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REVIEWS: CURRENT TOPICS

Diet and the role of 11β-hydroxysteroid dehydrogenase-1 on obesity

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Abstract

11β-Hydroxysteroid dehydrogenase-1 (11β-HSD-1) is a key regulatory enzyme in glucocorticoid metabolism, specifically in regulating intracellular concentrations of cortisol, the primary glucocorticoid. While the excessive level of circulating cortisol in Cushing's disease is of adrenal origin, it is the intracellular and not the systemic level of cortisol that is elevated in obesity. This tissue-specific dysregulation of glucocorticoids observed in obesity results from alterations in 11β-HSD-1 in both liver and mesenteric adipose. While cortisol has been identified as playing a permissive role in obesity, little is known about how diet may regulate message, expression and activity of 11β-HSD-1. In this review, we have integrated three lines of evidence that, taken together, suggest that dietary composition can play a primary role in promoting increased intracellular cortisol and in that way form the basis of a mechanism that results in excessive adiposity. We review evidence from studies of adrenalectomized rats, as well as studies linking 11β-HSD-1 to the pentose phosphate pathway and other metabolic pathways via the enzyme hexose-6-phosphate dehydrogenase. Emerging evidence from dietary manipulation experiments suggesting that macronutrient composition may elicit changes in 11β-HSD-1 and promote obesity is discussed.

Keywords: Stress hormones; Sugar; Cortisol; Sucrose; Fructose

1. The centrality of glucocorticoids in animal models of obesity

Most forms of obesity share a dependence on the availability of glucocorticoids, so named for their role in blood glucose maintenance [1]. Solomon and Mayer [2] and Yukimura and Bray [3] were first to implicate glucocorticoids as a necessary factor in genetic obesity, observing that obesity was prevented following bilateral adrenalectomy (ADX) and fully restored by glucocorticoid replacement. Analogous findings were reported for rats fed a cafeteria diet [4] and rats with electrolytic lesions of the ventromedial hypothalamic nuclei [5]. In lean rats, ADX causes an attenuation of the rate of weight gain and a shift in body composition to lessen carcass fat [6]. Whether or not ADX elicits a decrease of caloric intake and/or body weight appears to depend on the duration of the post-ADX observation period. Longer-term experiments typically report a significant reduction in intake and body weight, as well as a significant decrease in carcass fat. Glucocorticoid replacement reverses all of these phenomena [7–9].

1.1. Glucocorticoids and dietary obesity

There is far less known about the role of adrenal hormones and dietary obesity. ADX leptin-deficient (ob/ob) mice lose carcass fat, have normal glucose tolerance and maintain normal circulating insulin. However, when ADX ob/ob mice are fed a diet that is either high in glucose or fat, they retain their obese phenotype that includes hyperinsulinemia, excess body fat and abnormal glucose tolerance [10]. Kang et al. reported that a high-fat (HF), but not a high-glucose diet, allowed ADX ob/ob mice to maintain high levels of energy retention in the absence of hyperinsulinemia [11]. We have reported that HF diets attenuate the effects of ADX in both obese and lean Zucker rats [12] and that mice fed an HF diet maintain elevated levels of circulating leptin after ADX [13], once again illustrating that HF diets can reduce or reverse some of the effects of ADX. Similarly, ADX rats that are given access to a sucrose solution in addition to their customary chow diet are also normal with respect to corticotrophin-releasing factor and dopamine β-hydroxylase messenger RNA

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expression in the brain, food intake, caloric efficiency, fat deposition, and circulating triglyceride, leptin and insulin [14].

2. A novel hypothesis about glucocorticoids and obesity

Although glucocorticoid production and secretion are increased in human obesity, plasma cortisol levels in obese people are not consistently elevated [15]. This observation is congruent with the viewpoint that the steroids play only a permissive role in obesity. However, it has long been recognized that glucocorticoids have a profound influence on adipose tissue distribution and function as evidenced by Cushing's patients. This would imply that the relationship between body fat and glucocorticoids is more than simply permissive. Seckl et al. [16] have advocated an examination of the role of 11β-HSD-1 in obesity. 11β-HSD-1 controls intracellular glucocorticoid concentrations via its dehydrogenase and reductase activities. When 11β-HSD-1 acts as a dehydrogenase, it inactivates cortisol/corticosterone (human/rat). As a result, cortisol is converted into its inert 11-keto form (cortisone/11 dehydrocorticosterone). When 11β-HSD-1 acts as a reductase, the inactive metabolite is converted into active glucocorticoid. Adipose tissue taken from obese humans has three to four times the 11β-HSD-1 reductase activity of adipose taken from lean humans ([17]; refer to Table 1).

Mice that overexpress 11β-HSD-1 develop truncal obesity and display glucose tolerance, hyperphagia and elevated blood lipids and serum leptin [18]. Hence, these mice appear to be a close model to humans with Cushing's syndrome, a condition characterized by elevated circulating glucocorticoids and visceral obesity. Visceral obesity may be secondary to enhanced local activation of steroid via elevated levels and activity of 11β-HSD-1 in adipose tissue, which result in abnormally elevated levels of cortisol/corticosterone in adipose tissue. This obesity is distinct from that of Cushing's patients in that the source of the elevated glucocorticoids is adipose tissue as opposed to the adrenal cortex.

2.1. 11β-HSD-1 and tissue-specific regulation of glucocorticoid action

Two isozymes of 11β-HSD, 11β-HSD-1 and 11β-HSD-2, interconvert active glucocorticoid and its inactive 11-keto metabolite. 11β-HSD-2 functions primarily as a dehydrogenase in vivo, inactivating the hormone by converting the 11-hydroxy group to an 11-keto group. It is mainly expressed in mineralocorticoid target tissues, the kidney and the colon, where it protects the mineralocorticoid receptor from activation by glucocorticoids which are present at much higher concentrations than mineralocorticoids. 11β-HSD-2 is not expressed in the pituitary or most regions of the adult central nervous system. Recently, it has been suggested that the type 2 isoform may play a protective role by decreasing glucocorticoid action in adipocytes as transgenic mice that overexpress 11β-HSD-2 in adipose tissue are resistant to diet-induced obesity ([19]; refer to Table 1). 11β-HSD-2 mRNA has also been detected in the hypothalamus, suggesting that it may play a role in energy balance [20]. In contrast, 11β-HSD-1 functions predominantly as an oxidoreductase in vivo, generating active hormone from inactive metabolite. It is highly expressed in adipose, liver, pituitary and brain [21].

The search for an ideal selective pharmacological antagonist for 11β-HSD-1 is on-going. Glycyrrhetinic acid does inhibit 11β-HSD activity but without isoform specificity [22]. Much of what is known about 11β-HSD-1 therefore comes from studies of knockout (KO) mice or transgenic mice that overexpress the enzyme. Masuzaki et al. [18] reported that mice that overexpress 11β-HSD-1 under the control of the enhancer–promoter region of the adipocyte fatty acid-binding protein aP2 gene develop visceral obesity, impaired glucose tolerance, hyperphagia and elevated blood lipids and leptin. Overexpression of the enzyme is also associated with several other forms of human and rodent obesity (see below). 11β-HSD-1 KO mice have adrenal hyperplasia but attenuated glucocorticoid-induced activation of gluconeogenic enzymes in response to fasting, as well as lower glucose levels in response to stress [23]. It has been proposed that these mice might compensate for the mutation by increasing adrenal activity so as to maintain homeostasis. Consistent with this, Harris et al. [24] found that these KO mice have elevated plasma corticosterone and ACTH levels at the diurnal nadir as well as a prolonged corticosterone peak. Similar disruptions in glucocorticoid rhythmicity have been reported in human and rodent obesities. Further, the 11β-HSD-1 null mice have exaggerated ACTH and corticosterone responses to restraint stress, as well as impaired stress responsivity. We have observed a similar syndrome in intact Sprague–Dawley (S-D) rats fed an HF diet [25].

Kotelevtsev et al. [26] reported that 11β-HSD-1 KO mice have attenuated activation of the key hepatic gluconeogenic enzymes, glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (PEPCK). The mice are resistant to hyperglycemia induced by overnight fasting followed by placement in a novel environment. Importantly, giving access to an HF diet significantly lowered fasting plasma glucose in KO mice compared to wild-type controls. Morton et al. [27] found that 11β-HSD-1 KO mice exhibit an improved lipid profile and increased hepatic insulin sensitization. Specifically, the mice have lower plasma triglyceride levels, increased hepatic expression of the fat-catabolizing enzymes, carnitine palmitoyltransferase-I, acyl-CoA oxidase and uncoupling protein-2, increased HDL cholesterol and elevated liver mRNA and serum levels of apolipoprotein A-I. In summary, these studies collectively imply that the 11β-HSD type 1 isoform is important in energy homeostasis and that the null mutant adopts compensatory responses in systems implicated in several different models of obesity.

Correlational studies also indicate that 11β-HSD-1 is overexpressed in both human and rodent obesities. For example, Aoki et al. found that insulin-resistant diabetic C57BL/KsJ-db/db mice have higher blood glucose, plasma insulin and corticosterone, in addition to increased 11β-HSD-1

Table 1
Summary of data implicating local glucocorticoid metabolism in obesity and obesity-related disturbances

Species	Treatment/condition	Phenotypic and physiological changes	Known dietary influences
Human	Cushing's syndrome	Adrenal overproduction of cortisol; subsequent elevation of systemic GC levels Visceral obesity, glucose intolerance Depression, excessive hair growth, irregular periods or amenorrhea in women, infertility in men Elevated blood pressure	
Human	Obesity	Elevated 11β-HSD type 1 activity in subcutaneous tissue in women; activity positively correlated to BMI [34]	
Mouse	11β-HSD type 1 KO	Adrenal hyperplasia, attenuated GC-induced activation of gluconeogenic enzymes in food-deprived state, decreased glucose levels in response to stress [26,23] Elevated plasma corticosterone and ACTH at diurnal nadir; prolonged peak [24] Improved lipid profile, increased hepatic expression of fat catabolizing enzymes (carnitine palmitoyltransferase-I, acyl-CoA oxidase, uncoupling protein-2), increased HDL, elevated hepatic mRNA and serum apolipoprotein A-I levels [27]	HF diet lowers fasting plasma glucose levels [26]
Mouse	Overexpression of 11β-HSD type 1 in adipose	Truncal obesity, glucose intolerance, hyperphagia and elevated serum lipids and leptin [18]	
Mouse	Overexpression of 11β-HSD type 2 in adipose	Reduced fat mass accumulation on HF diet; associated with decreased food intake, increased energy expenditure, improved glucose tolerance and insulin sensitivity [19] Decreased adipose tissue gene expression of leptin and resistin and increased expression of adiponectin, peroxisome proliferator-activated receptor γ and uncoupling protein-2 [19].	Resistance to diet-induced obesity on HF diet [19]
Mouse (ob/ob)	ADX	Loss of carcass fat; normal glucose tolerance, normal circulating insulin levels [10]	HF diet—obese phenotype maintained including glucose tolerance [10,11] High—obese phenotype maintained including impaired glucose tolerance [10]
Rat	ADX	Decreased weight gain; decreased body fat [6]	HF diet reverses some effects of ADX, including elevated leptin levels [13] Sucrose access restores CRF and β-hydroxylase mRNA levels in brain, food intake, caloric efficiency, fat deposition and systemic TG, leptin and insulin [14]
Rat (fa/fa)	Obesity	Increased 11β-HSD type 1 activity in omental fat; enhanced activity reversed by ADX [29]	

activity and elevated hepatic 11β-HSD-1 mRNA levels compared to db/+m heterozygote controls [28]. They suggested that the increased hepatic corticosterone concentration may antagonize the action of insulin and cause insulin resistance. Livingstone et al. [29] reported that 11β-HSD-1 activity in omental fat excised from obese male Zucker rats is double that of lean controls. They also found that ADX reversed the difference in 11β-HSD-1 activity observed between obese and lean Zucker rat omental fat. Paulmyer-Lacroix et al. [30] reported that 11β-HSD-1 mRNA expression is increased by more than 2.5-fold in the stromal compartment of visceral adipose tissue compared with subcutaneous adipose tissue. They also reported that 11β-HSD-1 was increased in mature adipocytes taken from abdominal subcutaneous and visceral fat depots of obese patients when compared to lean controls. Similarly, Rask et al. [17] found that obese women have elevated 11β-HSD-1 activity in subcutaneous adipose tissue when compared to lean controls and that the activity of the enzyme positively correlates with body mass index.

11β-HSD-1 obviously plays an important role in normal cell functioning. Bujalska et al. [31] compared human omental to subcutaneous adipose stromal cells and observed that 11β-HSD-1 activity in omental stromal cells increases during differentiation into mature adipocytes. 11β-HSD-1 activity acts primarily as a dehydrogenase (converting the active hormone to inactive metabolite) in preadipocytes, yet the opposite is true in mature adipocytes. They suggest that the oxidoreductase activity of 11β-HSD-1 ensures the local generation of active steroid and in that way further induces adipocyte differentiation. Yau et al. [32] used 11β-HSD-1 KO mice to study aging-related hippocampal changes that are thought to be caused by excess corticosterone. Unlike wild-type controls, these KO mice perform significantly better in a Morris water maze, suggesting that age-related learning deficits that are thought to be the result of high

levels of corticosterone exposure are ameliorated with deactivation to 11-dehydrocorticosterone.

2.2. The regulation of 11β-HSD-1 activity vs. 11β-HSD-1 message

Despite rapid advances in our appreciation of the role of this enzyme, there is still little that is known about the factors that regulate its dehydrogenase and reductase activities. Increased 11β-HSD-1 message, protein and activity in the omental or mesenteric fat of obese patients and genetically obese rats, respectively, are thought to promote elevated intracellular glucocorticoid concentrations in a tissue-specific manner. Genetically engineered mice that overexpress the enzyme in omental adipose become obese. HF diets promote transient increases in circulating corticosterone, increased circulating insulin and insulin resistance, as well as increased circulating leptin [33]. Any one of these factors might promote the increased oxidoreductase activity of 11β-HSD-1 reported in obese humans [34]. Similarly, increased oxidoreductase activity (and not just increased message/protein) may be the consequence of any one of these variables that are affected by an HF diet or may result from increased substrate availability for 11β-HSD-1 caused by changes in intermediary metabolism.

2.3. Hexose-6-phosphate dehydrogenase and its role in glucocorticoid metabolism

Hexose-6-phosphate dehydrogenase (H6PDH) and its putative "cooperativity" with 11β-HSD-1 within the lumen of the endoplasmic reticulum (ER) has become an active area in the search for a mechanism to explain the tissue-specific regulation of 11β-HSD-1 activity. H6PDH, the microsomal analogue to cytosolic glucose-6-phosphate dehydrogenase (G6PDH), generates a pool of reduced nicotinamide adenine dinucleotide phosphate [NADP(H)] that plays a critical role in determining the set point for 11β-HSD-1 reductase activity [35,36]. H6PDH catalyzes the first two (including the rate-limiting) steps of the pentose phosphate pathway within the ER, while G6PDH serves as the first and rate-limiting enzyme of the same pathway in the cytosol. H6PDH also differs from G6PDH in that it has broad substrate specificity and can use various hexose-phosphates. Investigations into the underlying genetics of cortisone reductase deficiency (CRD), in which activation of cortisone to cortisol does not occur, led to the discovery of not only a defect in the gene HSD11B1 but also of mutations in the gene H6PDH [37]. These mutations in individuals with CRD follow a triallelic digenic model of inheritance and result in low 11β-HSD-1 expression as well as a decrease or complete absence of NADPH generation in the ER. Preliminary support for this relationship came from the much earlier observation that H6PDH is localized in steroidogenic cells, liver cells and renal tissue [38], where 11β-HSD-1 is also highly expressed. Lavery et al. [39] generated H6PDH KO mice and showed that H6PDH null mice were unable to convert inactive 11-dehydrocorticosterone to corticosterone, while dehydrogenase activity increased, ultimately leading to decreased circulating levels of active glucocorticoid. Bujalska et al. [40] reported the same effects in CHO cells that were first transfected with 11β-HSD-1 cDNA and then transfected with H6PDH siRNA.

It is generally accepted that cellular membranes are relatively impermeable to pyridine nucleotides, which led to the initial suggestion that the two enzymes generate reduced NADPH from separate pools of NADP+. This has recently been challenged by McCormick et al. [41] who found that cytosolic pentose phosphate pathway flux can also impact 11β-HSD-1 activity in rat adipocytes and microsomes. In support of the hypothesis that NADPH generated within the lumen of the ER is the key source of cofactor for 11β-HSD-1, Bánhegyi et al. [42] showed cooperativity between 11β-HSD-1 and H6PDH in liver via the inhibition of the glucose-6-phosphate transporter (G6PT) by S3483. Both inhibition of G6PT and the absence of glucose-6-phosphate as substrate led to significantly reduced cortisone activation and H6PDH activity in isolated rat liver microsomes. Enzyme activity studies confirming the presence of distinct intralumenal and cytosolic pools of pyridine nucleotide in the hepatic ER [43] and ER of adipocytes [44] provide additional support for the close relationship between 11β-HSD-1 and H6PDH.

This body of research demonstrates that 11β-HSD-1 activity is dependent on the activity of H6PDH, which is reliant on the availability of its substrate, primarily glucose-6-phosphate. While there is evidence to suggest that diet and macronutrient composition can influence glucocorticoid metabolism and carbohydrate intake can impact pentose phosphate pathway flux [45], it is not clear how intake is involved in changing the activity or expression levels of these enzymes. Additionally, there is no clear mechanism to explain how 11β-HSD-1 or H6PDH expression and/or activity levels are increased or decreased in a tissue-specific manner in obesity.

3. Influence of diet on message, expression and activity of 11β-HSD-1

3.1. High-fat diets

Obesogenic diets, including HF diets, may impact glucocorticoid metabolism via their impact on 11β-HSD-1. Rodent studies suggest that inhibition of 11β-HSD-1 may be useful in protecting against HF diet-induced obesity. 11β-HSD-1 null mice demonstrate resistance to diet-induced obesity when fed an HF diet ([7,46]; refer to Table 1). Morton et al. [46] showed that 11β-HSD-1 activity is lower in subcutaneous, epididymal and visceral fat depots in obesity/metabolic syndrome-resistant (A/J) mice compared to 11β-HSD-1 activity levels in C57BL/6J Lep ob/ob mice, a strain prone to obesity. Transgenic mice that overexpress 11β-HSD-1 in mesenteric adipose display phenotypic and metabolic disturbances that favor obesity, including increased 11β-HSD-1 activity in subcutaneous and epididymal fat (2.4- and 2.7-fold, respectively) [18]. This is comparable to what is observed

in obese vs. lean humans. Fat accumulation in the abdominal region of transgenic mice fed a low-fat diet (10% fat) was comparable to that of nontransgenic mice fed an HF diet (45% fat), and this disproportionate accumulation of adipose tissue in visceral depots was even more exaggerated when the transgenic mice were fed the HF diet. This work cumulatively supports the notion that 11β-HSD-1 levels and/or activity can predispose rodent models to increased adiposity. There is, however, no evidence to suggest HF diets in the absence of specific genetic background can impact tissue-specific 11β-HSD-1 message, expression or activity.

One recent clinical trial suggests that percentage of energy from dietary fat can affect glucocorticoid metabolism independent of fat loss. Stimson et al. [47] showed that healthy obese men fed either ad libitum or isocaloric HF, low-carbohydrate diets (HFLC) (66% and 4%, respectively) had increased cortisol appearance and reduced urinary excretion of cortisol metabolites compared to their counterparts on ad libitum or isocaloric moderate-fat, moderate-carbohydrate (MFMC) diets (35%:35%). While weight loss was higher among the HFLC diet group, no differences in loss of fat mass were observed between the HFLC and MFMC groups, and changes in cortisol metabolism were deemed independent of weight loss. This suggests differential regulation of cortisol metabolism as a result of macronutrient composition of diet.

Adult male S-D rats fed an HF, high-sucrose diet in addition to an 11β-HSD-1 inhibitor (a 4-heteroarylbicyclo [2.2.2]octyltriazole) for 3 weeks had similar body weight and food intake as controls fed the same diet but had reduced mesenteric adipose and adipose cell size [48]. Interestingly, the inhibition of 11β-HSD-1 decreased the message level of enzymes involved in lipid synthesis [fatty acid synthase (FAS), stearoyl-CoA desaturase 1, diacylglycerol acyltransferase 1] and fatty acid cycling (adipose triglyceride lipase, PEPCK), while concomitantly increasing the message of fatty acid oxidation-promoting carnitine palmitoyltransferase I. While these data suggest diet-induced changes in accumulation of fat mass via a glucocorticoid driven mechanism, it is not clear how dietary macronutrient composition might play a role in the observed metabolic changes.

Macronutrient composition of diet (specifically carbohydrate content) has also been found to influence glucose homeostasis and lipid metabolism, yet a direct effect of carbohydrate intake on glucocorticoid metabolism has not been elucidated. When provided with access to solutions of sucrose, fructose or glucose, rats increase their energy intake by 10–20% above what they would consume if provided with rat chow alone [49]. Simple sugars have been shown to stimulate hepatic de novo lipogenesis, making them a likely candidate for promoting the fasting hypertriglyceridemia that has been associated with high-sucrose or high-fructose diets [50]. Minehira et al. [51] examined markers of whole body de novo lipogenesis and lipogenesis in subcutaneous adipose in response to two 4-day dietary interventions in 9 healthy lean subjects (male n=5, female n=4): (1) isocaloric feeding (100% of energy requirement with 50% of total energy as carbohydrate, 35% as lipid and 15% as protein) or (2) carbohydrate overfeeding (175% of energy requirement with 71% as carbohydrate, 20% as lipid and 9% as protein). Carbohydrate overfeeding increased basal and postglucose energy expenditure as well as net carbohydrate oxidation, while whole body net de novo lipogenesis after glucose loading was markedly increased at the expense of glycogen synthesis. mRNA levels for sterol regulatory element-binding protein-1c, acetyl-CoA carboxylase (ACC) and FAS were increased significantly by carbohydrate overfeeding. In a similar study of lean vs. overweight individuals, Minehira et al. [52] found that carbohydrate overfeeding did not stimulate whole body net de novo lipid biosynthesis nor expression of the lipogenic enzymes ACC and FAS or SREBP-1c in adipose to a greater extent in overweight compared to lean individuals. While both fructose and glucose stimulate SREBP-1c, which regulates de novo lipogenesis, both SREBP-1c and de novo lipogenesis are more strongly induced by fructose than glucose, providing evidence that different sugars can differentially regulate lipid metabolism [51]. When S-D rats are given long-term free access to standard chow as well as 32% sucrose, 32% fructose or 32% glucose solutions, or granulated sucrose, they exhibit differential responses [49]. While all sugar-fed rats have decreased glucose tolerance and increased weight gain and retroperitoneal fat, sucrose-fed rats have significantly more brown adipose tissue than either control or fructose-fed rats. Fructose-fed rats have elevated serum triglycerides compared to the others. Importantly, while the mechanism is unclear, these data indicate that different sources of dietary sugars appear to have different metabolic consequences.

Kyoto Wistar (WKY) and spontaneously hypertensive rats (SHR) fed fructose-enriched diets for 14 days exhibit significant increases in plasma insulin and triglyceride concentrations in addition to elevated blood pressure [53]. Similar results have also been reported in S-D rats fed a high-fructose diet [54]. Reaven et al. showed that SHR and WKY rats given ad libitum access to a diet composed of 66% fructose, 12% fat and 22% protein respond similarly. However, increases in blood pressure and plasma triglycerides were higher in the SHR rats. These data suggest not only a direct influence of dietary fructose on markers of lipid metabolism and blood pressure but also that underlying genetic background interacts with the carbohydrate composition of diet.

In their summary of recent findings about the short- and long-term metabolic effects of fructose in humans and rodents, Lê and Tappy find that the consumption of large quantities of fructose can lead to the development of a complete metabolic syndrome in rodents that includes hepatic and extrahepatic insulin resistance, dyslipidemia and high blood pressure irrespective of the fact that dietary fructose does not directly elicit insulin secretion. Short-term moderate- to high-fructose intake in humans can lead to elevated plasma triglycerides and changes in hepatic glucose homeostasis as well as adipose tissue insulin resistance but does not appear to elicit muscle insulin resistance or elevated blood pressure [55].

High fructose intake may contribute to postprandial lipemia via changes in the partitioning of fatty acids toward esterification. A randomized crossover study of 14 healthy subjects given test meals of either labeled fructose or glucose in addition to labeled palmitate showed that respiratory quotient and plasma triacylglycerol and VLDL-triacylglycerol were significantly higher in those administered the fructose meal. The concentrations of both insulin and labeled palmitate in nonesterified fatty acids were lower after fructose than after glucose meals [56]. This suggests that decreased insulin stimulation after fructose may cause less lipoprotein lipase activation in adipose tissue and, as a result, impaired triacylglycerol clearance.

3.2. Do dietary components, particularly CHO, influence the hypothalamic-pituitary-adrenal axis?

While evidence supports the differential effect of macronutrient composition on both lipid and glucose metabolism, it is not clear what role glucocorticoids and 11β-HSD-1 might play. ADX in a rat model has been shown to have a profound effect on the hypothalamic-pituitary-adrenal (HPA) axis, namely, by increasing ACTH secretion and sympathetic activity and decreasing food intake and weight gain [57]. Laugero at al. [14] found that voluntary consumption of sucrose solution, but not nonnutritive saccharin solution, can reverse the effects of ADX in rats by restoring corticotrophin-releasing factor (CRF) and dopamine-β-hydroxylase mRNA levels in brain. Voluntary sucrose solution intake also restores food intake, weight gain and circulating triglyceride, leptin and insulin levels in ADX rats suggesting that dietary sugar can trigger enhanced peripheral glucocorticoid production and/or affect behavior to compensate for the absence of adrenal activity. More recently, we have shown that rats given free access to 16% sucrose solution in addition to chow and water for 10 weeks have increased 11β-HSD-1 and H6PDH message in mesenteric adipose [45]. These changes in adipose are accompanied by a decrease in 11β-HSD-1 message and increase in H6PDH message in liver in comparison to controls given ad lib access to chow and water. Further, we show that while there are no differences in weight gain among the control and sugar-fed groups after 6 weeks of sucrose access, the sucrose-fed rats have significantly higher percentage of body fat. We have also found that sucrose, fructose and glucose have differential effects on the message of 11β-HSD-1 and H6PDH in adipose and liver in as little as 1 week of access to sugar solutions (previously unpublished data). These data suggest that alterations in the message of enzymes related to glucocorticoid metabolism may result from dietary manipulations and not solely changes in body composition or increased adiposity.

4. Conclusion

It is clear that glucocorticoids are involved in obesity, especially diet-induced obesity. Although elevated circulating corticosterone is not a defining characteristic of all obesities, the steroid nevertheless plays a critical role in its etiology. One plausible hypothesis that links these phenomena is a dysregulation of local levels of active steroid via altered activity of the enzyme 11β-HSD-1. A major tenet of the pathway proposed herein (Fig. 1) is that enzyme activity is induced in specific tissues by consumption of high-sugar diets.

Results from our laboratory point to sucrose as a particularly effective dietary component that is capable of altering 11β-HSD-1 message and at the same time promoted increased adiposity. Our preliminary inquiries suggest that NADPH is an essential trigger in promoting the oxidoreductase activity of 11β-HSD-1.

It has long been known that sucrose spares ADX-induced body weight and body fat loss [14]. London et al. [45] more recently demonstrated that sucrose promoted a decrease in hepatic 11β-HSD-1 message and simultaneously an increase in 11β-HSD-1 message in mesenteric adipose tissue. This difference in the effect of sucrose on 11β-HSD-1 in liver and in adipose has not been thoroughly explained. Increase adipose 11β-HSD-1 is thought to promote increased intracellular cortisol/corticosterone concentrations. The active hormone is then thought to be transported to the liver, where it can participate in both the up-regulation of PEPCK and subsequent increased gluconeogenesis. Decreased liver 11β-HSD-1 message is likely to be the consequence of down-regulation resulting from the influx of cortisol/corticosterone stemming from adipose (see Fig. 1). What is interesting is that both adipose and liver have increased H6PDH message in response to sucrose. Work being conducted in our laboratory suggests that acute (24 h) access to sucrose fails to induce all of these changes (London et al., in preparation).

Havel [50] has suggested a second explanation of why sucrose access results in obesity. He notes that fructose (a component of sucrose) bypasses the key glycolytic enzyme phosphofructokinase, thereby providing unregulated supply of glycerol-3-phosphate and acetyl-CoA so as to favor increased lipogenesis. We have suggested that the sucrose induced enhanced H6PDH message found in liver may help promote lipogenesis by increasing available NADPH. Thus, sucrose access favors obesity by having profound effects on both hepatic glucose production and at the same time increased lipogenesis. Perhaps this dual-effect accounts for why access to glucose fails to promote comparable levels of obesity since dietary glucose is subject to tighter metabolic regulation.

Two sources of evidence have helped to identify the interactions between intracellular glucocorticoid concentrations, diet and body composition (see Table 1). The first set of evidence has been derived from observations of tissue-specific changes in 11β-HSD-1 expression that have been observed in human obesity. The second has come from studies manipulating the expression of 11β-HSD-1 in animal models. Studies of animal models make it clear that the enzyme has pervasive effects throughout the animal. 11β-HSD-1 KO mice show perturbations in the HPA axis including adrenal hyperplasia [23,26] and disruptions in the normal diurnal nadirs and peaks of both corticosterone and ACTH [24]. Additionally, these

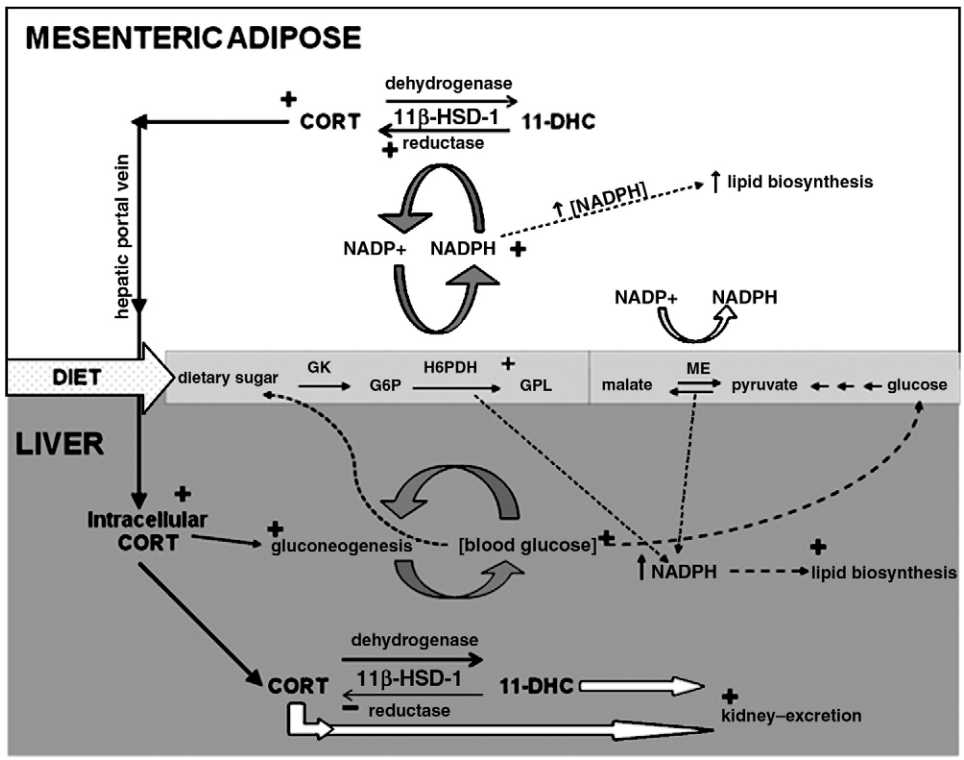

Fig. 1. Proposed pathway for high-sugar diet-induced dysregulation of glucocorticoid metabolism. It is hypothesized that a high-calorie, high-sugar diet increases pentose phosphate pathway (PPP) flux. As shown, microsomal PPP flux directly increases H6PDH activity, thereby increasing NADPH production in both mesenteric adipose and liver. In adipose, we propose increased NADPH promotes increased reductase activity of 11β-HSD-1, which in turn leads to increased cortisol levels. Excess cortisol drains into the liver via the hepatic portal vein where it increases cortisol concentrations and triggers an inappropriate increase in gluconeogenesis via up-regulation of PEPCK. This increase in glucose production provides additional substrate for glycolysis and Krebs cycle, PPP and lipid biosynthesis. We hypothesize that 11β-HSD-1 is down-regulated in liver as a compensatory mechanism resulting in decreased enzyme expression and reduced reductase activity. In turn, enhanced excretion of cortisol metabolites occurs. The overall increase in NADPH in liver may promote enhanced lipid biosynthesis, thereby raising blood triglycerides and promoting fat storage. CORT, corticosterone; 11-DHC, 11-dehydrocorticosterone; GK, glucokinase (or hexokinase); GPL, phosphogluconolactone; G6P, glucose-6-phosphate; ME, malic enzyme.

11β-HSD-1 null mice have improved lipid profiles and enhanced expression of fat catabolized enzymes in liver [27]. Conversely, overexpression of 11β-HSD-1 in adipose of mouse results in hyperphagia, truncal obesity, glucose intolerance and elevated levels of serum lipids and leptin [18]. These observations parallel the enhanced 11β-HSD-1 activity in adipose that has been reported in both human obesity [34] and obese rats [29]. This obesity-linked enhancement in 11β-HSD-1 activity in obese rats is effectively reversed by ADX [29]. ADX also decreases body fat and weight gain in ob/ob mice [10] and wild-type rats [6], and administration of an HF diet maintains the obese phenotype and reverses many of the effects of ADX in both a mouse and rat model [10,11,13]. Laugero et al. [14] showed that sucrose access in ADX rats can similarly restore food intake, caloric efficiency, fat deposition, TG, leptin and insulin, and impacts the HPA axis. Interestingly, adipose-specific overexpression of 11β-HSD-2 in mice confers protection against diet-induced obesity in mice fed HF diet characterized by reduced food intake, reduced fat mass accumulation, increased energy expenditure, improved insulin sensitivity and glucose tolerance [19]. These examples illustrate the interplay between diet and glucocorticoid metabolism as well as the potential for obesity intervention by targeting both isoforms of 11β-HSD.

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