Role of Corticosterone and Expression of 11 β-Hydroxysteroid Dehydrogenase Type 1 in Liver on Post-Exercise Hyperglycemia in the Obese Diabetic Mouse

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Abstract

Exercise training is recommended for the treatment of diabetes mellitus for the benefits on blood glucose control, obesity, and cardiometabolic risk factors. Exercise decreases adipose tissue content and fasting blood glucose, and improves insulin sensitivity. The diet-induced or spontaneous insulin-resistant obese and diabetic rat models to study the effects of exercise training have been widely used because of the favorable outcome on glucose homeostasis. However, the effects of exercise on overall glucose control in the db/db mouse of diabetes remain unclear. The db/db mouse resembles the human condition of type 2 diabetes mellitus and is characterized by hyperleptinemia, hyperglycemia and obesity resulting from a mutation in the leptin receptor gene. The db/db mouse exhibits hypercorticosteronemia, which is also reflective of the human condition. Depending on the exercise training regimen, glucose metabolism is either slightly improved or is further compromised. In this communication, the effects of voluntary and forced treadmill exercise running on glucose control in the db/db mouse are mentioned. In addition, the effects of acute exercise on glucose homeostasis are discussed, along with potential mechanisms explaining the post-exercise hyperglycemia seen in the db/db mouse.

Keywords: Exercise; db/db mouse; 11β-hydroxysteroid; Dehydrogenases; Gluconeogenesis; Leptin; Corticosterone

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) has reached pandemic levels in the last decade in developed and developing countries as a result of increased obesity rates. The association between T2DM and cardiovascular diseases is well-established, and diabetics are at increased risk of myocardial infarct, heart failure and sudden death compared to no diabetics [1]. Obese diabetics also present with dysregulation in white adipose tissue metabolism, such as aberrant production of leptin [2]. Leptin is an adipocyte-derived peptide that circulates in the plasma at levels proportional to amount of adipose tissue content. This peptide has a key role in the regulation of energy intake and satiety through central mechanisms as well as peripheral actions on energy expenditure. Excessive secretion of this adipokine from adipose tissue, as expected, can potentially lead to leptin resistance or hyperleptinemia in T2DM. Common sequelae of hyperleptinemia include failure to regulate food intake, aberrations in energy homeostasis and fat distribution, worsening of the diabetic state and the development of other cardiovascular risks factors such as lipid disorders and hypertension [3]. The risk of cardiovascular disease and associated cardiometabolic burdens can be largely prevented by implementation of effective non-pharmacological approaches, such as increasing the level of physical activity [4]. Advances in our understanding of the role of exercise, from both a mechanistic aspect and application to lifestyle modification in patients with T2DM is clearly dependent on the use of relevant animal models [5]. In this review, the use of the hyperleptinemic db/db mouse model of T2DM in exercise-based studies is discussed as well as the potential involvement of endogenous glucocorticoids and the cortisol-cortisone shunt in the regulation of glucose metabolism in this model.

Benefits of Exercise in T2DM

Regular physical activity is recommended for the treatment of T2DM, obesity, and related metabolic disorders. Exercise performed on a regular basis increases muscle content, improves blood glucose control, lowers plasma lipids and blood pressure, and increases insulin sensitivity [6,7]. Impaired mitochondrial dysfunction and energy metabolism can be improved, leading to enhanced exercise capacity for the diabetic patient [8,9]. Deflections in postprandial hyperglycemia and impaired fasting glucose, both risk factors in the development of cardiometabolic disorders can be prevented with exercise training [10]. Controlling blood glucose levels by exercise delays the progression of long-term complications of symptomatic cardiovascular disease and protects against the development of type 2 diabetes independent of obesity, age, history of hypertension and parental history of diabetes [6].

The db/db Mouse Model

Rodents because of their size, easy handling, affordable costs, and rapid maturation rates remain the obvious choice as model to examine the role of exercise on the diabetic state. Further, the variety and availability of inbred strains make them ideal for study because of the genetic uniformity as well as the predictable phenotypes that gradually develop over a short period of time. Various models and strains of diabetic and obese rodents are available for exercise-based studies, including the diet-induced model (DIO), low-dose streptozotocin (STZ) model, Zucker diabetic fatty and spontaneous insulin resistant models of type 2 diabetes [5]. These commonly used models are responsive to the stimulus of exercise and have provided valuable information on

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the consequences of exercise training on cardiovascular and metabolic outcome in the diabetic state [11-15]. For these reasons, the use of these particular models is justified in exercise studies and for translational-based application in the treatment of humans with this metabolic disorder. However, in recent years, the use of the db/db mouse model of diabetes to investigate the impact of exercise training has gained popularity. Yet, since the early studies by Coleman and colleagues in the mid-1960s and 1970s characterizing the metabolic and endocrine profile of the db/db mouse [16-18], this model is still underrepresented compared to the other rodent models used in exercise studies. The db/db mouse is a model of T2DM and is considered a close counterpart to the human condition in terms of presenting phenotype, metabolic and cardiovascular perturbations. Diabetic-related complications in the db/db mouse result from the long-lasting effects of a mutation in the leptin receptor gene (LepR$^{db/db}$) disrupting post-receptor signaling [19]. This mutation affects hypothalamic responses to food intake, leading to hyperphagia and the gradual development of obesity. By 2-3 weeks of age, db/db mice show signs of insulin resistance and from 4 weeks of age are hyperglycemic. The db/db mouse also exhibits hypercorticosteronemia (hypercortisolemia in humans) as a result of hypertrophy of the adrenal cortex [18], a well-established risk factor associated with the development of insulin resistance and hyperglycemia [20,21]. Another hallmark feature of the db/db mouse, as expected, is hyperleptinemia from defective leptin signaling. This rarely is the underlying cause of diabetes but nonetheless observed in the obese diabetic patient [22].

The db/db Mouse and Exercise Training

Treadmill running remains the preferred exercise paradigm for training in rodents. The duration and intensity of exercise can be easily manipulated keeping the overall training volume identical in experimental groups. Oxygen consumption of mice and hence intensity of effort can be estimated simply based on treadmill belt speed without the need for direct measurement of oxygen use in each mouse [23], another reason why this form of exercise is considered the paragon of excellence in exercise physiology. Treadmill running comes with its drawbacks however, including motivation, innate low ambulatory function for some mice strains, and increased stress. Constant monitoring is also needed to avoid injury of mice with low ambulatory activity.

Assessing the effects of exercise training on glucose control in the db/db mouse was first addressed using swim training as regimen [24]. Combination of low and moderate swim training intensity over a period of 4 weeks decreased blood glucose concentrations but db/db mice remained hyperglycemic, hyperinsulinemic, and insulin resistant to an oral glucose challenge. Diabetic mice exhibited the typical obesity of this model after swim training despite a slight decrease in weight gain. However, when db/db mice were treated with common antihyperglyemic agents, an improvement in blood glucose and insulin concentrations was observed. Regardless of these negligible effects of blood glucose regulation with exercise alone, more recent studies have shown that mild-to-moderate exercise training is of benefit on vascular function and lipid metabolism. In fact, 5 weeks of voluntary wheel running improved vascular endothelial function and decreased common lipid levels, but failed to reduce body weight and correct plasma glucose concentrations [25]. Could these negligible effects of training on glycemic control and body weight be the result of a low training stimulus or work volume and can the diabetic state be improved simply by increasing the intensity of the training?

To address this, we exposed db/db mice to voluntary wheel running and forced treadmill running for a period of 12 weeks [26]. The training regimen for mice assigned to the treadmill running group was designed to elicit a greater stimulus based on intensity and training volume (3-fold higher than voluntary running), and with expectations that this would decrease both the obesity and hyperglycemia in db/db mice. After 12 weeks of voluntary wheel running, body weight dropped by ~5% while fasting blood glucose levels decreased by ~21% compared to sedentary db/db mice (Figures 1 and 2). Forced treadmill running however, did not overcome the disturbances associated with the db/db mouse. In fact, both body weight and blood glucose were increased by ~8-10% and mice remained insulin resistant (Figure 3). When the data was expressed as percent change from the onset of exercise training, the greatest changes in body weight and fasting blood glucose levels were observed in db/db mice subjected to treadmill running (Table 1). Based on these observations, increasing the training volume by altering intensity does not always correlate with greater weight loss and improved metabolic control in the db/db mouse. Results from earlier studies in obesity models have suggested that an exaggerated stress response associated with forced treadmill exercise could explain these unfavorable changes in the db/db mouse. Daily short-term exposure to stress can induce adrenal gland hypertrophy and disruption
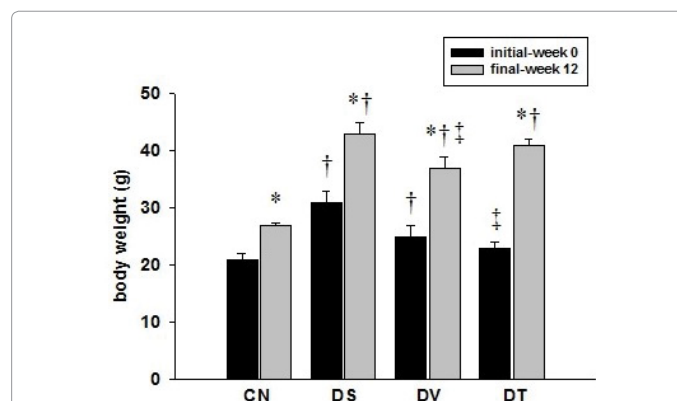

Figure 1: Changes in body weight in lean and diabetic mice with exercise training. Exercise training was performed over a period of 12 weeks.

CN: Lean Control; DS: Diabetic Sedentary; DV: Diabetic Voluntary Running Mice; DT: Diabetic Treadmill Running Mice. Values are reported as mean ± SEM for 12 to 18 mice per group. *: Compared to initial week 0; †: Compared to CN mice; ‡: Compared to DS mice
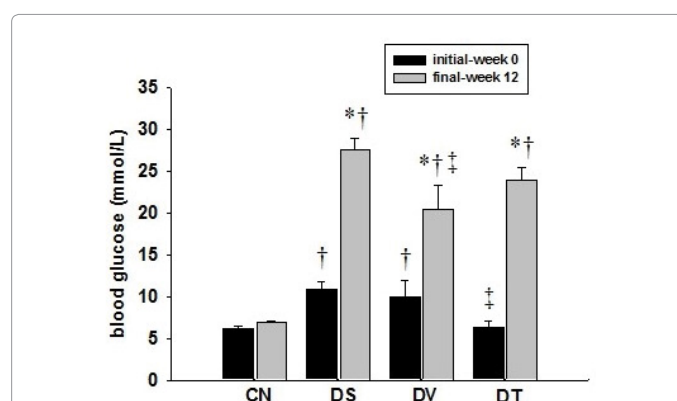
Figure 2: Changes in fasting blood glucose concentrations in lean and diabetic mice with exercise training. Exercise training was performed over a period of 12 weeks.

CN: Lean Control; DS: Diabetic Sedentary; DV: Diabetic Voluntary Running Mice; DT: Diabetic Treadmill Running Mice. Values are reported as mean ± SEM for 12 to 18 mice per group. *: Compared to initial week 0; †: Compared to CN mice; ‡: Compared to DS mice
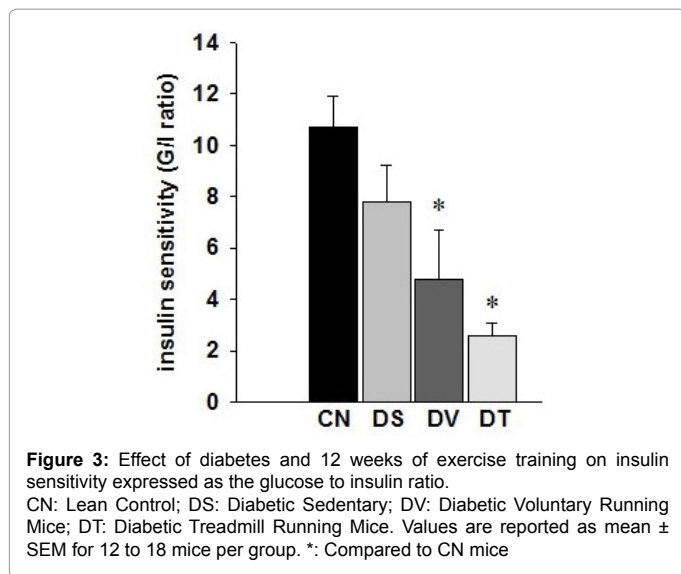
Figure 3: Effect of diabetes and 12 weeks of exercise training on insulin sensitivity expressed as the glucose to insulin ratio.
CN: Lean Control; DS: Diabetic Sedentary; DV: Diabetic Voluntary Running Mice; DT: Diabetic Treadmill Running Mice. Values are reported as mean ± SEM for 12 to 18 mice per group. *: Compared to CN mice

Group	Percent change in body weight	Percent change in blood glucose
Lean control	40 ± 1	19 ± 1*
Diabetic sedentary	45 ± 2	187 ± 6*
Diabetic voluntary	61 ± 4*†	185 ± 21*
Diabetic treadmill	83 ± 2*†‡	327 ± 13*†‡

Values are reported as mean ± SEM from 12-18 mice in each group and expressed as percent change from the week 1. C57BL/KsJ-lept^{db}-lept^{db} mice were used [26]. *: Compared to lean control. †: Compared to sedentary diabetic mice. ‡: Compared to diabetic voluntary runners.

Table 1: Percent changes in body weight and blood glucose levels after 12 weeks of exercise training in control and diabetic mice.

of the hypothalamus pituitary-adrenal axis (HPA), further increasing the susceptibility of the obese diabetic mouse to metabolic aberrations [27-29].

The Corticosterone Response to Exercise in the db/db Mouse

Supporting the link between the stress imposed by daily forced running and metabolic perturbations are the findings that treadmill exposure is associated with increased corticosterone secretion, elevated activity of the renin-angiotensin system, and insulin resistance [20,27-29]. Hedonic feeding behavior is also reported after the cessation of exercise [30], disrupting central signaling mechanisms in the regulation food intake which are already affected by leptin resistance. Enhanced endogenous glucocorticoid synthesis from hypertrophy of the adrenal gland is an inherent feature of the db/db mouse [16-18] and our earlier studies highlight the importance of this feature on dysregulated glucose control during and after acute exercise as well as in response to chronic training (Table 2). Acute treadmill exercise is associated with greater corticosterone synthesis and lipolysis in db/db mice when compared to heterozygote lean controls derived from the same strain, leading to post-exercise hyperglycemia [31]. The increase in corticosterone production in the db/db mouse after exercise was not caused by activation of the HPA axis because release of both corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) levels were reciprocally decreased, indicating no disruption in feedback regulation. Corticosterone synthesis and spillover in urine are elevated in db/db mice after treadmill running compared to voluntary running, suggesting that db/db mice exhibit a greater stress response to treadmill running [32] (Table 3). A sympathetic nervous system response may

further contribute to increased blood glucose levels in the db/db mouse as normetanephrine content was elevated in urine of db/db mice, suggesting involvement of hepatic glycogenolysis in blood glucose regulation after treadmill training [32]. Interestingly, patients with T2DM presenting with hyperglycemia prior to exercise exhibit post-exercise hyperglycemia and hyperinsulinemia, indicating a worsening of metabolic control. Excessive norepinephrine secretion is also reported in both hypertensive and non-hypertensive T2DM after exercise [33-36]. Clearly, studies examining the role of sympathetic tone and function on glucose homeostasis in the db/db mouse during exercise are warranted and intriguingly also because of recent evidence indicating a beneficial effect of leptin treatment in reversing the development of autonomic nervous system neuropathy in older db/db mice [37-39].

Exercise and Hepatic Gluconeogenesis in the db/db mouse

During acute exercise, normoglycemia is maintained by a precise balance between hepatic glucose production from gluconeogenesis and peripheral glucose utilization. When hepatic glucose production is greater than the peripheral use of glucose, this results in hyperglycemia. The hyperglycemia observed in the obese Zucker rat and Zucker diabetic fatty rat is related, in part, to elevated rates of hepatic gluconeogenesis, which can be reversed with chronic exercise training [40,41]. In these rat models, the expression of major hepatic glucose production enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) is increased relative to lean non-diabetic littermates, and treadmill exercise training reduces their expression, improving the hyperglycemic state. The effects of both acute and chronic exercise training on the expression of gluconeogenic enzymes in the db/db mouse have received little attention to date. However, recent evidence from our laboratory suggests that the post-exercise elevation in plasma glucose levels in the db/db mouse may be caused by increased expression of PEPCK (Table 4). From a mechanistic aspect, activation of the glucocorticoid receptor (GR) by corticosterone could stimulate the expression of PEPCK, resulting in

Parameter	Lean mice	Lean+exercise	Db/db mice	Db/db+exercise
Glucose (mg/dl)	165 ± 20	187 ± 20	420 ± 19*†	571 ± 22*†‡
NEFA (mmol/L)	0.6 ± 0.1	0.63 ± 0.1	0.68 ± 0.1	0.94 ± 0.1*
Corticosterone (ng/ml)	193 ± 50	432 ± 48*	470 ± 46*	560 ± 54*

Blood was collected 30 minutes before exercise and immediately after exercise. 7-8 week old db/db mice were used and lean littermates served as controls. Exercise was performed on a treadmill for 30 min at 12 m/min. Values are reported as mean ± SEM for 10 mice in each group. NEFA: Non-Esterified Fatty Acids; *: Compared to lean mice; †: Compared to lean exercise mice; ‡: Compared to db/db mice

Table 2: Effects of acute exercise on plasma glucose, non-esterified fatty acids and corticosterone levels in control and db/db mice.

	Lean control	Lean runners	Diabetic control	Diabetic runners
Corticosterone (pg/ml)				
-Voluntary running	99 ± 24	264 ± 65	319 ± 49*	241 ± 96
-Treadmill running	133 ± 5	171 ± 19	269 ± 26*†	820 ± 226*†‡
Normetanephrine (ng/ml)				
-Voluntary running	5.00 ± 0.09	5.28 ± 0.05	2.96 ± 1.50*†	3.12 ± 0.35*†
-Treadmill running	5.19 ± 0.07	5.07 ± 0.15	2.45 ± 0.80*†	3.65 ± 0.37*†‡

Values are reported as mean ± SEM for 6 mice in each group. Five-week-old db/db mice and lean littermates were trained either on a treadmill or in a wheel system for a period of 5 weeks [32]. Urine was collected using metabolic changes over a 24h period. *: Compared to lean control mice; †: Compared to lean runners; ‡: Compared to db/db control mice

Table 3: Effects of voluntary wheel and treadmill running on urine corticosterone and normetanephrine levels in lean and db/db mice.

an increase in glucose production. In liver of db/db mice, in which the GR is abundantly expressed and endogenous corticosterone synthesis is increased [18,42], upregulation of the GR and PEPCK contributing to post-exercise hyperglycemia is an attractive mechanism that merits further investigation (Table 2).

Hepatic 11β-hydroxysteroid Dehydrogenase and Exercise in the db/db Mouse
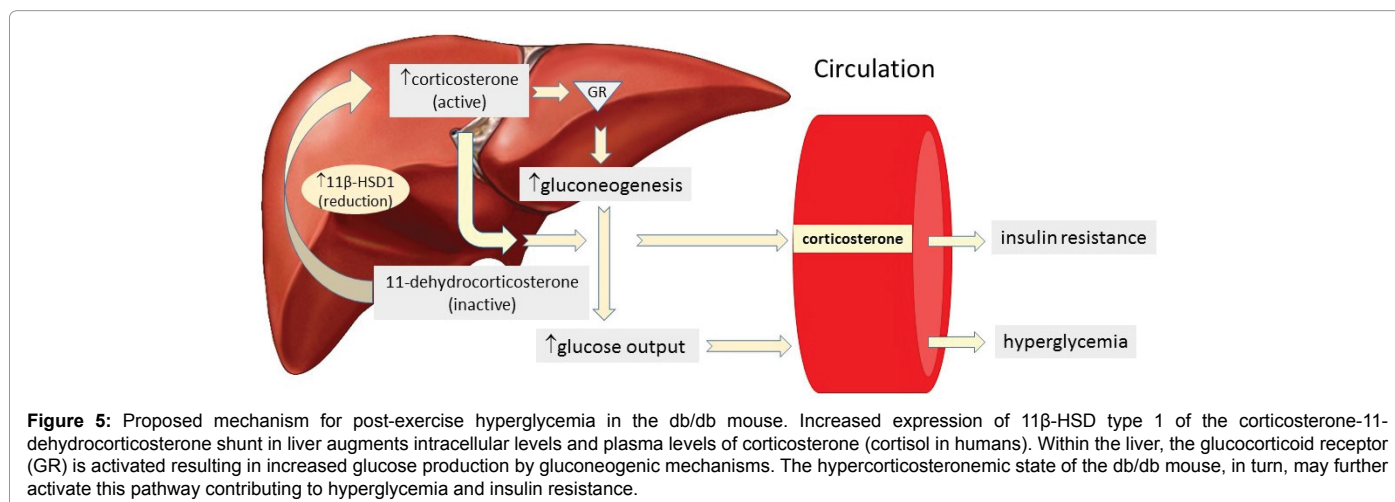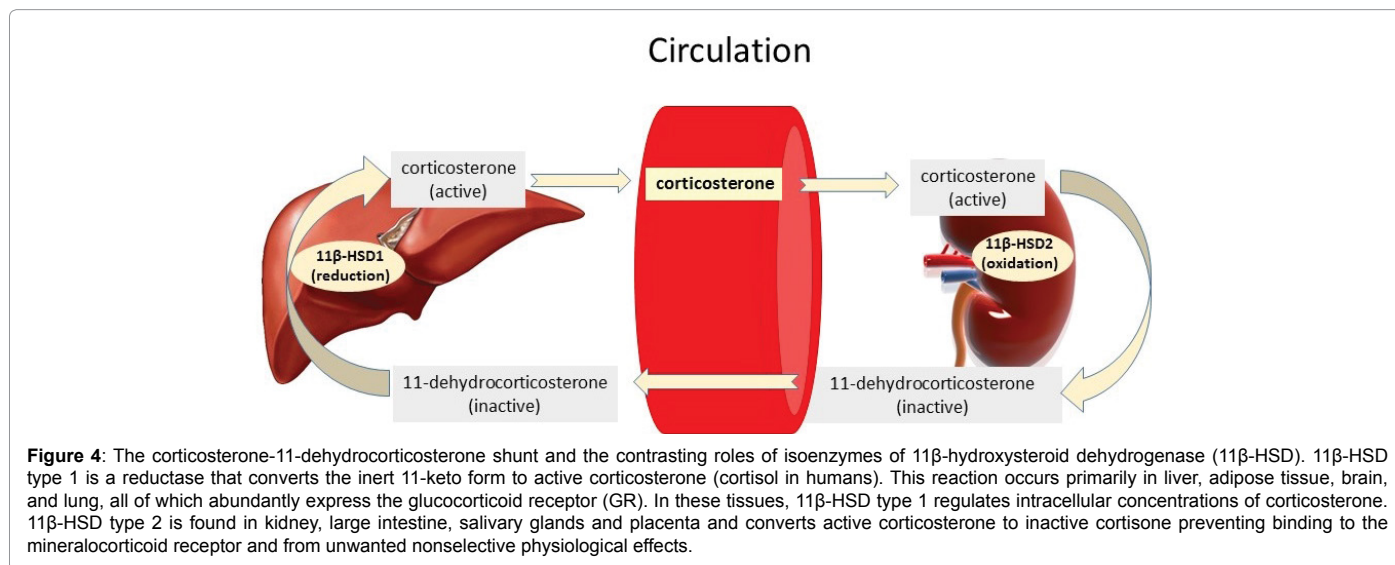
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Protein	Lean mice	Lean+exercise	Db/db mice	Db/db+exercise
GR	1.0	+1.77	+2.89*	+3.21*†
PEPCK	1.0	+1.33	+1.45	+1.75*

To highlight the changes induced by exercise or diabetes, values are presented as delta change in protein expression relative to control. For these data [31], liver from lean control littermates were used, which have one mutant and one normal copy of the leptin gene (db/+). GR: Glucocorticoid Receptor; PEPCK: Phosphoenolpyruvate Carboxykinase. Protein expression was normalized to actin. Exercise was performed on a treadmill for 30 min at 12 m/min in 8 week old db/db mice. Mice were sacrificed 8 hours after exercise for protein expression. Values are reported using 6-10 mice in each group. *: Compared to lean mice; †: Compared to lean exercise mice

Table 4: Changes in protein expression of glucocorticoid receptor and phosphoenolpyruvate carboxykinase in liver of db/db mice.

11β-hydroxysteroid dehydrogenase (HSD) isoenzymes of the corticosterone-11-dehydrocorticosterone shunt may be contributing to post-exercise hyperglycemia in the db/db mouse. Corticosterone can bind the mineralocorticoid receptor and cause inappropriate activation of mineralocorticoid pathways. To prevent these effects, 11β-HSD type 2 converts active corticosterone into inert 11-keto forms (11-dehydrocorticosterone in rodents, corticosterone in humans) in the kidney (Figure 4). The insert glucocorticoid is then transported to the liver where 11β-HSD type 1 reconverts the inactive form into active corticosterone. 11β-HSD type 1 is expressed in tissues such as skin, muscle, and adipose tissue, and dysregulation of 11β-HSD type 1 in liver and adipose tissue in obesity increases the intracellular levels of corticosterone and contributes to the plasma glucocorticoid pool [43]. The effects of acute exercise on the expression of 11β-HSD type 1 in liver has been examined as a possible mechanism for the post-exercise excursion in blood glucose levels seen in db/db mice [31]. Our latest work indicates that increased expression of 11β-HSD type 1 stimulates corticosterone synthesis, leading to increased protein expression of gluconeogenic enzymes and hepatic glucose production after exercise in the db/db mouse (Figure 5). This mechanism is consistent with the observations that overexpression of 11β-HSD1 is associated with visceral adipose tissue accumulation, hepatic gluconeogenesis, hyperglycemia,

Figure 4: The corticosterone-11-dehydrocorticosterone shunt and the contrasting roles of isoenzymes of 11β-hydroxysteroid dehydrogenase (11β-HSD). 11β-HSD type 1 is a reductase that converts the inert 11-keto form to active corticosterone (cortisol in humans). This reaction occurs primarily in liver, adipose tissue, brain, and lung, all of which abundantly express the glucocorticoid receptor (GR). In these tissues, 11β-HSD type 1 regulates intracellular concentrations of corticosterone. 11β-HSD type 2 is found in kidney, large intestine, salivary glands and placenta and converts active corticosterone to inactive cortisone preventing binding to the mineralocorticoid receptor and from unwanted nonselective physiological effects.

Figure 5: Proposed mechanism for post-exercise hyperglycemia in the db/db mouse. Increased expression of 11β-HSD type 1 of the corticosterone-11-dehydrocorticosterone shunt in liver augments intracellular levels and plasma levels of corticosterone (cortisol in humans). Within the liver, the glucocorticoid receptor (GR) is activated resulting in increased glucose production by gluconeogenic mechanisms. The hypercorticosteronemic state of the db/db mouse, in turn, may further activate this pathway contributing to hyperglycemia and insulin resistance.

and insulin resistance in obesity [43-45]. Considering that the db/db mouse is leptin-resistant, the role of leptin in the regulation of 11β-HSD type 1 synthesis could lead to increased understanding of the role of hypercorticosteronemia on hepatic glucose production. Indeed, leptin treatment to both STZ diabetic rats and in the genetic model of spontaneous T1DM (Bio Breeding, BB) was effective in correcting ACTH and corticosterone levels and restoring glucose levels by normalizing hepatic gluconeogenesis [46]. Enhanced CRH and ACTH production with resulting hypercortisolemia has been reported in obese women with abdominal body fat distribution [47] as well as in the obese Zucker (fa/fa) rat [48]. Chronic leptin replacement in the obese ob/ob mouse [49], which is leptin deficient, corrects the hypercorticosteronemia by establishing negative feedback to the HPA axis highlighting the importance of adipose tissue in corticosterone secretion [50]. As expected, with leptin resistance, the HPA axis feedback loop is disrupted in the db/db mouse.

Conclusion and Future Directions

Inactivity contributes to the development of obesity and diabetes, and exercise is recommended as a non-pharmacological approach for the treatment of these metabolic disorders. Regular exercise can prevent the progression of diabetes-related complications and improve overall cardiovascular health. Based on the results of exercise-based studies glucose control is not achieved in the obese diabetic db/db mouse [25,26,51-54]. This should not raise any doubts regarding the suitably of this model for training studies, because benefits on other cardiovascular risk factors have been reported. When comparing voluntary exercise as a training regimen to forced treadmill running, however, a slight improvement in glucose control occurs when mice run on their own volition. Voluntary running, by decreasing the production stress-related hormones [55], could explain this effect on glucose control although the effects of chronic voluntary running on these markers are unclear. On the other hand, the db/db mouse exhibits enhanced endogenous glucocorticoid synthesis at rest, and further synthesis occurs during and after exercise, leading to post-exercise hyperglycemia by gluconeogenic mechanisms. Further contributing to hyperglycemia in the db/db mouse is the observation that 11β-HSD type 1 expression of the corticosterone-11-dehydrocorticosterone shunt in liver is upregulated during exercise. It is important to note that the role of kidney and expression of inactivating isoenzymes present in other tissues of this shunt has not been demonstrated in exercise-based studies using the db/db. Lastly, the effects of exercise on peripheral glucose metabolism and hepatic glucose production are also complicated by the fact that the db/db mouse is hyperleptinemic, which may affect running behavior. Evidence for a role of leptin in ambulatory behavior is based on the observation that leptin treatment to leptin-deficient ob/ob mice stimulates energy expenditure and wheel running behavior [56,57], suggesting that leptin is an important regulator of activity in mouse models of defective leptin signaling.

Acknowledgement

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