Trends in Endocrinology & Metabolism

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REVIEWS

Opinion

Time for a New Perspective on Prolactin in Metabolism

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The pituitary hormone prolactin (PRL) regulates a variety of functions beyond reproduction. The association between physiological (pregnancy) and pathological (prolactinoma) hyperprolactinemia and metabolic alterations led to the concept of this hormone being diabetogenic. However, large cohort clinical studies have recently shown that low circulating PRL levels are associated with metabolic disease and represent a risk factor for type 2 diabetes (T2D), whereas high PRL levels are beneficial. Moreover, PRL acts on the pancreas, liver, adipose tissue, and hypothalamus to maintain and promote metabolic homeostasis. By integrating basic and clinical evidence, we hypothesize that upregulation of PRL levels is a mechanism to maintain metabolic homeostasis and, thus, propose that the range of PRL levels considered physiological should be expanded to higher values.

Highlights

The longstanding notion of PRL being only diabetogenic is incorrect.

Recent experimental and clinical studies show that PRL helps maintain a healthy metabolism.

The beneficial effects of PRL occur at high values within normal circulating levels and above the conventional hyperprolactinemia threshold (25 μg/l). By contrast, low PRL values are associated with metabolic disease.

PRL levels between 25 μg/l and 100 μg/l, conventionally defined as hyperprolactinemia, occur physiologically and are proposed to be defined as homeostatic functionally increased transient prolactinemia (HomeoFIT-PRL), since they may contribute to maintaining and promoting metabolic homeostasis.

Drugs elevating systemic PRL are promising therapeutics for obesity-derived metabolic alterations, such as T2D.

Prolactin: A Misunderstood Metabolic Hormone

PRL is a protein hormone secreted by the anterior pituitary (AP) lactotrophs and was named for its role in milk production during lactation [1]. However, PRL exerts many other biological actions, including effects on osmoregulation, growth and development, immune function, brain and behavior, angiogenesis, endocrinology, and metabolism [2–5]. Consistent with the functional diversity of PRL, its receptors (PRLRs) are found in most tissues and cell types [6], and the hormone circulates throughout the human lifespan at levels that are similar between women and men (slightly higher in women) although they are significantly elevated during pregnancy and lactation [7]. Nevertheless, the role of PRL in males is still unclear [5]. Of note, PRL levels in female rodents are similar to those in male and female humans, although male rodents show significantly lower levels compared with female rodents [7,8].

The metabolic effects of PRL have been largely overlooked due to the longstanding notion that PRL is diabetogenic, a concept posed by Bernardo Houssay, who was awarded the 1947 Nobel Prize in Physiology and Medicine, and who proposed that all AP hormones were diabetogenic [9]. Consistent with this idea, physiological hyperprolactinemia during pregnancy promotes leptin resistance, hyperphagia, adiposity, and the insulin-resistant state needed for diverting nutrients to the developing offspring [5]. In agreement, pathological hyperprolactinemia due to **prolactinoma** (see Glossary) has been linked to obesity, impaired glucose tolerance, and insulin resistance in both men and women [10]. However, the long-held diabetogenic notion was recently contradicted by strong clinical [11–26] and experimental [12,20,27] work showing that low PRL levels are associated with metabolic alterations, whereas high PRL levels below and above the conventional hyperprolactinemic threshold (25 μg/l) promote metabolic homeostasis in diabetes and obesity-derived metabolic diseases (Table 1). Contrasting observations could be reconciled by the key realization that the outcome depends on circulating PRL levels, with low and extremely high values being deleterious, while 'higher' levels may be beneficial for metabolic fitness (Figure 1). Here, we address the emerging role of PRL as a promoter of metabolic

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homeostasis and whether PRL levels (within and above the physiological range) are relevant for metabolic outcomes. This knowledge may ultimately lead to therapeutic benefits in diabetes and obesity-related metabolic diseases. Despite solid evidence, the beneficial effects of PRL on metabolic disorders were not considered in recent reviews on the topic [4,28].

PRL Secretion

Lactotrophs comprise ~15–25% of the total number of pituitary cells in both sexes. Mature human PRL has a molecular mass of 23 kDa and comprises 199 amino acids [29], arranged on a tertiary structure of four antiparallel alpha helices, similar to the structure of phylogenetically related hormones, such as growth hormone and placental lactogen [3]. The secretion of PRL is under inhibitory control by the hypothalamic dopamine (DA) tubero-infundibular system (TIDA) [30,31]. Circulating levels of PRL demonstrate a mean of 9.9 μg/l in women and 8.4 μg/l in men [32], which are considered normal (physiological), whereas levels >25 μg/l are conventionally defined as hyperprolactinemia [33]. Nevertheless, different physiological conditions (stress, circadian rhythms, estrogen stimulation, insulin-induced hypoglycemia, etc.) transiently elevate the levels of circulating PRL (up to 90 μg/l) [34,35]. Furthermore, during pregnancy and lactation, PRL levels can reach up to >200 μg/l [36]. Most circulating PRL is released by the AP; however, PRL is also produced at extrapituitary sites, including the brain, prostate, immune cells, skin, and adipose tissue [37].

Metabolic Effects of Physiological Hyperprolactinemia during Pregnancy and Lactation

High PRL levels stimulate food intake and body weight gain [38,39] by inducing hypothalamic leptin resistance in females but not in males [40]. These sexually dimorphic effects fit into the scenario of high lactogen levels (PRL and placental lactogen) occurring during pregnancy, together with leptin resistance, hyperphagia, weight gain, increased adiposity, beta cell expansion, and insulin resistance, to promote nutrient availability for offspring development and survival [5,7,20]. During lactation, the most demanding metabolic state in mammals, PRL acts in concert with other hormones and local mammary gland mechanisms to promote metabolic adaptations [41]. PRL redirects milk precursors (glucose, amino acids, and lipids) to the mammary gland for milk production. In fact, PRL promotes lipid mobilization from adipose tissue to the mammary gland in association with reduced lipid synthesis and uptake in adipocytes and increased mammary gland lipid production [42,43] and, while there is no systemic insulin resistance, there is adipose tissue insulin resistance to suppress lipolysis [7]. The effects of PRL in pregnancy and lactation have been considered 'diabetogenic'; however, they are a homeostatic or **homeorhetic response** to the special metabolic demands of the mother–offspring unit. In agreement, PRL is essential for the beta cell expansion that occurs during pregnancy, such that female mice that are either heterozygous for PRLR or beta cell-specific PRLR null, develop gestational diabetes [44,45]. Moreover, in humans, low circulating levels of PRL during gestation are a risk factor for the development of postpartum diabetes [22], indicating that PRL is necessary for metabolic homeostasis during pregnancy.

Pathological Hyperprolactinemia and Metabolic Disease

Conditions inducing pathological hyperprolactinemia include diseases (prolactinomas, hypothyroidism, hepatic dysfunction, and others) and medication (antipsychotics, antidepressants, prokinetics, estrogens, and others) (see [33,35,46] for excellent reviews on this topic). The presence of prolactinoma elevates PRL levels to >200 μg/l [33] and is frequently associated with weight gain and obesity [47]. Body mass index (BMI), insulin resistance (HOMA-IR), and metabolic syndrome (MS) prevalence are reduced after DA agonist therapy to reduce PRL levels [48]. However, the improvements are not always related to PRL levels [48–50], and it is assumed that the DA therapy by itself has beneficial metabolic effects [51]. In animal models, the evidence for the deleterious effect

Glossary

Homeorhetic response: adaptation of metabolic functions to sustain a challenged or demanding physiological state. A typical example would be the metabolic changes occurring in the mother to sustain pregnancy and lactation.

Homeostatic functionally increased transient prolactinemia (HomeoFIT-PRL): prolactinemia in the range between 25 μg/l and up to ~100 μg/l necessary for maintaining metabolic homeostasis. It can also occur in metabolically demanding physiological situations, such as stress, hypoglycemia, and exercise, and is not associated with any pathophysiological cause.

Prolactinoma: a benign tumor of the pituitary gland that produces excessive amounts of PRL. Symptoms of prolactinoma may include infertility, osteoporosis, reduced libido, low levels of sex hormones, galactorrhoea (milk production without pregnancy and lactation), and amenorrhea (absence of menstruation).

Table 1. PRL Serum Levels Inversely Associate with Metabolic Diseases[a,b]

Metabolic disease	Subjects (*N*)	Lowest PRL level (μg/l)		Highest PRL level (μg/l)		Refs
T2D	Women (8615)	Q1 <7.99	Higher risk	Q4 >15.8	Lower risk	[11]
	Women (134)	Mean 5.39	With T2D	Mean 18.38	Without T2D	[21]
	Men and women (1510)	Q1 <6.41	Higher risk	Q4 >12.95	Lower risk	[14]
	Men and women, (3993)	Q1	Higher prevalence	Q4	Lower prevalence	[17]
	Men and women, (2377)	Q1 <6.5	Higher prevalence	Q4 >11.0	Lower prevalence	[18]
Postpartum diabetes/prediabetes	Women (367)	<115 pregnancy	Higher postpartum risk	>115 pregnancy	Lower postpartum risk	[22]
Fasting glucose levels and HbA1c	Women w/T1D (42)	Inverse association with PRL levels				[23]
Insulin resistance, elevated glycemia and HbA1c	Men and women (1683)	Inverse association with PRL levels				[15]
Insulin resistance	Men and women, (2377)	Q 1 <6.7	Higher HOMA-IR	Q4 >11.5	Lower HOMA-IR	[18]
	Men(27)	<12.0	Higher HOMA-IR	>12.0	Lower HOMA-IR	[20]
Obesity, MS, and insulin resistance	Children (162)	Mean 6.2	Obese	Mean 8.5	Lean	[19]
		Mean 4.1	Obese with MS	Mean 7.9	Obese without MS	
MS and adiposity	Women w/PCOS (322)	Inverse association with PRL levels				[13]
MS	Men w/SD (2948)	Inverse association with PRL levels				[24]
	Women w/PCOS (1007)	<7.0	Higher prevalence	>7.0	Lower prevalence	[16]
	Men w/SD (2531)	Q1 <5.0	Highest risk	Q4 = 11.1–35	Lowest risk	[25]
Major cardiovascular events	Men w/SD (1687)	Q1–Q4 <12.0	Higher incidence	Q5 = 12–35	Lower incidence	[26]
NAFLD	Men and women (859)	Q1 <6.5	Higher prevalence	Q4 >12.8	Lower prevalence	[12]

[a]Clinical studies within the past 10 years showing an inverse association between PRL circulating levels and risk, prevalence or incidence of metabolic diseases.
[b]Abbreviations: HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; Q, quartile; SD, sexual dysfunction.

of severe hyperprolactinemia on metabolism is solid. The selective disruption of DA D2 receptors in pituitary lactotrophs or the transgenic expression of the human chorionic gonadotropin β-subunit that markedly elevate circulating PRL levels are associated with hyperphagia, elevated body weight and fat mass, hepatic steatosis, glucose intolerance, and insulin resistance [52–54].

Physiological Circulating Levels and Metabolic Function of PRL in Humans

By contrast to long-held observations supporting the negative metabolic outcome of hyperprolactinemia in patients with prolactinoma, the effect of PRL levels within and above the physiological threshold on metabolic homeostasis has been recently addressed. These new studies unveiled a remarkable inverse association of low PRL levels with T2D, MS, and insulin resistance (Table 1 and Figure 1).

The concept of low circulating PRL levels as a clinical syndrome appeared for the first time in 2009 [25] in association with sexual dysfunction in which male patients with PRL serum levels <5 μg/l showed a higher risk of MS [24,25]. Also, a lower incidence of major cardiovascular events occurred in patients with the highest PRL levels (highest quintile, = 12–35 μg/l) [26]. PRL values

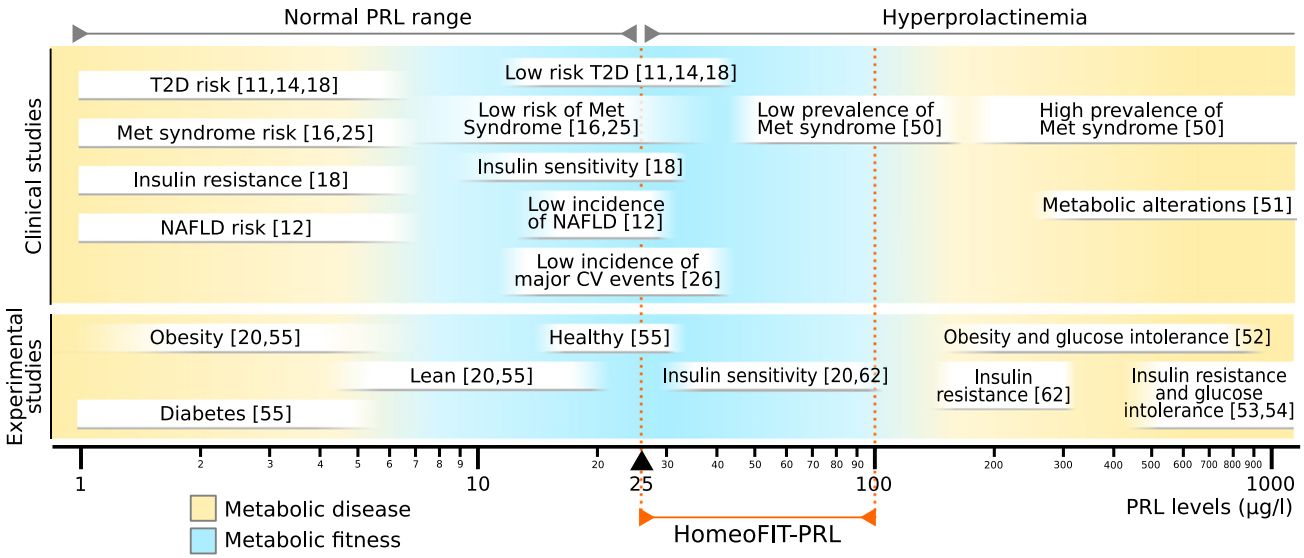

Figure 1. Prolactin (PRL) Circulating Levels and Metabolic Outcomes. Schematic representation showing the range of PRL levels associated with metabolic alterations or fitness as reported by clinical and experimental studies. Normal PRL values range from 1 µg/l to 25 µg/l and are frequently organized in quartiles. Hyperprolactinemia is defined by PRL levels >25 µg/l. Homeostatic functionally increased transient PRL (HomeoFIT-PRL) ranges from 25 µg/l to up to ~100 µg/l (and corresponds to hyperprolactinemic values having no reproductive or pathological associated cause). Reproductive and pathological hyperprolactinemia has no clear upper limit and derives from reproductive or pathological (prolactinoma, PRL-inducing medication, hypothyroidism, etc.) causes. Type 2 diabetes (T2D), metabolic syndrome (Met Syndrome), insulin resistance, obesity, glucose intolerance, and non-alcoholic fatty liver disease (NAFLD) occur in association with very low and very high PRL circulating levels, both depicted in yellow; whereas metabolic fitness (low risk and incidence of metabolic alterations, increased insulin sensitivity, etc.) associate with high PRL levels within and above the normal range, in the HomeoFIT-PRL zone depicted in blue. Supporting references [11,12,14,16,18,20,25,26,50–55,62] are indicated by the number inside each box depicting the metabolic condition.

are lower in patients with polycystic ovary syndrome (PCOS) than in subjects without the disease, and inversely associate with signs of MS [waist circumference, triglycerides, and high-density lipoproteins (HDL)] [13,16] and with insulin resistance (HOMA-IR) [13]. Also, lower serum PRL levels during pregnancy independently predict a higher risk of postpartum diabetes and prediabetes incidence [22].

Beyond reproductive outcomes, three studies published in 2013 support the notion that low PRL levels (<7 µg/l) have a negative impact on metabolism in the general population. Two of them were large cohort studies in adults, showing an inverse association between PRL levels and prevalence of T2D and impaired glucose regulation [17,18]. These studies have been extended and confirmed in different populations [11,14,15,21]. The third study involved children (mean age 10.7-years old) and found that low PRL levels occurred in obesity and were a risk factor for the development of MS, independently of potential confounders [19]. In addition, PRL levels within the physiological range were shown to be positively associated with insulin sensitivity, measured as HOMA-IR, in men and women [15,20], and a prospective study in women revealed that PRL levels in the highest quartile (compared with the lowest quartile) were associated with a lower risk of T2D, after a mean follow up of 3.7 years [14]. Notably, a recent powerful study involving >8000 women from the Nurses´ Health Studies (NHS and NHSII) revealed that high physiological circulating PRL levels (between 15 µg/l and 35 µg/l) were associated with a lower risk of developing T2D within two decades of follow-up and after adjusting for multiple confounders [11]. Finally, in men and women with non-alcoholic fatty liver disease (NAFLD), circulating PRL levels were lower than in control subjects, and even lower in patients with severe hepatic steatosis compared with those with moderate disease [12].

Altogether, the evidence that circulating PRL levels are relevant to human metabolic health and disease is compelling and solid (Table 1 and Figure 1). It is an open question whether the low (<7 μg/l) or very high (>100 μg/l) circulating levels of PRL observed in several metabolic diseases are purely correlative or have a causal role in the development of such diseases, although experimental evidence supports the latter.

Prolactin Regulation of Metabolic Homeostasis: Mechanistic Insights

Extensive experimental data support an active role of PRL favoring metabolic homeostasis and protecting from obesity-associated metabolic dysfunction in males and females. Circulating PRL levels are reduced in animal models of obesity, insulin resistance, and diabetes [20,55–58]. PRL treatment in diabetic mice reduced glucose levels [59] and, in obese rodents, it ameliorated insulin resistance and fatty liver, while promoting a healthy expansion of adipose tissue [20,27]. Conversely, lack of PRL signaling (in PRLR-null mice or following adenovirus-mediated PRLR knockdown in liver) resulted in exacerbated insulin resistance, fatty liver, and adiposity [20,60]. In agreement with these findings, 4-week-old PRL-null male mice were glucose intolerant, although this effect was not observed at older ages or in females [61]. In a mouse model of diabetes induced by 90% pancreatectomy, treatment with PRL reaching 43 μg/l decreased hepatic glucose output and improved whole-body insulin sensitivity. By contrast, a PRL dose reaching 205 μg/l, resembling pathological hyperprolactinemia, impaired systemic insulin sensitivity in the same study [62]. Similarly, transgenic mice with chronic hyperprolactinemia (up to 4000 μg/l) showed severe metabolic alterations [52,54]. These observations indicate that 'adequate' PRL levels are needed to promote and maintain metabolic homeostasis. The beneficial effects of PRL can be attributed to actions on key metabolic tissues: beta cells, liver, adipose tissue, and hypothalamus (Figure 2).

PRL promotes beta cell proliferation and insulin secretion [63], prevents beta cell apoptosis [64], and is required for pancreas ontogenesis during the perinatal period [65]. In liver, PRL modulates lipid metabolism, prevents fatty liver disease, and regulates liver insulin sensitivity [12,27,60,66]; and, in fat, PRL favors the metabolic fitness of adipose tissue by regulating fat lipid metabolism and promoting the formation of new fat cells, while preventing adipocyte hypertrophy [20,67–70]. Moreover, PRL is essential for brown fat formation and activity in newborn mice on a 129svj background [71]; in this mouse strain, a lack of PRLRs leads to the appearance of thermogenic adipocytes (browning or beigeing) on white adipose depots, protecting against diet-induced obesity [72]. However, this phenotype is not observed in C57BL/6 mice, which are more susceptible to metabolic disease [20,72].

The metabolically beneficial effects of PRL occur directly on the target tissues via several molecular mechanisms that activate the PRLR canonical signaling pathway (i.e., Janus kinase-2 and signal transducer and activator of transcription). The effect of PRL on promoting systemic insulin sensitivity is mediated, at least in part, by central actions on the hypothalamus [73]. PRL effects on the hypothalamus lead to vagal signals favoring increased liver insulin sensitivity [73]. Also, in 90% pancreatectomized rats, PRL infusion into cerebral ventricles stimulated liver insulin sensitivity, inhibited beta cell apoptosis, and reduced body weight and adiposity by mechanisms that involve increasing hypothalamic DA levels and leptin signaling [74]. Thus, the positive effects of PRL on metabolism involve both systemic and central actions (Figure 2).

The Need for a New Classification for PRL Levels

There is a relatively wide window between PRL levels considered normal (within the range of 1–25 μg/l) [75] and symptomatic hyperprolactinemia (usually >100 μg/l). The in-between range, from 25 μg/l to ~100 μg/l (Figure 1), outside of pregnancy and lactation, can occur in response to transient stimuli, such as insulin-induced hypoglycemia [34,76], stress

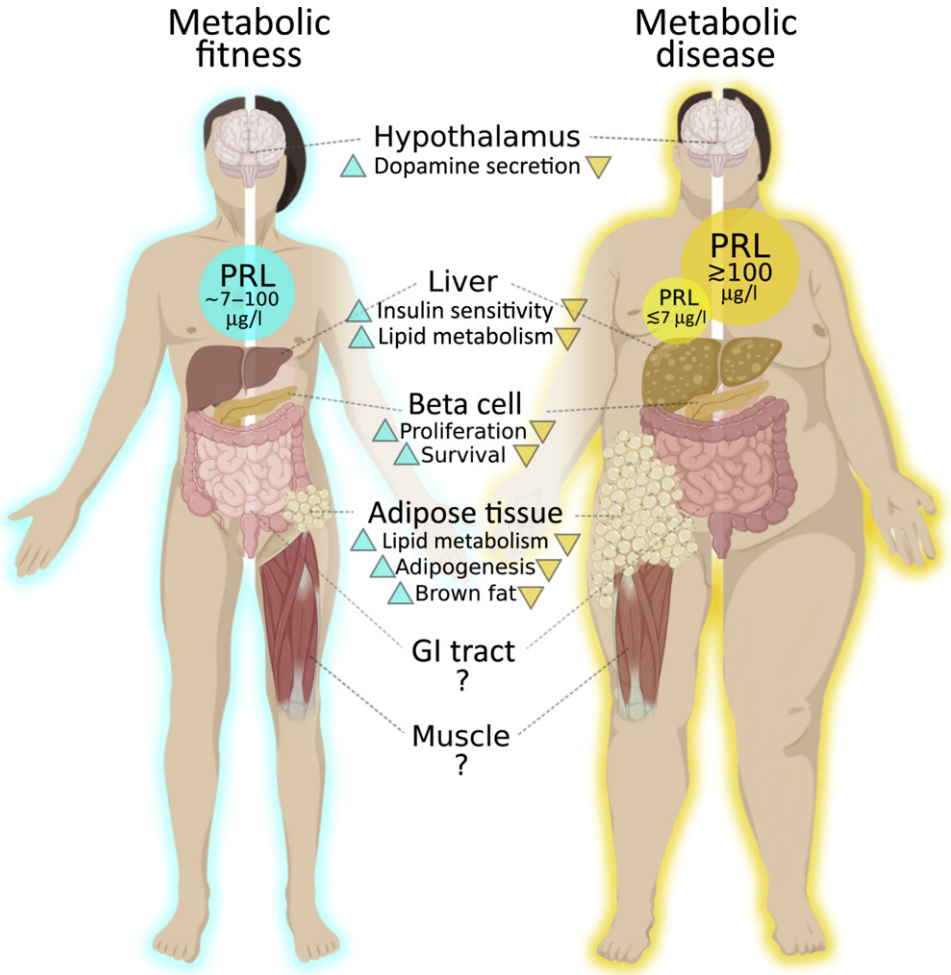

Figure 2. Prolactin (PRL) Acts on Different Target Tissues to Promote Metabolic Homeostasis. The beneficial effects of PRL promoting insulin sensitivity and protecting from type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) can be mediated by its actions on different metabolic tissues. Under normoprolactinemia and in the homeostatic functionally increased transient PRL (HomeoFIT-PRL) zone (between 7 µg/l and up to ~100 µg/l), the hormone promotes hepatic insulin sensitivity, adequate lipid metabolism, pancreatic beta cell proliferation and survival, healthy white adipose tissue growth (increased adipogenesis, reduced hypertrophy, and proper adipose lipid metabolism), and brown fat activity and development. In addition, PRL acts on the hypothalamus to promote dopamine (DA) secretion involved in overall metabolic fitness. Conversely, in metabolic diseases, PRL levels are low (<7 µg/l) or too high (usually >100 µg/l) contributing to fatty liver, improper beta cell function, dysfunctional adipose tissue, and reduced dopaminergic hypothalamic tone. PRL actions on other key metabolic tissues, such as muscle and gastrointestinal (GI) tract, are unknown, and warrant further investigation. Functional increases and decreases are depicted by blue and yellow arrows, respectively. Figure created using BioRender (https://biorender.com/).

[77,78], sexual arousal [79], intensive exercise training [80], circadian peaks [81], and other unclear situations that cannot be associated with any apparent pathophysiological cause (such as hypothyroidism, prolactinoma, medication, etc.). In animal models of diabetes and obesity, treatment with PRL achieving circulating levels of ~40–80 µg/l counteracted metabolic alterations [20,62], and, in humans, PRL levels in the normal high range, and >25 µg/l and close to 40 µg/l were associated with a lower prevalence of metabolic disease [11,13,25,26] (Table 1 and Figure 1). Therefore, it is reasoned that PRL levels within the range of 25 µg/l to ~100 µg/l are beneficial for metabolic homeostasis; thus, occurrence of these

levels in the absence of pathological causes may represent a physiological response to an increase in metabolic demand. Accordingly, we suggest defining PRL levels within this range, in the absence of other explanations, as **homeostatic functionally increased transient prolactinemia** (HomeoFIT-PRL) (Figure 1 and Table 2, Key Table). Due to the current classification of PRL levels >25 μg/l as hyperprolactinemia, patients with PRL levels in this range are frequently excluded from studies evaluating PRL levels associated with metabolic disease [14,18,20], but it is precisely these patients who should undergo further investigation. The fact that different regulators increase PRL to HomeoFIT-PRL, a zone that is beneficial for maintaining a healthy metabolism, merits its study, and the interpretation of PRL levels in patients with or without metabolic disease should include assessment on the background of this new metabolic classification of PRL levels (Table 2).

Regulation of PRL Levels in Metabolic Disease or Fitness

Two of the key questions to be clarified are determining which factors downregulate PRL levels in T2D and other metabolic diseases, and what increases PRL to upper threshold levels in circumstances associated with metabolic fitness. In obesity, there is decreased 24-h PRL secretion [82] and reduced response to PRL secretory stimuli, such as insulin hypoglycemia [83], thyrotropin-releasing hormone [84], and serotonin [85]. In apparent contradiction, reduced hypothalamic dopaminergic action occurs in obesity [86,87] and, since PRL is tonically inhibited by DA, increased PRL levels should be expected; however, the opposite occurs, with low PRL levels seen in obesity and metabolic disease. Thus, alterations of PRL levels in metabolic disease may be the result of hypothalamic–pituitary dysfunction [82]. Therefore, to find targets to normalize or increase PRL levels to the upper threshold, we need to better understand the underpinnings of PRL regulation in different physiological and pathological metabolic settings.

Cutoffs of PRL Levels That Pose a Risk or Are Protective for Metabolic Disease

Measuring PRL levels in patients is valuable because they could predict future risk of T2D, as suggested by Li *et al.* [11]. However, the establishment of a cutoff value for PRL levels as a prognostic

Key Table

Table 2. Conventional and Metabolic Classification of PRL Levels[a]

Conventional classification of PRL levels				
Normoprolactinemia: 1–25 μg/l			Hyperprolactinemia: >25 μg/l	
Proposed metabolic classification of PRL levels				
HypoPRL	Normoprolactinemia		HomeoFIT-PRL	Hyperprolactinemia
Quartile 1 (lowest)	Quartiles 2–3	Quartile 4 (highest)	Physiological: 25–100 μg/l	Pathological: >100 μg/l
Metabolically detrimental	Metabolic maintenance	Metabolically beneficial		Metabolically detrimental

[a]Conventional threshold values defining normoprolactinemia and hyperprolactinemia. Based on the opposite influence of PRL levels on metabolic homeostasis, a metabolic classification is proposed in which hypoprolactinemia (HypoPRL) corresponds to Quartile 1, which are levels usually <7 μg/l that are metabolically detrimental. Normoprolactinemia (usually 7–25 μg/l) represents levels organized into two intervals, Quartiles 2–3 (usually 7–15 μg/l) and Quartile 4 (usually 15–25 μg/l), which are for metabolic maintenance and metabolically beneficial, respectively. The HomeoFIT-PRL zone defines PRL values outside reproductive states between 25 μg/l and 100 μg/l, which are metabolically beneficial (may occur in metabolically challenging conditions, such as stress, exercise, hypoglycemia, and others). Hyperprolactinemia is defined by conditions inducing high PRL levels due to pathologies (prolactinoma, hypothyroidism, hepatic dysfunction, and others) and medication (antipsychotics, antidepressants, prokinetics, estrogens, and others). The hyperprolactinemia levels are usually >100 μg/l, have no set upper limit, and are detrimental. Physiological hyperprolactinemia occurring in pregnancy and lactation (reaching >100 μg/l) is a homeorhetic response (not detrimental) and is not included in this metabolic classification.

tool for metabolic diseases creates a practical problem rooted in the circadian variability and pulsatility of PRL secretion, the susceptibility of PRL secretion to external stimuli, intraindividual variation, and the variability of the assay determining PRL levels. We indicate some of the factors that could be considered when measuring PRL levels and trying to establish HomeoFIT-PRL values in the Clinician's Corner [88].

Therapeutic Potential of PRL-Enhancing Drugs in Metabolic Diseases

A causal link between circulating PRL levels and the prevalence of MS and T2D would suggest that positive metabolic effects of PRL occur in association with levels in the upper normal as opposed to the lower normal range (Figure 1). This observation implies a highly specific regulation of PRL levels. A pharmacological intervention inducing PRL secretion at this fine-tuned level may be unlikely; however, elevating PRL levels within the HomeoFIT-PRL zone may be possible by controlling the dose of PRL-releasing drugs according to clinical experience [89].

It is necessary to determine which drugs can elevate PRL levels to improve the metabolic state of patients with T2D. In addition, pharmacologically induced hyperprolactinemia is being evaluated as a means to counteract diabetic complications. An on-going clinical trial is using levosulpiride (a DA D2 antagonist) to increase circulating PRL levels in patients with diabetic macular edema and diabetic retinopathy. The mechanistic rationale behind this is that higher circulating PRL increases its intraocular conversion to vasoinhibin (a PRL fragment that inhibits angiogenesis and vasopermeability), resulting in the clinical improvement of retinal vascular alterations [90]. The impact of PRL conversion to vasoinhibin on PRL secretion and circulating levels is unknown, as is the metabolic role of vasoinhibin.

Dopamine Agonists and Antagonists and PRL Treatment Improve Metabolic Homeostasis

The fact that the DA D2 receptor agonist bromocriptine is an antidiabetic drug (Cycloset, FDA approved) that lowers circulating PRL levels is counterintuitive with our proposal that elevated PRL levels are beneficial for metabolic diseases. The reason for this controversy may relate to DA having effects on metabolism that are independent of PRL. Preclinical studies have shown that hypothalamic DA levels are depressed in obesity and T2D [91] and coincide with lower circulating levels of PRL [20,56]. Furthermore, animal and human studies have indicated that bromocriptine acts at the hypothalamic level to inhibit excessive sympathetic activity, hepatic glucose production, and fat lipolysis, which, in turn, lead to insulin sensitivity and glucose tolerance [91,92].

As mentioned earlier, PRL acts on specific DA neurons in the arcuate nucleus of the hypothalamus to promote DA secretion [31]. Interestingly, these neuronal populations not only modulate PRL secretion, but also regulate the activity of other neurons within the arcuate nucleus that are involved in metabolism [93], such as orexigenic and anorexigenic neurons [94]. Thus, it is possible that higher circulating PRL levels potentiate the protective effect of bromocriptine by combining the indirect action of PRL on neurons with metabolic function, via the activation of DA hypothalamic neurons, with the beneficial effects of PRL in peripheral metabolic tissues. In apparent contradiction, PRL was recently shown to block some of the protective effects of bromocriptine on insulin sensitivity and glucose tolerance in obese mice [95]; however, the circulating levels of exogenous PRL in those animals were not measured by the specific assay and may have been very high (>150 μg/l), given the dose and method used to infuse PRL; in addition, as discussed earlier, hyperprolactinemia exerts deleterious effects on glucose homeostasis, which could have blocked the beneficial effects of bromocriptine. Conversely, and in agreement with the idea that bromocriptine actions are independent of PRL, a recent study showed that bromocriptine promotes glucose tolerance in diet-induced obese mice with PRL deficiency [96].

Clinician's Corner

Given that PRL is subject to many influences that alter its release, several factors need to be considered when trying to establish PRL quartiles and HomeoFIT-PRL levels. Measuring PRL levels under fasting conditions in the morning controls for circadian variability, as well as the standardization of blood collection. To overcome the interlaboratory variation (given by the equipment, method, and standards used to quantify PRL), we propose that every laboratory establishes its own quartiles for PRL based on historical measurements. In this way, the fourth quartile could comprise levels 10–18 μg/l in one laboratory and 18–24 μg/l in another, and the first quartile values of 1–4 μg/l in one laboratory and 4–7 μg/l in another, depending on the laboratory ranges. Reporting quartile PRL values (besides concentration in μg/l) would eliminate interlaboratory variations. Based on the literature, we propose that PRL levels within the first quartile are considered of metabolic risk, whereas those in the highest quartile and in the HomeoFIT-PRL zone are considered protective (see Tables 1 and 2, and Figure 1 in the main text). Additional considerations relate to sex and female menstrual cycle and menopausal status [88]. The exclusion of patients from studies investigating PRL and metabolic disease due to PRL levels >25 μg/l, without further definition of the exclusion criterion, constitutes a selection bias and should be avoided.

In support of the idea that increasing dopaminergic activity and PRL levels is beneficial for metabolism, the DA receptor antagonist amisulpride, at low levels, exerts an antidiabetic action by reducing glucose levels in diet-induced obese mice [97]. This effect is proposed to occur via a preferential antagonism of the presynaptic DA D2/D3 receptors, thus increasing dopaminergic transmission [97]. At the same time, this drug elevates PRL levels within the upper normal and HomeoFIT-PRL zone, although it has yet to be determined whether the positive effects of the drug involve increased PRL levels.

Concluding Remarks and Future Perspectives

Extensive clinical and experimental evidence indicates that the outcome of PRL effects on metabolism depends on the circulating levels of the hormone. Physiological hyperprolactinemia in pregnancy and lactation is a homeorhetic response that helps to sustain the metabolic demand of the mother–offspring unit. However, pathological hyperprolactinemia as a result of prolactinoma produces deleterious metabolic alterations. At the other end of the spectrum, low PRL levels are also detrimental for metabolic homeostasis, whereas medium–high PRL levels within a normal range and PRL levels in the proposed HomeoFIT-PRL zone (between normal levels and symptomatic hyperprolactinemia) are protective for metabolic disease. The proposal that transiently medium–high PRL levels promote and maintain challenged metabolic homeostasis, substantiates the notion that PRL values considered normal should include levels in the HomeoFIT-PRL zone. However, an understanding of the mechanisms responsible for the upregulation of PRL levels under challenged metabolic homeostasis is needed to support this consideration. The beneficial effects of PRL on metabolism are mediated by systemic and central effects that may involve increased DA secretion; therefore, drugs that elevate both DA action and PRL levels have therapeutic potential in the treatment of obesity and T2D.

Future studies should focus on demonstrating whether the beneficial metabolic effects of amisulpride are mediated, at least in part, by its hyperprolactinemia-inducing action, as well as whether decreased PRL levels contribute to the reduced dopaminergic tone seen in obesity and T2D, and, finally, whether elevating PRL levels in clinical practice, with the use of adequate doses of PRL-elevating drugs, is beneficial for obesity and T2D (see Outstanding Questions). Regarding the metabolic state of a patient, PRL levels can no longer be interpreted on the basis of a conventional 'normoprolactinemic range' but, instead, on their quartile distribution within this range, and the HomeoFIT-PRL range (Table 2). These efforts require the proper stratification of patients according to their PRL levels and the careful evaluation of whether current diagnosis of hyperprolactinemia represents physiological levels.

Despite being discovered nearly 90 years ago, the multifaceted role of PRL in physiology and disease continues to expand and is far from being understood. Metabolism represents a relatively new avenue of PRL action with promising benefits for human health. The challenges of PRL research outlined here likely apply to the endocrinology field as a whole, where there is much to learn regarding the true physiological levels of hormones.

Outstanding Questions

Which factors are responsible for decreased PRL circulating levels in metabolic diseases? Hypothalamic, pituitary, and peripheral factors should be considered. Also, further research should help to establish whether and how the levels of PRL are altered in response to metabolic challenges, and whether patients who respond with decreased PRL secretion are at higher risk versus those responding by increased PRL levels. Accordingly, the hypothesis that elevated PRL levels are a homeostatic response to metabolic challenge needs to be tested experimentally.

What is the threshold of PRL circulating levels that helps maintain metabolic homeostasis? A range between the highest normal quartile and up to ~100 μg/l levels under situations of metabolic demand appear plausible.

Are patients with PRL levels between 25 μg/l and up to ~100 μg/l, for which no apparent pathological cause is found, in higher metabolic demand for PRL, and how could this be substantiated? Studies should focus on, rather than exclude, patients with PRL levels in this range.

What are the effects of PRL on key metabolic tissues ,such as muscle and the gastrointestinal tract? The effective doses and molecular mechanisms mediating PRL effects on target metabolic tissues should be addressed.

What is the contribution of PRL produced by extrapituitary sources, such as the adipose tissue, to PRL systemic levels?

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