sensing in the Brain and the Liver

Circulating lipids enter the brain and liver and are acted upon by the converting enzyme acyl-coA synthetase (ACS), increasing the level of long-chain fatty acid (LCFA)-CoAs. Inhibition of carnitine palmitoyltransferase-1 (CPT-1) increases the amount of LCFA-CoAs in the brain and reduces GP, while CPT-1 inhibition in the liver increases GP. By contrast, decreasing LCFA-CoA levels via overexpression of malonyl-CoA decarboxylase (MCD) in the brain increases GP, and MCD overexpression in the liver reduces GP in lipid-challenged rodents. Similar biochemical and physiological mechanisms are proposed for glucose sensing in both the brain and the liver. After entering the brain and liver, glucose is metabolized into acetyl-CoA and malonyl-CoA, leading to an elevation of LCFA-CoAs. Acetyl-CoA carboxylase (ACC) converts acetyl-CoA to malonyl-CoA. This subsequent elevation of LCFA-CoAs reduces GP in the brain and increases GP in the liver.

Comparison of Brain and Liver Lipid-Sensing Mechanisms in Experimental Models

A thorough examination of biochemical pathways involved in liver and brain response to lipid sensing reveals a similar biochemical/molecular profile, but with opposing physiological mechanisms (Table 1). First, mice with liver-specific overexpression of lipoprotein lipase exhibit an accumulation of liver LCFA-CoAs, with reduced liver insulin action and increased GP (Kim et al., 2001). In contrast, accumulation of hypothalamic LCFA-CoAs via lipid administration reduces GP (Lam et al., 2005b; Obici et al., 2002a). Second, inhibition of liver CPT-1 (which elevates LCFA-CoA levels) induces liver insulin resistance and increases GP (Dobbins et al., 2001), whereas selective inhibition of hypothalamic CPT-1 reduces GP (Obici et al., 2003). Third, selective overexpression of MCD in the liver (which lowers malonyl-CoA and LCFA-CoA levels) increases liver insulin action and reduces GP in mice fed a high-fat diet (An et al., 2004), whereas selective overexpression of MCD in the hypothalamus increases GP in response to lipid infusion (He et al., 2006). Although these models differ in some respects (i.e., transgenic versus lipid versus high-fat diet), these findings collectively indicate that an accumulation of LCFA-CoAs in the liver increases GP and reduces GP in the brain.

The fact that LCFA-CoAs are the potential signaling molecules in both the liver and brain for GP regulation fosters two observations/speculations (Figure 2). First, the liver and brain share biochemical/molecular pathways but have opposing physiological mechanisms linked to glucose sensing. The metabolism of glucose via glycolysis forms malonyl-CoA, which inhibits CPT-1 and elevates LCFA-CoAs. Accordingly, influx of glucose into the liver, pancreas, and muscle has been demonstrated to increase malonyl-CoA/LCFA-CoA levels (Ruderman and Prentki, 2004). A similar biochemical pathway has been proposed for glucose sensing in the hypothalamus (Lam et al., 2005c). Furthermore, direct administration of glucose into the hypothalamus indeed reduces GP (Lam et al., 2005a), whereas elevated liver malonyl-CoA and LCFA-CoA following systemic glucose infusion induce liver insulin resistance and increase GP (Kraegen et al., 2006). Second, the biochemical/molecular pathway implicated in liver lipid-induced insulin resistance includes molecules that may mediate the activation of hypothalamic LCFA-CoA-induced K_{ATP} channels that consequently reduce GP. Does a PKC-mediated biochemical pathway play a role in hypothalamic lipid-sensing mechanisms? Toll-like receptor 4 (TLR4) has recently been implicated in lipid-induced insulin resistance, and TLR4 is expressed in both the liver and brain (Shi et al., 2006). Does the TLR4 signaling pathway in both the brain and liver play a role in GP regulation? Finally, LCFAs with different degrees of unsaturation have been implicated in the differential impairment of insulin action (Clore et al., 2004; Dobbins et al., 2002; Storlien et al., 1991; Xiao et al., 2006). Could this

reflect the inability of some specific types of fatty acids to signal the brain to inhibit GP? To date, oleic acids (Obici et al., 2002a) and Intralipid (26% oleic acid, 50% linoleic acid, 9% linolenic acid, 10% palmitic acid, and 3.5% stearic acid) (Lam et al., 2005b) have been implicated in the signaling that regulates GP in the hypothalamus. Future studies are needed to characterize the metabolic effects of specific fatty acids in the liver and brain.

An Imbalance in Brain/Liver Lipid-Sensing Mechanisms in Obesity and Diabetes

The characterization of GP regulation in experimental models is important. However, a more urgent question needs to be addressed: Does the imbalance of brain/liver lipid-sensing mechanisms contribute to the development of liver insulin resistance in the context of obesity-associated diabetes? In other words, could liver lipid-induced gluconeogenesis lead to an imbalance and elevation of GP because of an inability of brain lipid mechanisms to inhibit GP in obesity and diabetes (Figure 1B)? To address this question in vivo, hypothalamic lipid sensing mechanisms were tested in overfed rats. Male Sprague-Dawley rats double their caloric intake and develop hyperinsulinemia and liver insulin resistance when fed a lard-enriched diet for 3 days (Morgan et al., 2004). Strikingly, i.c.v. oleic acid infusion in these rats failed to lower GP (Morgan et al., 2004). More importantly, when LCFAs were administered i.v. in this overfed model, inducing liver gluconeogenesis as a response, GP was elevated in parallel with decreased hypothalamic LCFA-CoA accumulation (Lam et al., 2005b). Inhibition of hypothalamic CPT-1 restores LCFA-CoA accumulation to normal conditions in this lipid-challenged overfed model and, more importantly, restores the balance of GP regulation during the pancreatic basal insulin clamp (Pocai et al., 2006). Taken together, these initial studies by Rossetti and colleagues suggest that the inability of the brain to sense lipids in diet-induced obesity is due in part to increased hypothalamic CPT-1 activity and lowered malonyl-CoA levels, which consequently lead to an imbalance in GP regulation and the development of liver insulin resistance (Pocai et al., 2006). It is interesting to note that hypothalamic lipid-sensing mechanisms are impaired not only in diet-induced hyperinsulinemia and obesity (Lam et al., 2005b; Morgan et al., 2004; Pocai et al., 2006) but also potentially in hyperinsulinemic-euglycemic clamp experimental models (see above) (Boden et al., 1994; Lam et al., 2003a; Lewis et al., 1997; Rebrin et al., 1996; Sindelar et al., 1997). These observations suggest that hyperinsulinemia (in the presence of hyperlipidemia) may hinder hypothalamic lipid sensing by interfering with the accumulation of LCFA-CoA or with downstream signaling pathways. This hypothesis remains to be investigated. Finally, the balance of GP regulation has only been tested so far in a 3 day high-fat-diet model. More work is needed to better characterize the balance of GP regulation in obesity and diabetes. Specifically, this working hypothesis could be tested in prolonged high-fat-diet and lipid-induced obesity/insulin resistance models or in partial pancreatectomized and streptozotocin-induced diabetic models. Such data would allow improved characterization and elucidation of the pathways underlying the balance of lipid-sensing mechanisms in the brain and liver under pathological conditions.

Conclusions

The global prevalence of obesity and diabetes is increasing at an alarming rate, and elevation of lipids has been posited as a causative link between obesity, insulin resistance, and diabetes. We propose that lipid-sensing mechanisms increase GP in the liver and decrease GP in the brain to achieve a balance in GP regulation. More importantly, we suggest that this balance is disturbed in obesity, leading to the development of liver insulin resistance and progression to type 2 diabetes. Based on these hypotheses, therapeutic approaches aimed at reversing diet-induced liver insulin resistance should include both a lowering of lipid accumulation in the liver as well as restoration of lipid accumulation in the brain.

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