

## Chapter 2

# Glucose- and Fructose-Induced Toxicity in the Liver and Brain

### 2.1 Introduction

Fructose is a monosaccharide found in many fruits and honey. In sucrose (table sugar), fructose is linked with glucose through an alpha 1–4 glycoside bond. Fructose and glucose have the same chemical formula ( $C_6H_{12}O_6$ ). However, fructose is a five-carbon sugar with a keto group on the second carbon, while glucose is a six-carbon sugar with an aldehyde group on the first carbon.

Both glucose and fructose are reducing sugars, but fructose is a ketose and glucose is an aldose. Unlike glucose, which is used by all cells in the body to generate energy and constitutes the nearly exclusive energy fuel for the brain, fructose is mainly metabolized by the liver.

In 1960, the food industry developed technologies for converting corn starch into high-fructose corn syrup (HFCS), which contains high levels of fructose (Marshall and Kooi 1957). For the food industry, the use of sugar created several technical problems. Sugar is not only expensive but is also hydrolyzed under acidic conditions (Salomonsson 2005), producing changes in the sweetness and flavor characteristics of the product. In addition, sugar has to be dissolved in water before its use. In contrast, HFCS is an inexpensive liquid, which is stable in acidic condition in foods and beverages. Between 1970 and 1990, the consumption of HFCS increased over 1,000 % (Bray et al. 2004). Humans have consumed fructose (16–20 g/day) for thousands of years, largely in fresh fruits and honey. Introduction of HFCS, which contains around 55 % free fructose, 42 % free glucose, and 3 % other sugars, has resulted in significant increase in consumption of fructose leading to typical daily consumptions amounting to 85–100 g/day. These days HFCS is used as a replacement to sucrose in processed foods and beverages such as jams, jellies, dairy products, baked desserts, cereals, canned fruits, candies, juices, sodas, and sports drinks (Bray et al. 2004). Because of low cost, sweetness, and increased shelf life of the above-mentioned products, the use of HFCS-containing foods has increased worldwide. In the USA, estimated annual per capita fructose consumption rose from 64 g/day during the 1970s to 81 g/day at the end of the 1990s (Elliott et al. 2002), with

an additional increase in fructose intake (2.5 g/day) resulting from increased fruit and vegetable consumption. Based on this information, it is postulated that increased consumption of HFCS-containing food and soft drinks may be closely associated with stimulation of lipogenesis, high plasma levels of triacylglycerols (TAGs), obesity, and cardiovascular disease (CVD) (Bray et al. 2004). In addition, when ingested in large amounts as part of a hypercaloric diet, fructose can cause hepatic insulin resistance, leptin resistance, increase in total and visceral fat mass, and accumulation of ectopic fat in the liver and skeletal muscle (Shapiro et al. 2008). In the long run, these effects may be closely associated with the pathophysiology of the metabolic syndrome (MetS). However, consumption of fructose in moderate amounts does not produce above mentioned effects due to decrease in glycemic response to glucose loads, and improvement in glucose tolerance (Tappy 2012). Thus, consumption of fructose in moderate amounts does not produce any changes in insulin signaling and on levels of TAG (Moore et al. 2001). Like humans, in rodents the intake of large quantities of fructose-containing food and drinks or HFCS induces insulin resistance (Morino et al. 2006), increases levels of plasma TAGs and VLDL-TAGs, and causes high blood pressure due to increased production of uric acid (Nakagawa et al. 2006; Parks et al. 2008). Similarly, consumption of a high-fat diet also results in increased levels of blood TAGs and glucose, and it is proposed that an overexpression of hepatic 1,6-bisphosphatase, which is involved in gluconeogenesis, may be responsible for hyperglycemia in type II diabetes, a metabolic condition characterized by an elevated blood glucose concentration that results from inadequate insulin action in insulin-sensitive tissues and from abnormal insulin secretion (Visinoni et al. 2008). Growing evidence indicates that a high-fructose diet produces insulin resistance not only by significantly reducing the protein expression of insulin receptor, insulin receptor substrate-1, but also by altering expression of Akt and GLUT4. Fructose feeding also produces ventricular dilatation, ventricular hypertrophy, decrease in ventricular contractile function, infiltration of inflammatory cells in the heart, and hepatic steatosis (Patel et al. 2009; Chang et al. 2007). In the liver, fructose feeding causes both microvesicular and macrovesicular steatosis with periportal fibrosis and lobular inflammation (Kawasaki et al. 2009). Consequently, the administration of fructose-rich diet has been used as a model for investigating the development of the MetS (Rayssiguier et al. 2006; Panchal and Brown 2011).

## 2.2 Metabolism of Glucose and Fructose in the Liver

Glucose is utilized by all body tissues to produce energy. The uptake of glucose is regulated by a variety of glucose transporters that differ in their tissue distribution, regulation, and kinetics (Thorens and Mueckler 2010). In addition, consumption of glucose triggers the release of insulin, which further promotes glucose uptake by increasing the translocation of glucose transporter 4 (GLUT4) in striated muscle (skeletal and cardiac) and adipose tissues to further facilitate its uptake. After its

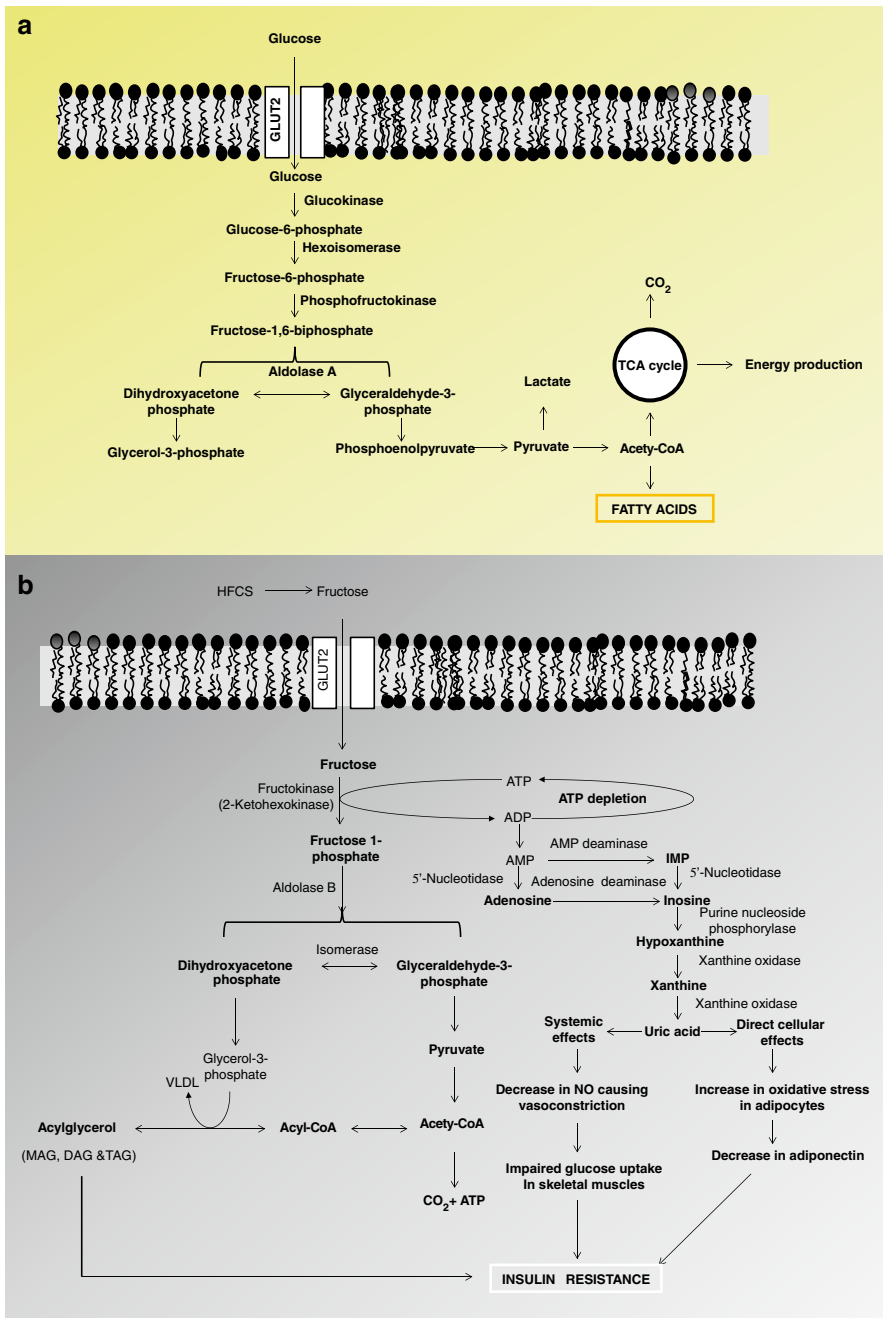
absorption into the liver and other tissues, glucose either is stored as glycogen or undergoes glycolysis (Kelley et al. 1988; Shulman et al. 1990). Glucose is synthesized in the liver via a combination of two biochemical processes: gluconeogenesis and glycogenolysis. The abnormal levels of endogenous glucose synthesis in patients with type II diabetes are predominately due to an increase in the rate of gluconeogenesis compared with nondiabetic subjects, as glycogenolysis is largely unchanged (Magnusson et al. 1992).

After its absorption through the gut, about 15–30 % glucose enters the liver through the portal vein. Glucose enters the hepatocytes by the membrane transporter GLUT2. Once in the cell, glucose is phosphorylated by glucokinase into glucose-6-phosphate. This metabolite is transformed into fructose 1,6-bisphosphate through the action of phosphofructokinase, a multisubunit allosteric enzyme (Fig. 2.1a). Fructose 1,6-bisphosphate is metabolized to triose phosphate and pyruvate by aldolase A. Pyruvate is then decarboxylated to acetyl coenzyme A and enters the tricarboxylic acid cycle (TCA cycle), a reaction sequence for energy production. The net equations for glucose breakdown (glycolysis and TCA cycle) are as follows:

1.  $\text{C}_6\text{H}_{12}\text{O}_6 + 2 \text{ ADP} + 2 [\text{P}]_{\text{i}} + 2 \text{ NAD}^+ \rightarrow 2 \text{ pyruvate} + 2 \text{ ATP} + 2 \text{ NADH}.$
2.  $\text{Acetyl CoA} + 3 \text{ NAD}^+ + \text{Q} + \text{GDP} + [\text{P}]_{\text{i}} + 2 \text{ H}_2\text{O} \rightarrow \text{CoA-SH} + 3 \text{ NADH} + 3 \text{ H}^+ + \text{QH}_2 + \text{GTP} + 2 \text{ CO}_2.$

The energy is then used to synthesize ATP and NADH, which are used by the cell to run cellular processes efficiently. In the absence of oxygen, the glucose cannot be metabolized as thoroughly, and so its metabolism yields lactic acid and fewer molecules of ATP and NADH. Intracellular ATP and citrate exert a negative feedback on phosphofructokinase, so that hepatic glucose catabolism is tuned to the energy status of the liver cells. Insulin regulates glucose metabolism not only by modulating the expression of glucokinase but also activities of key glycolytic enzymes. This allows much of the glucose arriving via the portal vein to bypass the liver and reach the systemic circulation. Thus, following the consumption of glucose-sweetened beverages with meals, plasma glucose and insulin concentrations are increased by 4–5 mM and 70–100  $\mu\text{U}/\text{ml}$ , respectively (Stanhope et al. 2008). This way catabolism of glucose by hepatocytes and other visceral cells produces energy for cell survival (Tappy 2012).

Brain tissue represents only 2 % of the total body weight. It utilizes and metabolizes 20–30 % of total glucose (Sieber et al. 1989). The brain oxidizes approximately 120 g of glucose per day (Sieber and Traystman 1992). The majority of brain glucose is converted to ATP energy for the maintenance of normal brain functions including cognition. During hypoglycemia other tissues cease to utilize glucose all together in order to increase glucose availability to the brain (Lehninger et al. 2005). GLUT1 (45 kDa) is a key regulator of glucose transport into and out of the brain across the blood–brain barrier (BBB) acting to maintain glucose homeostasis in the



**Fig. 2.1** Metabolism of glucose and fructose in the brain (a) metabolism of glucose and (b) metabolism of fructose

brain. It is also highly expressed in proliferating cells of the early developing embryo, cardiac muscle, human erythrocytes, and astrocytes (Morgello et al. 1995). GLUT1 is found in the cells forming blood–tissue barriers (Mann et al. 2003), such as the choroid plexus and blood–spinal cord barrier, and the ependymal lining of the cerebral ventricles (Vannucci 1994). GLUT1 in the BBB and GLUT3 in the neurons are not sensitive to insulin that is why brain glucose metabolism is so widely viewed as being independent of insulin. However, GLUT4 is insulin responsive and is expressed particularly in brain regions involved in memory and cognition such as the hippocampus (Watson and Craft 2004).

Like visceral tissues, in the brain, glucose is either metabolized through glycolysis or stored in astrocytes as glycogen. During aerobic cellular respiration, the process of glycolysis in the brain yields pyruvate, which is converted into acetate during transition reaction. As stated above, acetate is used in the citric acid cycle for the production of ATP through the electron transport chain within the mitochondria.

Absorption of fructose from the intestine into the portal blood is facilitated by glucose transporter 5 (GLUT5) at the brush border and basolateral membranes of the jejunum. Fructose through the portal vein enters the liver, where like glucose it is transported into the hepatocytes by GLUT2. In the hepatocytes, fructose is phosphorylated by fructokinase (2-ketohexokinase) producing fructose 1-phosphate. Fructokinase exists in two alternatively spliced isoforms known as fructokinase C and fructokinase A (Hayward and Bonthron 1998). Fructokinase C is expressed primarily in the liver, kidney, and intestines, whereas fructokinase A is more ubiquitous (Diggle et al. 2009). Although, both fructokinases can metabolize fructose, fructokinase C is considered as the primary enzyme involved in fructose metabolism due to its lower  $K_m$  (Asipu et al. 2003). Because of its higher  $K_m$ , fructokinase A is not considered presently to be actively involved in fructose metabolism but rather has been postulated to act on as yet unknown substrates (Asipu et al. 2003). In contrast to hexokinase, the fructokinase pathway of fructose metabolism bypasses phosphofructokinase, an enzyme that tightly regulates glycolysis. Thus, while glucose metabolism is *negatively* regulated by phosphofructokinase, fructose can *continuously* enter the glycolytic pathway. Fructose 1-phosphate is transformed into dihydroxyacetone phosphate and glyceraldehyde-3-phosphate by the action of aldolase B (Fig. 2.1b) (Jianghai et al. 2012). Some of these three-carbon molecules are either converted into glucose through gluconeogenesis or transformed into triacylglycerol (TAG). In the extrahepatic metabolism, fructose bypasses fructokinase and allows carbon from fructose to enter glycolysis downstream of this enzyme. The three-carbon molecules can eventually be used for the synthesis of glycerol and fatty acids, which through esterification can form TAGs. Another important aspect of fructose metabolism is that unlike other sugars, it raises uric acid levels in humans and rodent's sera (Stirpe et al. 1970; Stavric et al. 1976) (see below).

The liver and gut are major sites for the metabolism of fructose. As stated above, fructose enters the glycolytic pathway at the triose level, after the generation of fructose 1-phosphate via fructokinase, which is not regulated by energy status. In addition,

fructokinase consumes ATP at a greater rate than does phosphofructokinase-1; fructose decreases intracellular ATP while increasing AMP levels (Cha et al. 2008; Lane and Cha 2009). It is demonstrated that fructose-induced depletion of ATP is similar to ATP depletion in ischemia. This effect not only produces transient arrest in protein synthesis (Maenpaa et al. 1968) but also increases the production of inflammatory proteins, induces endothelial dysfunction, and promotes oxidative stress (Cirillo et al. 2009). These processes lead to greater fructose uptake by the liver with little of the consumed fructose reaching the circulation. In addition, ATP depletion also produces intracellular phosphate depletion and AMP generation, with stimulation of AMP deaminase and the stepwise degradation of AMP to purine products including uric acid (van den Berghe et al. 1977). As uric acid rises inside the cells, it spills out into the circulation. Accumulating evidence suggests that fructose is distinct from glucose in its ability to cause intracellular phosphate depletion, ATP depletion, and uric acid generation in the liver (Lanaspa et al. 2012). Approximately 70 % of the uric acid is excreted through the kidneys and 30 % of the uric acid is excreted through the gastrointestinal tract. Overproduction of uric acid through over-consumption of fructose and purine-rich foods may result in hyperuricemia. Coffee consumption not only decreases serum uric acid levels, but also lowers the risk of developing gout (Choi et al. 2007) through various mechanisms (Kela et al. 1980; Petrie et al. 2004), including the inhibition of xanthine oxidase (Kela et al. 1980; Petrie et al. 2004), lowering of insulin levels (Wu et al. 2005), and increase in insulin sensitivity in rats (Arnlov et al. 2004).

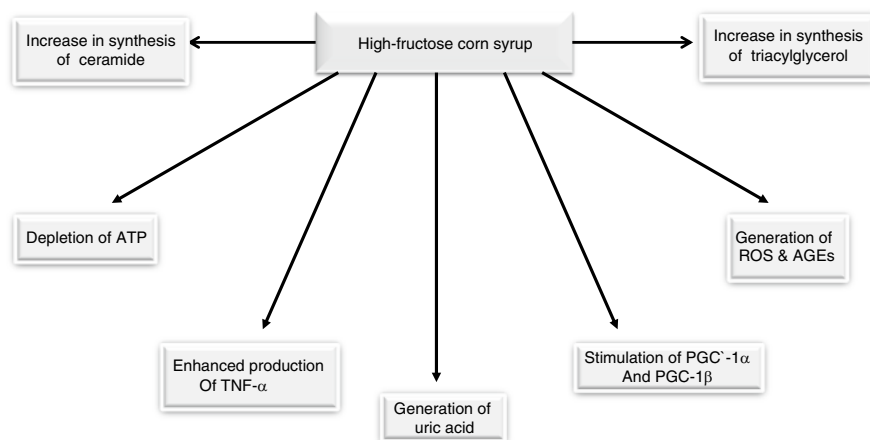
Glucose stimulates the release of insulin from the pancreas. Glucose-induced insulin secretion is regulated by (a) transport of glucose into the  $\beta$  cells through the translocation of the GLUT2; (b) generation of ATP through the oxidation of glucose; (c) elevation of ATP/ADP ratio induces closure of cell-surface ATP-sensitive  $K^+$  ( $K_{ATP}$ ) channels, leading to cell membrane depolarization and activation of voltage-gated  $Ca^{2+}$  channels; (d) extracellular  $Ca^{2+}$  influx into the  $\beta$  cell; and (e) a rise in cytosolic  $Ca^{2+}$  triggering the exocytosis of insulin granules (Gong and Muzumdar 2012).

Unlike glucose, in the hepatocytes fructose is largely transported via GLUT2 and it does not stimulate insulin release from the pancreas, because the pancreas lacks the GLUT5 transporter for fructose (Curry 1989). As stated above, fructose is rapidly phosphorylated by fructokinase, yielding fructose 1-phosphate. Unlike phosphofructokinase, which is involved in the metabolism of glucose, fructokinase is not inhibited by ATP and thus may not be involved in maintaining the cellular energy states (Samuel 2011). Consumption of fructose-enriched diet results in the generation of glycerol-3-phosphate (G-3-P), which causes fat to become fixed in fat tissue. Fructose tricks our body into gaining weight by turning off our body's appetite control system. Fructose does not suppress ghrelin (the "hunger hormone") and doesn't stimulate leptin (the "satiety hormone"), which together results in feeling hungry all the time, even though one has eaten. Thus, consumption of diet enriched in fructose contributes to overeating and obesity in rodents due to increase in leptin secretion (Froesch 1972; Teff et al. 2002; Havel 2002). Consumption of fructose also influences activities of mitochondrial enzymes. Thus, fructose consumption also results in an increase flux of acetyl CoA through the TCA cycle with a

concomitant increase in cellular energy status (increased ATP/ADP ratio and NADH/NAD<sup>+</sup> ratio). A high NADH/NAD<sup>+</sup> ratio in the mitochondria results in substrate inhibition of isocitrate dehydrogenase in the TCA cycle. This inhibition not only increases the export of citrate to the cytosol, but also activates acetyl-CoA carboxylase and increases the synthesis of malonyl-CoA, a precursor of fatty acid synthesis (Locke et al. 2008; Cox et al. 2012). Elevated cytosolic concentrations of malonyl CoA is known to inhibit the carnitine shuttle via carnitine palmitoyltransferase (CPT), resulting in reduced entry of fatty acids into the mitochondria and decrease in fatty acid oxidation (Locke et al. 2008; Cox et al. 2012). In animals and humans, L-carnitine is biosynthesized primarily in the liver and kidneys from the amino acids lysine or methionine with vitamin C (ascorbic acid) being essential to the synthesis of L-carnitine (Steiber et al. 2004). L-carnitine is necessary for the transport long-chain fatty acids from the cytosol to sites of  $\beta$ -oxidation in the mitochondria. Acetate is a by-product of  $\beta$ -oxidation and provides usable energy via the citric acid cycle. Under normal conditions, the availability of carnitine is not a limiting step in  $\beta$ -oxidation. However, an elevation in carnitine content may increase the rate of fatty acid oxidation causing a reduction in glucose utilization, preserving muscle glycogen content, and producing maximal rates of ATP production (Owen and Sunram-Lea 2011). High plasma fatty acid levels in obesity may require more carnitine for efficient  $\beta$ -oxidation. Chronic high-fat feeding not only produces severe age-related decrease in carnitine homeostasis, but also coincides with reduction in hepatic expression of carnitine regulatory genes and increase in sequestration of carnitine in the skeletal muscle acylcarnitine pool. Whole body carnitine homeostasis is regulated at multiple levels, including dietary intake, intestinal absorption, de novo biosynthesis, and renal reabsorption (Noland et al. 2009). In neuronal cells, the L-carnitine shuttle mediates translocation of the acetyl moiety from the mitochondria into the cytosol and promotes the synthesis of acetylcholine and of acetylcarnitine (Nalecz and Nalecz 1996). The neurochemical effects of acetylcarnitine include modulation of brain energy and phospholipid metabolism, cellular macromolecules (such as neurotrophic factors and neurohormones), synaptic morphology, and synaptic transmission of multiple neurotransmitters (Furlong 1996).

Fructose is a lipogenic sugar. The consumption of fructose or high-fructose corn syrup increases the deposition of fat in the liver due to elevation in fatty acyl coenzyme A and diacylglycerol (DAG) (Stanhope and Havel 2008). DAG promotes hepatic insulin resistance (Morino et al. 2005), possibly through the activation of novel-PKC (Samuel et al. 2007). Novel-PKC decreases tyrosine phosphorylation and/or increases serine phosphorylation of the insulin receptor and IRS-1, resulting in decreased insulin sensitivity, increased hepatic glucose production, and increased fasting glucose and insulin concentrations, and impaired glucose tolerance. In addition, fructose has been shown to induce increase in the synthesis of ceramide, TAG, and uric acid along with increase in the expression of the factor of transcription SREBP-1c, the principal inducer of hepatic lipogenesis (Fig. 2.2) (Matsuzaka et al. 2004; Vila et al. 2008; Seneff et al. 2011). This effect of fructose on SREBP-1c requires peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\beta$  (PGC-1 $\beta$ ). Fructose also activates the hepatic transcription factors carbohydrate-responsive





**Fig. 2.2** Harmful effects of high-fructose corn syrup

element-binding protein (ChREBP), which upregulates the expression of hepatic fatty acid synthase and acetyl-CoA carboxylase (Koo et al. 2008). Fructose administration also produces greater postprandial hypertriglyceridemia than glucose, and it can also result in higher apolipoprotein B (apo B) levels (Swarbrick et al. 2008). Apo B assembles atherogenic lipoproteins and promotes the development of atherosclerosis (Olofsson and Boren 2005). Therefore, long-term consumption of diets containing 25 % of energy from fructose produces a lipoprotein profile that is associated with the development of atherosclerosis. The consumption of fructose stimulates food intake (Miller et al. 2002; Cha et al. 2008; Lane and Cha 2009). In addition, a definite relationship has been shown to occur between MetS and hyperhomocysteinemia, which is associated with initiation of cardiovascular and cerebrovascular diseases. Rats fed a fructose-enriched diet have a 72 % higher homocysteine levels after 5 weeks compared to chow-fed controls (Oron-Herman et al. 2003). Elevation in homocysteine levels has also been reported to occur in vascular diseases, coronary artery disease, and in patients with type II diabetes (Okada et al. 1999).

Fructose feeding is also an effective way for inducing fatty liver (Ouyang et al. 2008). It is proposed that metabolic disturbances caused by high-fructose consumption underlie the induction of insulin resistance in both humans and animal models (Stanhope and Havel 2009). Insulin resistance is manifested by the failure of endogenous insulin to hinder hepatic gluconeogenesis and to induce glucose peripheral uptake. Such dysfunction is compensated by hyperinsulinemia and associated with alteration in glucose and lipid homeostasis leading to muscular fat storage as well as visceral fat deposition (Lonardo et al. 2005). Peripheral insulin resistance is promoted by interplay among three major organs, namely, the liver, adipose tissue, and skeletal muscles, with alterations in insulin signaling that involves changes in insulin receptors and post-receptor defects at the molecular level (Farooqui et al. 2012).



These include alterations in the relative abundance of the two insulin receptor isoforms, decrease in insulin affinity to its receptors, improper insulin receptor kinase activity, decrease in autophosphorylation, and abnormalities in glucose transporter translocation and activation (De Fronzo 1997). Fructose-induced insulin-resistant state is characterized by a profound metabolic dyslipidemia, which appears to result from hepatic and intestinal overproduction of atherogenic lipoprotein particles. In addition, fructose feeding also decreases leptin secretion in humans and produces leptin resistance (Teff et al. 2004). In rats, high-fructose diet not only produces hepatic leptin resistance through the enhancement in the amount of suppressor of cytokine 3 (SOCS3) but also decreases serine/threonine phosphorylation of key proteins in leptin signaling (Vila et al. 2008; Li et al. 2010).

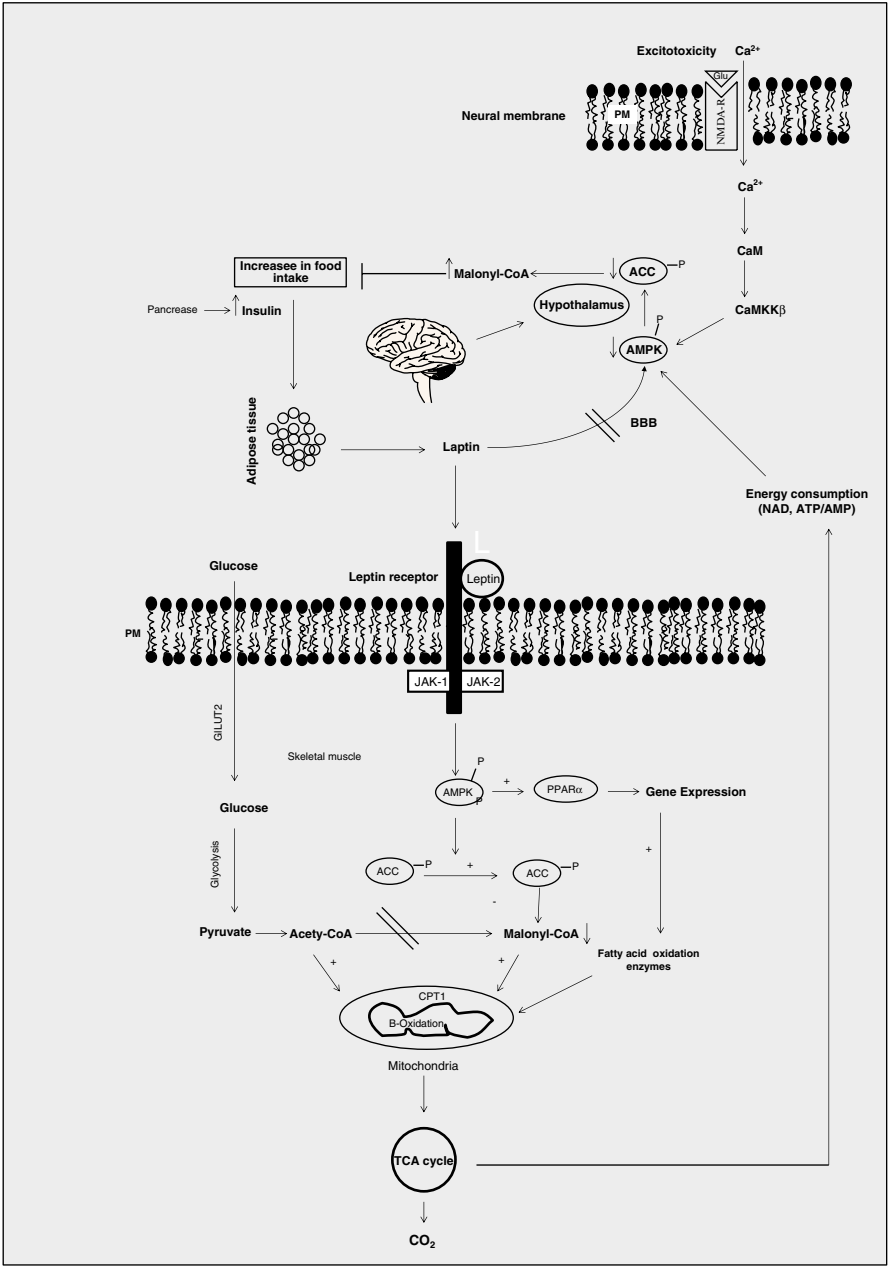
At the molecular level, fructose stimulates the expression of protein tyrosine phosphatase 1B (Li et al. 2010). Fructose-fed rats exhibit impaired c-Jun NH<sub>2</sub>-terminal kinase (JNK) and mitogen-activated protein kinase signaling and increase the expression of FOXO1 due to SOCS3 expression (Vila et al. 2008). In turn, these changes lead to decrease in peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ), reduction in fatty acid oxidation, and accumulation of TAG in the liver. Conversely, the activation of PPAR $\alpha$  reverses leptin resistance in fructose-fed rats (Li et al. 2010). In addition, fructose feeding also increases hepatic ceramide levels, suggesting that incomplete fatty acid oxidation due to PPAR $\alpha$  impairments provides substrate for ceramide synthesis (Vila et al. 2008). This may also result in activation of protein phosphatase 2A and thus contributing to deficiencies in leptin signaling and exacerbate metabolic disease (Vila et al. 2008). Collectively, these studies indicate that exposure of the liver to increased quantities of fructose leads to induction of insulin resistance, rapid stimulation of lipogenesis, and accumulation of TAG in rodent (Seneff et al. 2011). The adipocytes store TAG in the form of lipid droplets inducing adipocyte hypertrophy. Adipocyte hypertrophy is accompanied by the accumulation of multinucleated macrophages, which attempt to protect the contents of dysfunctional adipocytes from further glycation, fructation, and oxidation (Seneff et al. 2011). The exposure of macrophages to advanced glycation end products (AGEs) results in formation of dysfunctional macrophages, which enter into the artery wall and initiate the formation of plaque leading thrombosis (Seneff et al. 2011). Thus, emerging evidence from recent epidemiological and biochemical studies clearly suggests that the liver metabolizes fructose and produces a large increase in TAG (Basciano et al. 2005; Havel 2005; Stanhope and Havel 2009). In the liver, TAG interferes with insulin signaling (Kim et al. 2007). Based on the above information, it is proposed that a high-fructose diet is analogous to a high-fat diet in many metabolic ways (Havel 2005). It is also reported that alterations in metabolic, endocrine, and adipose tissue functions induced by the consumption of a fructose-rich diet (FRD) to an adult female rat can be prevented, at least partly, by pretreatment with progesterone (P4) (Castrogiovanni et al. 2012). The molecular mechanism involved in this process is not fully understood. However, pretreatment with P4 has been reported to modulate the FRD-induced up-regulation of leptin production and down-regulation of plasminogen activator inhibitor-1 (PAI-1) production

(Castrogiovanni et al. 2012). Thus, growing evidence supports the concept that P4 exerts a dual effect upon fat tissue metabolism: It enhances *in vivo* lipogenic activity, induced by administration of an FRD, and inhibits the PAI-1 overproduction caused by this diet.

## 2.3 Metabolism of Glucose and Fructose in the Brain

Glucose is a major circulating sugar and primary fuel for the animal brain for energy production. Glucose enters in neural cells by the membrane transporter GLUT1 and GLUT4. In neural cells glucose is metabolized by a mechanism, which is similar to liver. The hypothalamus plays an important role in the control of food intake and energy expenditure (Cha et al. 2008). Insulin receptor-expressing neurons in the rat are localized in important hypothalamic and hindbrain areas that modulate glucose homeostasis, energy intake and expenditure, and neuroendocrine and autonomic functions (Unger et al. 1991). Activation of insulin receptors in the hypothalamus causes activation of PtdIns 3K and MAPK signaling pathways (Unger et al. 1991). Activation of insulin receptor produces short-term changes in neuronal activity (Spanswick et al. 2000) or prolonged changes in gene transcription and neuronal plasticity (Levin et al. 2006).

Malonyl CoA, an intermediate in fatty acid synthesis, serves as an indicator of energy status in the hypothalamic neurons. Thus, increase in hypothalamic malonyl CoA indicates energy surplus, causing a decrease in food intake and an increase in energy expenditure. In contrast, a decrease in hypothalamic malonyl CoA signals an energy deficit, inducing an increase in appetite and a decrease in body energy expenditure (Fig. 2.3). The cellular levels of malonyl CoA are determined not only by its rate of synthesis, which is catalyzed by acetyl-CoA carboxylase (ACC), but also by the rate of removal of malonyl CoA, by fatty acid synthase. Physiologically, the levels of hypothalamic malonyl CoA are determined through phosphorylation/dephosphorylation of ACC by 5'-AMP-dependent kinase (AMPK) in response to changes in the AMP/ATP ratio, an indicator of energy status. Thus, changes of hypothalamic malonyl CoA during feeding and fasting cycles are closely associated with changes in the phosphorylation state and activity of ACC mediated through AMPK-dependent mechanism. AMPK acts as a “fuel sensor” that increases fatty acid  $\beta$ -oxidation during periods of increase in energy demand or decreases fatty acid  $\beta$ -oxidation during periods of low demand, secondary to respective decreases and increases in ACC activity and malonyl CoA levels (Dyck and Lopaschuk 2006). Metabolism of glucose in the brain produces ATP through the glycolytic pathway. This increase in ATP produces a decrease in AMP level (Lane and Cha 2009; Cha et al. 2008). Because AMP is an activator of AMPK, a drop in AMP level may result in dephosphorylation and inactivation of AMPK. 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, which signals the anorexi-genic–orexigenic neuropeptide system to suppress food intake. In addition, the hypothalamus contains an atypical and brain-specific carnitine palmitoyltransferase-1



**Fig. 2.3** Hypothetical model showing the effect of malonyl CoA on the hypothalamus and skeletal muscles. Glucose transporter 2 (GLUT2); Janus kinase 1 (JAK1); Janus kinase 2 (JAK2); acetyl-CoA carboxylase (ACC); 5'-AMP-dependent kinase (AMPK); carnitine palmitoyl-CoA transferase-1c (CPT-1c); peroxisome proliferator-activated receptor (PPAR); and calmodulin (CaM). Toxicity of glucose and fructose and generation of advanced glycation end products (AGEs). Reactive oxygen species (ROS); Janus kinase (JAK); protein kinase C (PKC); and mitogen-activated protein kinase (MARK)

(CPT-1c), which binds malonyl CoA. CPT-1c does not regulate the entry and oxidation of fatty acids in the mitochondrial membrane. CPT-1c has a unique function or activation mechanism (Fig. 2.3). CPT-1c knockout (KO) mice have lower food intake, weigh less, and have less body fat, consistent with the role as an energy-sensing malonyl-CoA target. CPT-1c not only protects against the effects of a high-fat diet, but CPT-1cKO mice also exhibit decrease in the rate of fatty acid oxidation. It is suggested that CPT-1c may be a downstream target of malonyl CoA that regulates energy homeostasis. These observations support the view that the brain can directly sense and respond to changes in nutrient availability and composition to affect body weight and adiposity (Lane et al. 2008; Wolfgang et al. 2007; Wolfgang and Lane 2011). Collective evidence suggests that the central metabolism of glucose suppresses food intake and increase energy expenditure via hypothalamic AMPK/malonyl-CoA signaling system (Cha et al. 2008). In contrast, fructose is not metabolized by the brain for producing ATP. Consumption of fructose has the opposite effect on the AMPK/malonyl-CoA signaling system. Fructose feeding rapidly lowers ATP, increases P-AMPK and P-ACC, and decreases malonyl CoA in the hypothalamus. Taken together, these findings indicate that the central administration of fructose results in increase in food intake and obesity (Cha et al. 2008). It is also reported that consumption of 60 % fructose diet for 6 weeks by male Syrian hamsters produces insulin resistance in the hippocampus, a region involved in memory formation. Insulin signaling is known to promote hippocampal-dependent memory formation (Park 2001). Peripheral insulin resistance and type 2 diabetes are linked with deficits in hippocampal-dependent declarative memory (Convit 2005; Messier 2005). Based on spatial water maze test, it is suggested that memory formation is correlated with activation of the hippocampal insulin signaling pathway (Dou et al. 2005) and direct infusion of insulin into the hippocampus enhances performance in a variety of memory tasks. In the brain, sucrose and fructose may produce neuropsychiatric effects. Consumption of high amount of sucrose by rats induces sugar bingeing and craving, which is accompanied not only by increased dopamine and opioid receptor binding and enkephalin mRNA expression, but also dopamine and acetylcholine release in the nucleus accumbens (Avena et al. 2006, 2008). Similarly, humans exposed to cake or ice cream show enhanced activation of certain areas in the brain by positron emission tomography scanning, possibly due to alteration in dopaminergic activity (Wang et al. 2004).

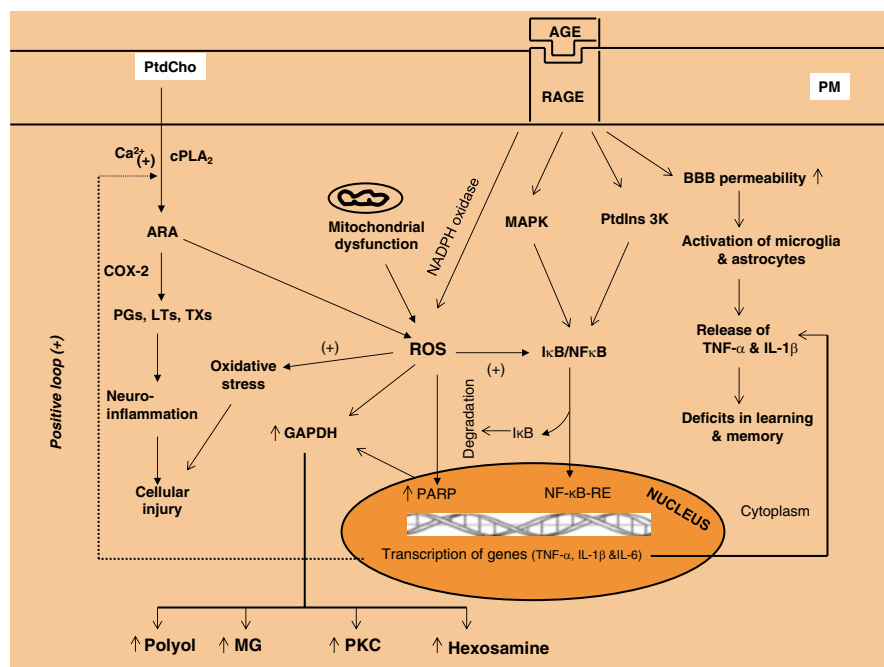
## 2.4 Toxic Effects of Glucose and Fructose in the Visceral Organs and Brain

Diabetes is a complex condition characterized by high levels of blood glucose due to defects in insulin production, insulin action, or both. Diabetic patients often develop secondary complications. Mostly these secondary complications arise in various tissues due to abnormal insulin-independent glucose uptake. Pathophysiological complications in diabetic patients are mainly caused by increased sorbitol

production, oxidative–nitrosative stress, endogenous antioxidant depletion, enhanced lipid peroxidation, metabolic changes, and altered hormonal responses (Brownlee 2005). However, the major mechanism that precedes all the above-mentioned pathways is increase in intracellular glucose level and its downstream metabolism. Hyperglycemia contributes to the generation of superoxides, which inhibit glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity *in vivo* by modifying the enzyme with polymers of ADP-ribose (Du et al. 2003). Specific inhibitors of poly(ADP-ribose) polymerase (PARP) prevent the inhibition of GAPDH. Under normal conditions, PARP resides in the nucleus in an inactive form. Under hyperglycemic conditions, increased production of ROS produces DNA damage and activates PARP in the nucleus. PARP splits the  $\text{NAD}^+$  molecule into nicotinic acid and ADP-ribose. PARP then proceeds to make polymers of ADP-ribose, which accumulate on GAPDH and other nuclear proteins. GAPDH is commonly thought to reside exclusively in the cytosol. However, it normally shuttles in and out of the nucleus, where it plays a critical role in DNA repair (Sawa et al. 1997; Du et al. 2003) (Fig. 2.4). In diabetes and MetS, alterations in glucose metabolism, due to insulin resistance, result in increase in generation of methylglyoxal (MG) (Beisswenger et al. 2003; Thornalley 1993a). As stated above, under normal conditions, glucose is metabolized to glyceraldehyde-3-phosphate (G3P) via glycolysis. G3P is then converted to 1,3-diphosphoglycerate by glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which is upregulated, and G3P is further metabolized to form pyruvate. During insulin resistance, abnormalities in insulin function may result in downregulation of GAPDH, slowing glucose metabolism and increasing metabolism via the polyol pathway (Thornalley 1993a; Alexander et al. 1988). The polyol pathway involves aldo-keto reductase enzymes which utilize a wide variety of carbonyl compounds as substrates and reduce them into sugar alcohols (polyols) through the participation of nicotinic acid adenine dinucleotide phosphate (NADPH). For example, glucose is transformed into sorbitol by the enzyme aldose reductase, and sorbitol is then oxidized to fructose by the enzyme sorbitol dehydrogenase (SDH), with  $\text{NAD}^+$  as a cofactor (Giacco and Brownlee 2010).

The hyperglycemia and metabolic abnormalities in diabetes and MetS also result in mitochondrial superoxide overproduction not only in endothelial cells of both large and small vessels but also in the myocardium. This increased superoxide production causes the activation of five major pathways, which are associated with in the pathogenesis of complications in diabetes and MetS. These pathways include polyol pathway flux, increased production of AGEs, increased expression of the receptor for AGEs (RAGE) and its activating ligands, activation of protein kinase C (PKC) isoforms, and overactivity of the hexosamine pathway (Fig. 2.4) (Giacco and Brownlee 2010). Persistent and excessive activation of PKC isoforms ( $\beta$  and  $\delta$ ) in cultured vascular cells enhances *de novo* synthesis of DAG from glucose via triose phosphate, whose availability is increased because increased ROS inhibit activity of the glycolytic enzyme GAPDH, raising intracellular levels of the DAG precursor triose phosphate (Inoguchi et al. 1992; Scivittaro et al. 2000).

Healthy aging is accompanied by significant decrease in glucose uptake and metabolism in specific cortical regions, an effect that is more pronounced in the elderly



**Fig. 2.4** Interactions between AGE and AGE receptors (RAGE) along with induction of ROS formation. Plasma membrane (PM); advanced glycation products (AGEs); receptor for advanced glycation end products (RAGE); blood–brain barrier (BBB); phosphatidylcholine (PtdCho); cytosolic phospholipase A<sub>2</sub> (cPLA<sub>2</sub>); cyclooxygenase (COX-2); arachidonic acid (ARA); reactive oxygen species (ROS); nuclear factor-kappaB (NF-κB); nuclear factor-kappaB response element (NF-κB-RE); inhibitory subunit of NF-κB (IκB); tumor necrosis factor-α (TNF-α); interleukin-1β (IL-1β); interleukin-6 (IL-6); prostaglandins (PGs); leukotrienes (LTs); thromboxanes (TXs); methylglyoxal (MG); mitogen-activated protein kinase (MAPK); phosphatidylinositol 3-kinase (PtdIns 3K); protein kinase C (PKC); nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase); poly(ADP-ribose) polymerase (PARP); and glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

patients with Alzheimer disease (AD) (Kalpouzos et al. 2009a, b). Decrease in utilization and metabolism of glucose has also been reported to occur in asymptomatic ApoE4 carriers as young as 20–30 years old in the same brain regions as clinically affected AD patients (Reiman et al. 2004; Barberger-Gateau et al. 2011). Alterations in the above parameters are the earliest sign of brain hypometabolism abnormality that occur in the living persons that are at risk of developing AD. This suggestion is supported by various clinical and experimental models, studies of family history and genetic susceptibility to AD, postmortem brain analysis, and from in vitro and animal models (Cunnane et al. 2011). An important issue that has to be addressed is to establish whether brain hypometabolism contributes to the development and/or progression of AD or whether these metabolic changes in brain glucose metabolism are caused by earlier neurodegenerative processes that reduce the demand for glucose in the affected brain areas (Cunnane et al. 2011).

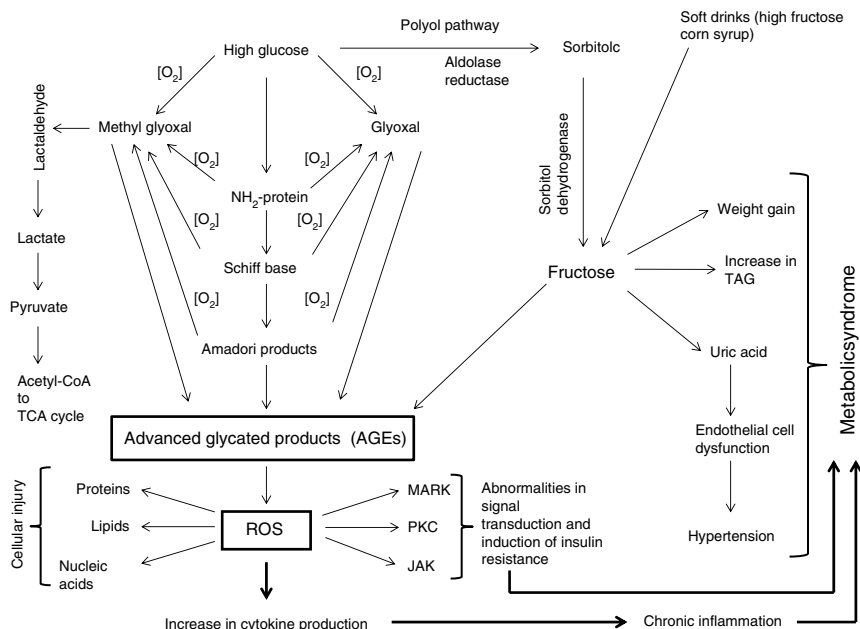
Although, glucose is the main cerebral energy substrate, but during fasting or low carbohydrate intake, glucose is replaced by ketone bodies as a primary replacement fuel (Owen et al. 1967). It is interesting to note that in the elderly and in ApoE4 carriers, increase in blood ketone bodies and their uptake by the brain counterbalances lower brain glucose uptake (Barberger-Gateau et al. 2011; Freemantle et al. 2009). High levels of blood ketone bodies are known to facilitate cognitive performance in ApoE4 noncarriers but not in the carriers (Reger et al. 2004). This suggestion is supported by a larger scale study with 152 subjects, who were diagnosed with mild to moderate AD (Henderson et al. 2009).

An excess of fructose and glucose in the bloodstream is known to produce extensive glycation damage to vulnerable proteins (McPherson et al. 1988; Kikuchi et al. 2003). Glycation (fructated or glucated) is a nonenzymic and posttranslational modification of proteins initiated by the primary addition of a sugar aldehyde or ketone to the amino groups of proteins. Glycation not only induces impaired function, but glycated proteins become highly susceptible to oxidative damage. Glycated proteins are also resistant to degradation by lysosomal enzymes. For example, glycated hemoglobin (hemoglobin damaged by glucose exposure) is used as marker for diabetes, and glycated LDL are poorly recognized by lipoprotein receptors and scavenger receptors (Zimmermann et al. 2001). Over time, these proteins and their debris accumulate in the blood serum and along the arterial walls. These damaged proteins are collectively known as AGEs (Brownlee 2001; Giacco and Brownlee 2010). AGEs play a critical role in aging, diabetes, atherosclerosis and cardiovascular diseases, and in neurodegenerative diseases. Hyperglycemia is closely linked with accelerated AGEs formation (Méndez et al. 2010). The major AGEs in vivo are formed from highly reactive intermediate carbonyl groups, known as  $\alpha$ -dicarbonyls or oxoaldehydes, including 3-deoxyglucosone, glyoxal, and MG (Brownlee 2001; Kim et al. 2005). Some of these AGEs are also formed from increased fatty acid oxidation in arterial endothelial cells (Wautier and Schmidt 2004).

MG is a highly reactive metabolite of glucose. It is produced through enzymic and nonenzymic pathways. MG is primarily formed by the degradation of the glycolytic intermediates, dihydroxyacetone phosphate, and glyceraldehyde-3-phosphate (Thornalley 1993b). MG levels rise in hyperglycemia and diabetes (Brownlee 2001). The polyol pathway transforms excess of glucose into sorbitol, which in turn produces a variety of intracellular changes in vascular tissues including conversion of glucose to fructose by sorbitol dehydrogenase (Fig. 2.5). In the polyol pathway, aldose reductase has a low affinity for glucose. At the normal glucose concentration (nondiabetic subjects), this reaction is very slow and a very small percentage of glucose is utilized through this pathway. However, in diabetic subjects high levels of glucose (hyperglycemia) induce an overproduction of ROS via the mitochondrial electron transport chain, leading to the activation of aldose reductase and the subsequent elevation in conversion of glucose to sorbitol. This reaction is catalyzed by aldose reductase (Madonna and De Caterina 2011). American diet, which is high in fructose- and fat-enriched processed food products, contributes to the formation of MG (Vasdev et al. 2006).

Nonenzymically, MG is spontaneously formed in a process of glycolysis from dihydroxyacetone phosphate as a by-product during the formation of





**Fig. 2.5** Glucose and fructose toxicity and generation of AGEs. Mitogen-activated protein kinase (MAPK); reactive oxygen species (ROS); protein kinase C (PKC); c-Jun N-terminal kinase (JNK); and triacylglycerol (TAG)

glyceraldehydes-3-phosphate in the vascular endothelial cells and smooth muscle cells (Wu 2006). It should be noted that triose phosphate pool, in turn, is regulated by cellular levels of fructose, not by glucose. Interestingly, recent studies have shown that plasma levels of fructose are more involved in MG overproduction than glucose, which is mainly metabolized by the over-activated polyol pathway (Wang et al. 2008) (Fig. 2.5). The enzyme, glyoxalase 1 (GLO1), converts MG into the less reactive substance, D-lactate (Thornalley 2003). In addition, in vitro, overexpression of GLO1 prevents MG accumulation (Shinohara et al. 1998); conversely, GLO1 inhibition increases MG accumulation and decreases cellular viability (Kuhla et al. 2006). It is becoming increasingly evident that expression of GLO1 is associated with behavioral changes in rodents and humans. Thus in mice, GLO1 expression is not only associated with anxiety-like behavior (Hovatta et al. 2005; Loos et al. 2009; Benton et al. 2011; Distler et al. 2012) but also with depression (Benton et al. 2011) and neuropathic pain (Jack et al. 2011; Bierhaus et al. 2012). Accumulating evidence indicates that GLO1 increases anxiety by reducing levels of MG, which acts as a GABA receptor agonist and reduces GABAA receptor activation. A single intraperitoneal injection of low doses of MG produces anxiolytic effect within minutes. At high doses, acute MG administration produces sedative effects, including locomotor depression, ataxia, hypothermia, and lethargy (Distler et al. 2012). Acute MG administration also induces hyperalgesia equivalent to that caused by diabetes in mice (Bierhaus et al. 2012). Together, these studies indicate

that MG mediates multiple behavioral phenotypes and that MG's effects are opposite to those of GLO1 overexpression (Distler et al. 2012).

It is also shown that MG also lowers hydrogen sulfide ( $H_2S$ ) concentrations in cultured vascular smooth muscle cells both directly by scavenging  $H_2S$  and indirectly by downregulating cystathionine  $\gamma$ -lyase expression, suggesting an important interaction between MG and  $H_2S$  (Chang et al. 2010). Hyperglycemia increases the formation of MG, and this process may be an important molecular mechanism linking diabetes to endothelial damage, a systemic pathological condition which can be broadly defined as an imbalance between vasodilating and vasoconstricting substances produced by the endothelium (Deanfield et al. 2005). MG not only modifies lysine, arginine, and cysteine residues in peptides or proteins to yield irreversible advanced glycosylation end products (AGEs), but also increases the generation of reactive oxygen species (ROS) and oxidative stress in endothelial cells (Brownlee 2001; Kim et al. 2005; Madonna and De Caterina 2011). Accumulating evidence suggests that increase in MG is linked to the development of insulin resistance associated with type II diabetes mellitus and MetS (Dhar et al. 2011), as well as hypertension (Vasdev et al. 1998; Wang et al. 2005).

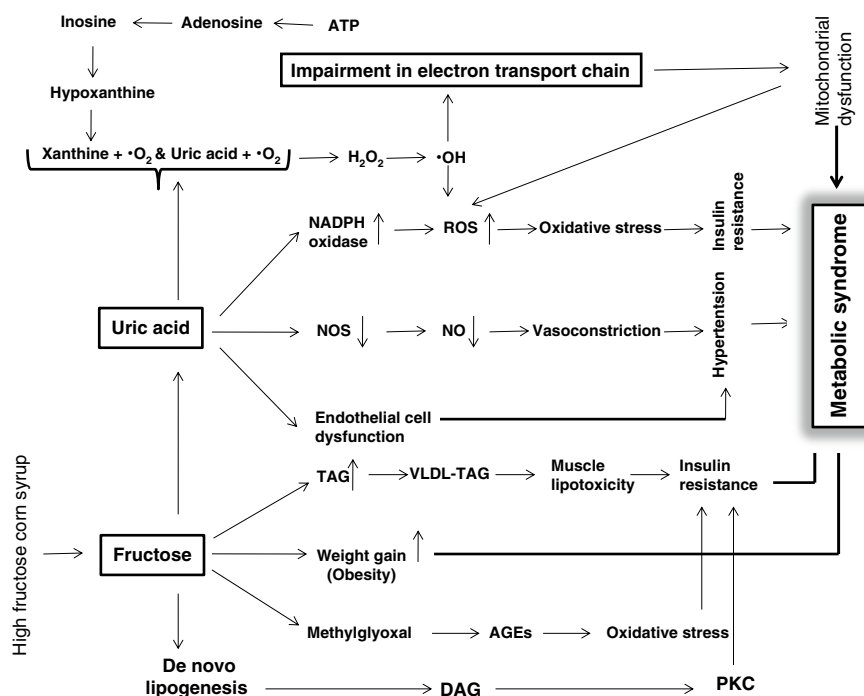
During AGE formation, glucose or fructose attaches itself with the  $\alpha$ -amino group of either the amino terminus of proteins or lysine residues via nucleophilic attack: The product is known as a Schiff base (Fig. 2.5), which undergoes an Amadori rearrangement forming ketoamines (Singh et al. 2001). These ketoamines, synonymously termed Amadori products, either undergo through an oxidative or nonoxidative pathway forming irreversible AGE modifications (Singh et al. 2001). Collective evidence suggests that hyperglycemia in diabetes and MetS causes excessive glycation of proteins found in serum (e.g., albumin, hemoglobin, and LDL) and in the vessel wall (e.g., collagen, fibronectin) (Singh et al. 2001). These modified circulating proteins can then bind to AGE receptors and activate them, thereby initiating vascular pathological changes in the vessel wall. AGEs not only contribute to oxidative stress, but also play an important role in initiating endothelial cell dysfunction (Funk et al. 2012). Intracellular production of AGE precursors can damage visceral and neural cells by three general mechanisms: (a) AGE-mediated modification of intracellular proteins causes alterations in their functions, (b) AGE may produce alterations in extracellular matrix components and with matrix receptors (integrins) on the surface of cells, and (c) plasma proteins modified by AGE precursors may bind to AGE receptors (RAGE) on cells (macrophages, vascular endothelial cells, and vascular smooth muscle cells) mediating the production of ROS, which in turn activates the pleiotropic transcription factor, nuclear factor-kappaB (NF- $\kappa$ B), causing multiple pathological changes in gene expression (Goldin et al. 2006).

Although molecular mechanism of RAGE receptor signaling is not fully understood, RAGE ligation is known to stimulate endothelial ROS production (Yan et al. 1994), and the NADPH oxidase inhibitor diphenyliodonium (DPI) significantly blunts this induction (Wautier and Guillausseau 2001). In addition, AGE/RAGE interactions also upregulate the expression of proinflammatory gene expression (VCAM-1, E-selectin, cytokines) in endothelial cells (Schmidt et al. 1995) and NADPH oxidase activation (Wautier and Guillausseau 2001; Higai et al. 2006).

AGEs and their precursors can diffuse out of the cell and modify extracellular matrix molecules nearby (McLellan et al. 1994), which changes signaling between the matrix and the cell and causes cellular dysfunction (Charonis et al. 1990).

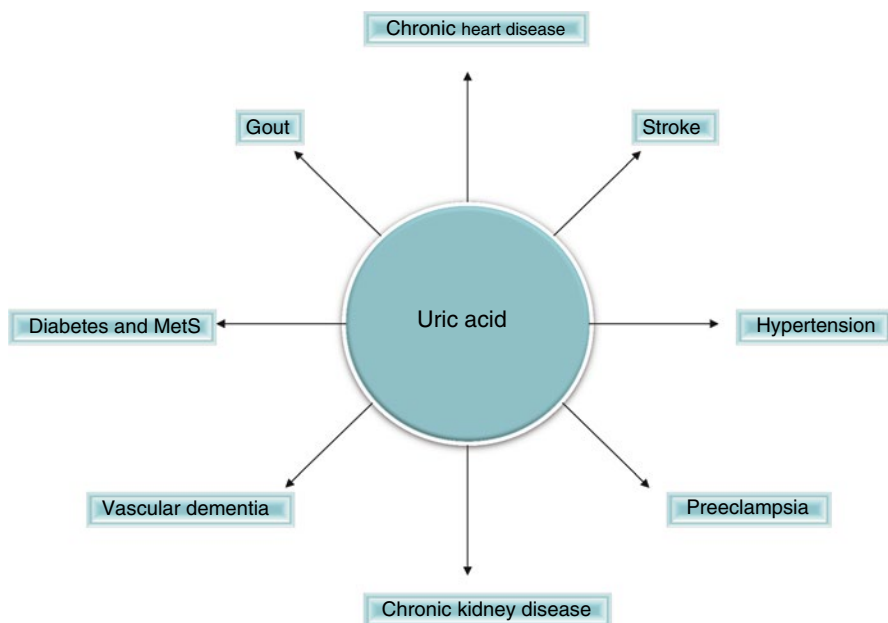
The macrophages exposed to AGEs become dysfunctional and, on entry into the artery wall, contribute to plaque formation and thrombosis (Seneff et al. 2011). As stated above, AGEs mediate their effects by interacting with RAGE, a group of cell surface receptor, which belongs to the immunoglobulin superfamily (Neeper et al. 1992; Ahmed 2005) (Fig. 2.4). RAGE is a type I transmembrane protein composed of three extracellular immunoglobulin-like domains (V, C1, and C2), a single transmembrane domain and a short cytoplasmic tail thought to be important in signal transduction (Hudson et al. 2008). RAGEs are expressed in the brain in neurons, microglia, and astrocytes (Lue et al. 2001; Sasaki et al. 2001; Yan et al. 1996). A $\beta$  is a specific ligand for RAGE, which interacts with the N-terminal domain of RAGE (Chaney et al. 2005). RAGE expression is elevated in AD pathology-enriched brain regions, including the hippocampus and inferior frontal cortex, when compared to the cerebellum where AD pathology is limited. The interactions of RAGE with its diverse ligands (AGEs, A $\beta$ , amphoterin, and S100B protein) mediate multiple physiological and pathological functions, including inflammation, oxidative stress, neurodegeneration, maintenance of homeostasis, tumorigenesis, promotion of neurite outgrowth, cell survival, cell migration, and neuronal differentiation (Fages et al. 2000; Ramasamy et al. 2005; Meneghini et al. 2010). These processes involve NF- $\kappa$ B, MAPKs, PtdIns 3K/Akt, Rho GTPases, JAK/STAT, and Src family kinases (Arumugam et al. 2004; Fang et al. 2010; Kislinger et al. 1999). Blocking the activation of RAGE with neutralizing antibody in the presence of retinoic acid disrupted the progression of normal neuronal differentiation. RAGEs are expressed on multiple cell types and AGE binding with RAGE stimulates mitogen-activated protein kinases (MAPKs), the phosphatidylinositol 3-kinase (PtdIns 3K), JAK/STAT (signal transducers and activators of transcription), and the Rho GTPases Rac-1 and Cdc42 pathways leading to the activation of NF- $\kappa$ B, which translocates to the nucleus where it activates the transcription of genes for cytokines, growth factors, and adhesive molecules, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), well-known inflammation promoters, and vascular cell adhesion molecule 1 (VCAM1) (Xing et al. 1998; Kalousova et al. 2002; Lukic et al. 2008; Wautier et al. 2001). In addition, AGE-RAGE interaction activates NADPH oxidase (a complex of enzymes which produces superoxide) and when this complex is upregulated, it increases intracellular oxidative stress and promotes cellular injury (Fig. 2.4). These processes result in the downregulation of superoxide dismutase isoforms, glutathione peroxidase, and heme oxygenase-2 in various body tissues (Roberts et al. 2006) not only leading to the elevation in plasma levels of malondialdehyde but also in impairment of vasodilatory response to acetylcholine.

Fructose-derived AGEs not only promote the formation of cross-linkages between key molecules in the basement membrane but also interact with specific receptors on the cell surfaces resulting in abnormal intracellular signaling and disrupting cell function (Fig. 2.4) (Suárez et al. 1989; Seneff et al. 2011). Unlike glucose, which is utilized by all organs, fructose is solely metabolized in the



**Fig. 2.6** Biochemical effects of fructose-derived uric acid. Superoxide anions ( $O_2^{\cdot-}$ ); hydroxyl ( $\cdot OH$ ); nicotinamide adenine dinucleotide phosphate oxidase (NADP oxidase); *upward arrow* indicates increase and *downward arrow* indicates decrease

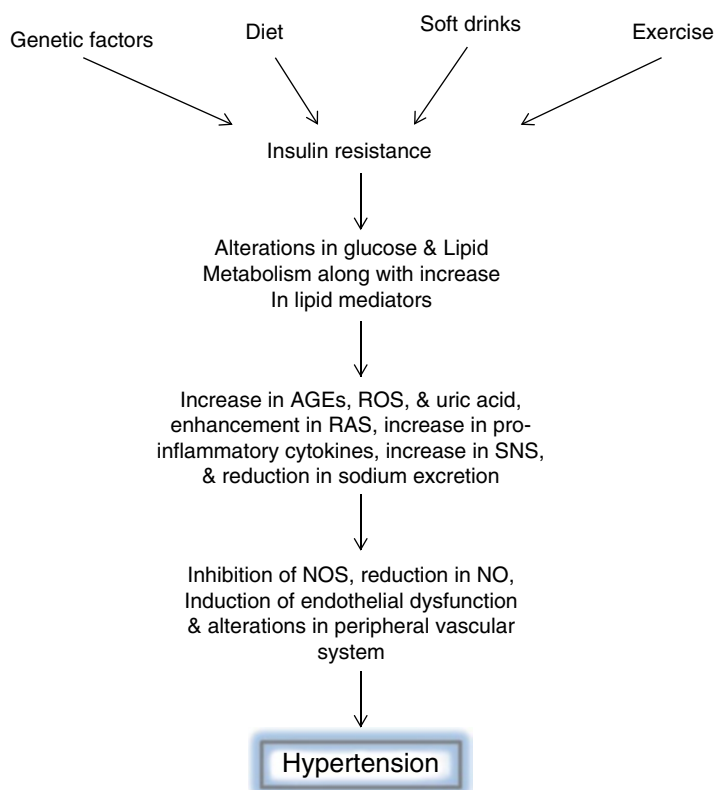
liver. The enzyme that metabolizes fructose (fructokinase) is not regulated by negative feedback, so all fructose that enters the liver cells is rapidly phosphorylated by ATP leading to ATP depletion, a finding, which has been consistently observed in *in vivo* animal models of diabetes and humans. ATP depletion activates enzymes of purine metabolism (AMP deaminase-1), which degrade adenine nucleotides to uric acid via xanthine oxidoreductase with the development of hyperuricemia (Hallfrisch 1990; Nakagawa et al. 2005) (Fig. 2.6). Thus, uric acid is synthesized in the liver from purine compounds provided by the diet or by the endogenous pathway of purine synthesis *de novo*. Serum uric acid levels, even within the normal range, are associated with other cardiovascular risk factors and predict cardiovascular events in adults (Gao et al. 2007; Gagliardi et al. 2009). Biologically, uric acid plays an important role in worsening of insulin resistance in animal models of diabetes by inhibiting the bioavailability of nitric oxide, which is essential for insulin-stimulated glucose uptake (Khosla et al. 2005). Serum uric acid levels are also associated with its deleterious effects on endothelial function, platelet adhesion and aggregation, or oxidative metabolism leading to hypertension and cardiovascular disease (Alper et al. 2005) (Fig. 2.7). In addition, increase in uric acid is also associated with elevated circulating levels of systemic inflammatory mediators, such as monocyte chemoattractant protein-1, NF- $\kappa$ B, interleukin-1 $\beta$ , interleukin-6, and tumor necrosis



**Fig. 2.7** Pathological conditions associated with elevated levels of uric acid

factor- $\alpha$ , and vascular smooth muscle proliferation (Johnson et al. 2003; Kanellis et al. 2004).

There are several proposed neurohormonal links between weight loss and blood pressure. Body mass index is an important mediator of the weight–blood pressure relationship. There is a mostly linear relationship between weight and blood pressure; as weight is regained, the blood pressure benefit is mostly lost. Physical activity, but more so physical fitness (the physiological benefit obtained from physical activity), has a dose-dependent blood pressure benefit but reaches a plateau at which there is no further benefit (Frisoli et al. 2011). However, even just a modest physical activity can have a meaningful blood pressure effect. High blood pressure is accompanied by sustained arterial pressure produced by a combination of acquired or genetic metabolic defects involved in blood pressure regulation. Blood pressure is regulated by environmental factors such as diet and lifestyle (Deshmukh et al. 1998). Although, uric acid increases blood pressure through the inhibition of nitric oxide synthase, but several other possibilities have been proposed. These possibilities include increase in sympathetic nervous system activity (Farah et al. 2006; Verma et al. 1999), insulin resistance, increased oxidative stress, elevation in circulating catecholamines (Tran et al. 2009), decrease in nitric oxide (NO) bioavailability, enhancement in renin–angiotensin system activity and angiotensin II levels (a potent vasoconstrictor) (Tran et al. 2009), increase in sodium reabsorption (De Fronzo 1981), impaired endothelium-dependent relaxation (Katakam et al. 1998),



**Fig. 2.8** Factors that modulate hypertension. Advanced glycation products (AGEs); reactive oxygen species (ROS); renin–angiotensin system (RAS); sympathetic nervous system (SNS); nitric oxide synthase (NOS); and nitric oxide (NO)

and increase in secretion of endothelin-1 (ET-1) (Juan et al. 1998) (Fig. 2.8). Many of these factors may also contribute to an increased vascular tone and impaired endothelial function. Furthermore, it is also reported that hyperinsulinemia itself may cause hypertension as long-term insulin administration causes an increased blood pressure in rats (Meehan et al. 1994), which is reversed upon discontinuation of the insulin (Hsieh and Huang 1993). Hypertension impairs functional hyperemia, the process by which brain activity and blood flow are coordinated. This impairment is induced by dysregulation of vasoactive mediators such as nitric oxide (NO) and endothelin-1, by oxidative stress, by structural alteration of the blood vessels, and by inadequate cerebral autoregulation (Iadecola and Davisson 2008), and all of these processes have been linked to insulin resistance (Crafts 2009).

In addition to high blood pressure, increase in uric acid levels also promotes gout (Yoo et al. 2009). In vitro, uric acid increases NADPH oxidase activity and oxidative stress in adipocytes, leading to increase in p38 MAP kinase activity and insulin

resistance (Sautin et al. 2007; Lee et al. 2009). Lowering uric acid in fructose-fed rats improves components of the MetS, including a reduction in blood pressure, serum triglycerides, hyperinsulinemia, and weight gain supporting the view that uric acid may play a causal role in fructose-mediated MetS in animal models (Nakagawa et al. 2006). Thus, intake of fructose- and purine-rich foods raises uric acid levels and may play a role in the epidemic of MetS that is occurring around the globe (Cirillo et al. 2006, 2009). Uric acid-mediated derangement of renal function is an independent predictor not only of cardiovascular disease outcome but also gout (Baker et al. 2005). In addition, several studies have indicated that uric acid is also associated with diabetic nephropathy along with production of cytokines and induction of inflammatory cascades. All these processes may contribute to progression of microvascular disease and thereby resulting in renal injury in diabetic nephropathy, a major cause of morbidity and mortality in patients with diabetes (Jalal et al. 2010, 2011).

Uric acid also functions as an antioxidant. The antioxidant effects of uric acid are protective in several neurological diseases, including multiple sclerosis and Parkinson disease. However, several observational studies have indicated that high levels of serum uric acid increase the risk of stroke. The current data show elevation in uric acid in high-fat diet associated with hypertriglyceridemia and hypercholesterolemia suggesting that an increased level of uric acid may be a risk factor for the presence of silent brain infarction (SBI). So serum uric acid level might be a good serum marker of underlying SBI or future stroke (Heo and Lee 2010) (Fig. 2.7).

The exact mechanism by which hypertriglyceridemia, hypercholesterolemia, along with generation of elevated levels of uric acid may promote SBI is unknown yet. However, there are many ways through which generation of uric acid may affect the brain. The proposed mechanisms include enhanced inflammatory activity, increased action of free radicals, and reduction in insulin transport into the brain in the subjects with MetS (Lusis et al. 2008). Considering that the majority of SBI are caused by small vessel occlusion, the risk factors of lacunar infarctions can be the plausible suspects of SBI in MetS. Conversely, uric acid can also function as a pro-oxidant, either by generating radicals during its degradation or by stimulating NADPH oxidase (Sautin et al. 2007). Uric acid can also stimulate innate immunity through the effects of microcrystalline uric acid on the function of dendritic cells and T cells (Shi et al. 2006).

## 2.5 Conclusion

Although, glucose is metabolized by liver and brain tissues for energy production, but fructose is primarily metabolized by the liver. Unlike glucose, fructose is not utilized by the brain and does not stimulate insulin secretion, due to its hepatic metabolism and the low level of expression of the fructose transporter GLUT5 in pancreatic  $\beta$  cells. Metabolism of fructose differs from glucose not only in the involvement of different transporters but also in the first three enzymes involved in its metabolism. The enzyme fructokinase uses ATP to transform fructose into fructose



1-phosphate. Unlike enzymes associated with glucose metabolism (glucokinase and phosphofructokinase), which are regulated by ATP, the fructokinase is not regulated by ATP. This results in production of fructose-1-phosphate, depletion of ATP, and generation of AMP, which is then metabolized to uric acid. Uric acid causes proinflammatory effects on vascular cells and adipocytes. It also functions as an antioxidant. Uric acid also stimulates innate immunity through the effects of microcrystalline uric acid on the function of dendritic cells and T cells. In the liver, high-fructose flux also leads to enhanced accumulation of hepatic TAG resulting in impaired glucose and lipid metabolism and increase risk of MetS and cardiovascular diseases. Fructose produces damaging effects in hepatocytes, tubular cells, adipocytes, and intestinal epithelial cells because it is highly reactive as a reducing agent and a precursor of AGE. The liver promotes removal of high levels of fructose aggressively from the bloodstream to prevent the damaging effects of glycation/fructation on serum lipids and proteins. Glycated/fructated proteins not only show impaired functions but are also more susceptible to oxidative damage. Glycated/fructated proteins are ultimately converted into toxic AGEs. In humans, metabolism of high levels of fructose and generation of AGE are associated with increased total energy intake, body weight, visceral adiposity, insulin resistance, and dyslipidemia. These abnormalities contribute to the pathogenesis of obesity, diabetes, MetS, fatty liver, cardiovascular diseases, and neurological disorders. Accumulating evidence suggests that fructose is distinct from glucose in its ability to cause intracellular phosphate depletion, ATP depletion, and uric acid generation in the liver. High levels of intracellular uric acid, AGEs, and ROS can induce inflammatory effects and oxidative stress not only in vascular cells and adipocytes but also in the liver and brain.

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