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Metabolic adaptation in lactation: Insulin-dependent and -independent glycemic control

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BACKGROUND

The metabolic syndrome including type 2 diabetes is associated with aberrant metabolism of glucose and lipid, that is, impaired metabolic flexibility. Proper metabolic adaptation is critical for mammals to survive conditions with restricted caloric intake, such as starvation. However, one process that exemplifies the amazing capacity of metabolic flexibility in mammals is lactation, an exquisite metabolic adaptation process that normally is not associated with restricted caloric intake. Instead of an exchange of energy source between carbohydrate and lipid, lactation is associated with mobilization of both glucose and fat from storage for milk production. A rewiring of inter-organ metabolic flux is induced during lactation, which has significant health impacts on both mothers and babies. In humans, little is known about the metabolic adaptations during active lactation and post-lactation, let alone the relevance of lactation to the long-term risk of type 2 diabetes in mothers. Recent studies of the metabolic control during lactation provide new insights into the physiology of metabolic adaptation regarding the role of insulin in glycemic control and energy homeostasis, which may lead to novel treatment strategies for type 2 diabetes and other metabolic diseases associated with insulin resistance.

Insulin is the central hormone of metabolism and physiology that orchestrates the transition between the fed and fasted states. Insulin is also viewed as the major regulator of blood glucose and is the mainstay of treatment for type 1 diabetes mellitus. However, when insulin is used as treatment for type 2 diabetes, a condition characterized by relative insulin deficiency and insulin resistance, one conundrum observed is that insulin promotes energy storage, which further exacerbates insulin resistance due to increased adiposity. Part of the underlying physiology is the anabolic effect of insulin. Insulin promotes fatty acid and amino acid uptake, energy storage, and cellular growth. Insulin resistance in diet-induced obesity is only selective for glycemic control, that is, the anabolic role of insulin in energy storage remains intact under the condition of insulin resistance.[1] Whereas extensive efforts have been directed to understand the bifurcation of insulin signaling in glycemic control and pro-anabolic regulation, a growing body of epidemiological and basic/translational evidence now suggests that non-insulin-mediated glucose uptake/utilization (NIMGU) may be a component that, when disrupted, can induce an elevation of blood glucose and promote the development of selective insulin resistance. Conversely, stimulation of NIMGU, such as what lactation does to maternal metabolism, may be a novel solution to the pathogenic paradox associated with insulin therapy under the nonpregnant and non-postpartum state.

INCREASED GLUCOSE PRODUCTION DURING LACTATION

Lactation *per se* promotes glucose usage, so it is expected that glycemic control is

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improved in lactation. Indeed, the intensity of lactation is found to be positively associated with the improvement of fasting glucose level.[2] Moreover, breastfeeding an infant during the 2-h 75 g oral glucose tolerance test lowers the 2-h plasma glucose trajectory further among all the postpartum women who choose to breastfeed.[3] Consistent with the acute effect of lactation, blood glucose concentrations, under both fasting condition and through 2-h glucose overload test, were lower in lactating mothers than nonlactating mothers at 3.6 years postpartum.[4]

Compared to formula feeding women, lactating women have higher basal endogenous glucose production as well as whole-body glucose disposal.[5] Higher basal glucose production appears to be from increased glycogenolysis in response to increased metabolic demand during lactation at similar or lower insulin concentrations compared to the nonpregnant, non-postpartum control group.[6] Animal studies showed that glucose clearance rate was significantly higher in rats from 3 days of lactation, which was further increased during the euglycemic insulin clamp, a process when exogenous glucose is administered to animals continuously.[7] However, glucose utilization in skeletal muscle and adipose tissue, the canonical insulin-responsive organs, is decreased in lactating animals.[8] The increase in glucose uptake and utilization during lactation mainly results from the mammary gland, which accounts for 45% of the overall glucose utilization in rats.[7]

DECREASED PLASMA INSULIN DURING LACTATION

Postpartum maternal fasting insulin levels are decreased regardless of breastfeeding.[9] Moreover, fasting insulin concentrations are lower in lactating women than nonlactating women at 3–5 months postpartum.[10] Adiposity is a key regulator of maternal insulin levels during lactation. Breastfeeding women with body mass index (BMI) < 30 have lower fasting insulin than those with BMI > 30.[10] Intriguingly, insulin concentrations under fasting or in response to glucose overload are also lowered in lactating women who are diagnosed with gestational diabetes mellitus (GDM), suggesting the reduction of insulin is induced by lactation, which is unlikely to be a consequence of improved insulin sensitivity.[2]

What is the mechanism for lower insulin in lactating women if it is not from improved insulin sensitivity? One possibility is β-cell rest.[4] Lactating women have significantly lower first- and second-phase glucose-stimulated insulin secretion, as shown by Stumvoll index, when compared to nonlactating women.[10] Another reason for lower plasma insulin is increased rate of insulin clearance. The uptake of ^{125}I-insulin by the mammary glands of lactating rats is 12-fold of nonlactating rats, whereas the insulin uptake in the liver, kidney, and heart is not changed, suggesting that lactation may increase insulin clearance through its uptake by the mammary gland.[11]

RESPONSIVENESS OF PERIPHERAL TISSUES TO INSULIN IN LACTATION

With simultaneous reduction of blood glucose and insulin, the nursing women seem to have improved insulin sensitivity compared to nonlactating ones. Indeed, HOMA IR, an index for insulin resistance,[2,10] is lower in lactating mothers, whereas the Matsuda index, an index for insulin sensitivity, is higher in lactating mothers compared to nonlactating mothers in several clinical studies.[12] Importantly, the improvement in Matsuda index persists 3 years postpartum, suggesting that lactation leaves a long-lasting impact on glycemic control.[12] Consistent with the aforementioned index changes in clinical studies, an euglycemic hyperinsulinemic clamp study in rats confirmed that whole-body glucose uptake is increased in lactating rats. The amount of insulin needed to induce half-maximal inhibition of glucose production and half-maximal stimulation of glucose utilization clearance was decreased by 60% and 50%, respectively, in lactating rats.[13]

Although systemic insulin sensitivity is improved in lactating mothers when examined by blood glucose and insulin levels, insulin responsiveness of nonmammary tissues is not enhanced during lactation. Mother rats weaned for 24 h at peak lactation secreted as much as three times more insulin than nonlactating rats when given equivalent amounts of intravenous glucose, suggesting insulin resistance in tissues other than mammary glands in rats weaned for 24 h compared with nonlactating rats. When examined *in vitro,* the adipocytes isolated from nonlactating rats showed insulin-stimulated glucose incorporation into fatty acids, whereas the adipocytes from lactating rats showed no response.[14] In contrast, mammary lipogenesis in rats at peak lactation is increased significantly by administration of low-dose insulin compared to nonlactating rats. In the same rats, however, insulin administration did not initiate any change in anabolic activities in the liver or lipolysis in white or brown adipose tissue,[11] indicating that insulin response is maintained in the lactating mammary gland, but not in the other peripheral tissues. Similar results were obtained from lactating women when using the hyperinsulinemic-euglycemic clamp method. Therefore, the enhancement of maternal insulin responsiveness during lactation may not result from improved insulin response in the canonical insulin-responsive tissues. Instead, it relies on the functionality of mammary glands, which assimilate glucose efficiently in the presence of

low insulin.

POTENTIAL MECHANISM FOR INSULIN-INDEPENDENT GLYCEMIC CONTROL DURING LACTATION

Both animal and clinical studies indicate that a condition of systemic insulin resistance is induced following the onset of lactation. It has been suggested that the condition of insulin resistance in peripheral tissues helps glucose partition to mammary glands, which is critical for milk production.[15] Unlike the canonical insulin resistance associated with obesity and prediabetes, the blood glucose and insulin levels do not increase in lactation despite an increase in glucose production. Although the mammary glands remain responsive to insulin in the presence of systemic insulin resistance for purposes other than glucose uptake, the contradiction between lower plasma insulin level and higher glucose uptake in mammary glands suggests that insulin may not be the sole key regulator. Additional factors, which are referred here collectively as the non-insulin-mediated mechanism, may play important roles in the glycemic control during lactation.

Differential expression of non-insulin-regulated glucose transporter

At the cellular level, glucose uptake is regulated by insulin through the insulin-regulated glucose transporter, GLUT4. Tissues with high expression of GLUT4 are insulin sensitive regarding glucose uptake. In contrast, glucose uptake mediated through non-insulin-regulated glucose transporter, such as GLUT1, manifests the feature of non-insulin-mediated glucose uptake. Glucose uptake by mammary epithelial cells is mediated by several GLUTs, and the differential expression of GLUT1 has been suggested as a mechanism for insulin-independent glucose uptake in the lactating mammary gland. Studies found that the mammary gland of lactating cows expressed large amount of GLUT1, while the mammary gland of nonlactating cows did not.[16] The expression of GLUT1 in mammary glands was significantly reduced 6 h after weaning in lactating rats.[17] Increased GLUT1 expression in mammary glands during lactation is also demonstrated in rats, mice, and humans. Prolactin level is increased during pregnancy and lactation, and it is suggested that prolactin increases the expression of GLUT1 in mammary glands.[18] In addition to GLUT1 which is the primary transporter for glucose uptake in mammary glands, other insulin-independent transporters, including GLUT3, 5, and 12, are also expressed in lactating bovine mammary glands, suggesting a potential contribution to NIMGU.[19]

Reduction of leptin surrounding parturition

Leptin, like insulin, is another central hormone with a key role in metabolic regulation in response to fasting and feeding. Primarily secreted from adipocytes, leptin is the representative adipokine that acts as a hormone to coordinate energy homeostasis systemically. It is well established that falling leptin levels are a key signal of the starved state.[20] Interestingly, plasma leptin drops by 30%–50% during the days surrounding parturition in mammals.[21] Noticeably, the significant reduction of leptin is not due to a substantial decrease of adiposity or the loss of placenta upon parturition.[22] This rapid reduction in plasma leptin is, therefore, suggested to serve as a signal promoting glucose conservation during the transition from late pregnancy to early lactation. However, due to the concomitant changes in other hormones during lactation, the significance of leptin reduction in the maternal metabolic remodeling remains elusive. A recent study reveals that partial leptin reduction restores hypothalamic leptin sensitivity and protects mice from diet-induced obesity.[23] The report shows that down-titration of leptin in mice through anti-leptin antibody alone is sufficient to improve glucose disposal, even when the adiposity remains unchanged in those mice.[23] These findings support that the reduction of leptin surrounding parturition may contribute directly to the glycemic control in lactating mothers through an insulin-independent mechanism.

Increase of monosaccharide diversity at the expense of glucose

Lactation is associated with massive production of lactose, a disaccharide composed of glucose and galactose subunits. In addition to lactation, the maintenance of cellular monosaccharide diversity is critical for cell function and survival. Without a complete set of monosaccharides, cells may accumulate misfolded protein in endoplasmic reticulum (ER) and fail to secrete or send molecules to targeted subcellular locations due to a defect in glycosylation. Since glucose is the major source for the supply of monosaccharides in cells, the rate of glucose flux to other monosaccharides is expected to be coupled to glucose uptake and may influence glycemic control systemically. Indeed, ER stress, a chronic condition that is well known for its contribution to the development of insulin resistance,[24] has been shown to regulate several key enzymes for the production of monosaccharides including UDP-glucose-4-epimerase (GalE),[25-27] the sole epimerase for mammals to produce galactose from glucose. Notably, hepatic overexpression of spliced Xbp1 (Xbp1s), a transducer of the unfolded protein response (UPR) induced by ER stress, not only augments cellular pool of monosaccharide at the expense of hepatic glycogen storage, but also substantially lowers the blood glucose,[25] supporting that stimulation of glucose flux to other monosaccharides may improve glycemic control in the absence of lactation.

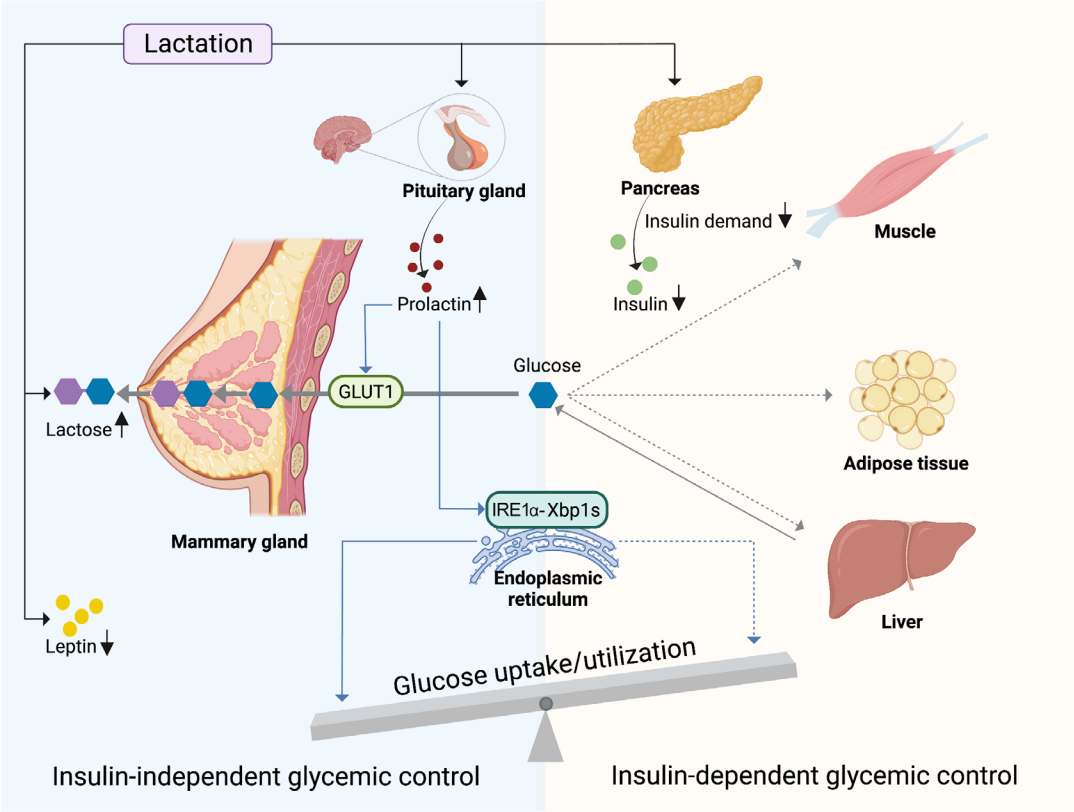

Figure 1: Insulin-independent glycemic control during lactation augments glucose uptake and utilization in mammary glands. Simultaneously, glucose uptake in insulin-responsive tissues such as the liver, adipose tissues, and skeletal muscle, that is, insulin-dependent glucose uptake and utilization, shows a reduction compared to the nonlactating state. ER stress and the UPR in mammary glands and adipose tissues during lactation may play a key role in coordination of the maternal metabolic remodeling. ER: endoplasmic reticulum; UPR: unfolded protein response; IRE1α: Inositol-requiring enzyme-1α.

ER stress and UPR in maternal metabolic remodeling during lactation

Chronic activation of ER stress and UPR has been well known for its adverse impact on insulin response in multiple tissues including muscle, liver, and adipose tissues.[28] Interestingly, recent findings indicate that ER stress is increased in the postpartum mammary gland in mice, and the proper activation of the Inositol-requiring enzyme-1α (IRE1α) branch of UPR is necessary for milk production.[29] Consistently, Xbp1s, the downstream target of IRE1α, is increased by prolactin treatment in adipocytes during lactation, and lactating moms with Xbp1 deficiency have decreased milk production and increased adiposity,[30] concurrent with the stimulatory role of Xbp1s in the flux of glucose to galactose through activation of GalE as mentioned above.[25] Conversely, when Xbp1s is overexpressed in adipocytes, uridine supply from adipocytes is augmented,[31] which is consistent with the role of adipocytes in uridine homeostasis.[32] Importantly, increased uridine supply not only favors the production of monosaccharides including galactose from glucose, but also diminishes the insulin response partially by interfering with insulin signaling pathway through protein *O*-GlcNAcylation.[33,34] Lastly, Xbp1s is induced in adipocytes by fasting,[31] whereas fasting *per se* is a process associated with a fall in circulating leptin. It warrants future investigation whether ER stress in adipocytes is involved in the fall of leptin by fasting and lactation. In summary, ER stress and UPR may serve as a connection of insulin-independent mechanisms, which plays a key role in the maternal metabolic remolding during lactation (Figure 1).

PERSPECTIVES

Low plasma insulin combined with insulin resistance in nonmammary tissues is a feature of glucose metabolism during lactation in animal models, including rodents and farming animals. This feature safeguards the calorie supply for lactose synthesis. Although the glucose uptake in mammary glands is significant and insulin independent, it remains a subject of debate whether insulin resistance is developed in lactating women depending on whether

insulin sensitivity is examined by systemic glycemic control or tissue responsiveness to insulin. However, it is unambiguous that the concomitant augmentation of NIMGU in lactation makes it possible to restore a low level of insulin without impairing glycemic control in the presence of increased glucose production. One beneficial effect associated with such maternal metabolic remodeling is the suppression of insulin-dependent energy storage and subsequent obesity progression. Indeed, clinical observations from different ethnic groups have found that lactation reduces the risk of maternal hyperglycemia and the prevalence of type 2 diabetes.[35] Given the significance of insulin resistance to the progression of metabolic disease, the physiology behind glucose metabolism and energy homeostasis during lactation is of great interest.

Investigations on NIMGU during established human lactation can use indirect or direct approaches like those previously tested outside the pregnancy and postpartum window.[5] The indirect approach includes a hyperinsulinemic-euglycemic clamp with a stable isotope of glucose and analysis of the data with a model similar to the one published by Jumpertz *et al.*[36] Specifically, for each subject, the steady-state Rd glucose is plotted against the respective steady-state insulin concentrations during three study conditions: 2 h of basal state, 2 h of a lower insulin infusion rate such as 10 mU/m^2/min, and 2 h of a higher insulin infusion rate such as 40 mU/m^2/min. Data obtained during these three study conditions may be used to calculate individual linear regression equations from which Rd glucose at theoretical zero insulin concentrations can be extrapolated. The direct approach would infuse somatostatin during the clamp procedure to inhibit endogenous insulin secretion.

Understanding the non-insulin-dependent glucose uptake/utilization and its link to energy homeostasis could lead to new therapeutic strategies for blood glucose management under conditions of insulin resistance and diabetes.

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Conflict of Interest

None declared.

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