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HYPOTHESES

Insights & Perspectives

D-galactose might mediate some of the skeletal muscle hypertrophy-promoting effects of milk—A nutrient to consider for sarcopenia?

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Abstract

Sarcopenia is a process of progressive aging-associated loss of skeletal muscle mass (SMM) recognized as a serious global health issue contributing to frailty and increased all-cause mortality. Exercise and nutritional interventions (particularly intake of dairy products and milk) demonstrate good efficacy, safety, and broad applicability. Here, we propose that at least some of the well-documented favorable effects of milk and milk-derived protein supplements on SMM might be mediated by D-galactose, a monosaccharide present in large quantities in milk in the form of disaccharide lactose (milk sugar). We suggest that ingestion of dairy products results in exposure to D-galactose in concentrations metabolized primarily via the Leloir pathway with the potential to (i) promote anabolic signaling via maintenance of growth factor (e.g., insulin-like growth factor 1 [IGF-1]) receptor mature glycosylation patterns; and (ii) provide extracellular (liver glycogen) and intracellular substrates for short (muscle glycolysis) and long-term (muscle glycogen, intramyocellular lipids) energy availability. Additionally, D-galactose might optimize the metabolic function of skeletal muscles by increasing mitochondrial content and stimulating glucose and fatty acid utilization. The proposed potential of D-galactose to promote the accretion of SMM is discussed in the context of its therapeutic potential in sarcopenia.

KEYWORDS

dairy, galactose, milk, muscle hypertrophy, sarcopenia

INTRODUCTION

The importance of the optimization of skeletal muscle mass (SMM) across the lifespan has been recognized in the context of health maintenance and disease prevention for a long time^[1]. Skeletal muscles are not only an integral part of the locomotor system responsible for posture, movement, and breathing, but also take part in the bidirectional

communication with other organs such as the liver, pancreas, and brain laying the foundations for integrative multiorgan signaling responsible for the achievement of homeostasis.^[1,2] Furthermore, skeletal muscles serve as the principal reservoir for the replenishment of blood amino acids that are taken up by tissues for protein synthesis and used by the liver as precursors for gluconeogenesis to support euglycemia.^[1] Consequently, maintenance of the SMM provides the necessary structural

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and metabolic support for the optimal functioning of the organism. At the tissue level, SMM is the product of simultaneous muscle protein synthesis (MPS) and muscle protein breakdown (MPB). If MPS outweighs MPB, positive protein balance is achieved and SMM increases usually as a result of muscle hypertrophy.

The SMM increases during periods of somatic growth, reaches maximal values in the 3rd decade, and starts to decline naturally around the 4th decade of life.^[3] Sarcopenia—the process of a progressive and generalized loss of SMM and strength, primarily associated with aging—has been recognized as a serious global health issue substantially contributing to frailty and the increased risk of falls, the inability to perform tasks of daily living, physical inactivity, increased risk of chronic diseases, and increased all-cause mortality.^[4–6] Consequently, the pursuit of effective, safe, and broadly applicable preventive and therapeutic strategies for sarcopenia have been proclaimed a vital medical and societal challenge.^[7]

Among many strategies that have been proposed for the prevention of sarcopenia, the combination of nutritional and exercise-related interventions seems to be the best in terms of effectiveness, safety, and broad applicability. Resistance exercise has been shown to stimulate MPS to a greater extent than MPB resulting in periods of positive net protein balance that favor skeletal muscle hypertrophy.^[8] Nutritional interventions, especially the ingestion of high protein-containing meals can stimulate the development and maintenance of SMM and potentiate the effects of resistance exercise by (i) further stimulating MPS via inducing transient hyperaminoacidemia, and (ii) inhibiting MPB through anabolic signaling (e.g., insulin signaling).^[9]

DAIRY PRODUCTS AND MUSCLE HYPERTROPHY

Among different nutritional interventions for the maintenance of the optimal SMM, dairy products (e.g., dairy proteins and milk) have been extensively studied for their substantial efficacy in achieving positive net protein balance during^[10] or after^[11] resistance exercise, in the periods of caloric restriction,^[12] and during aging^[13–16] in humans. Ingestion of high-protein dairy milk during 6 weeks of resistance training has been shown to increase lean mass, strength, and power in resistance-trained young males in comparison with the ingestion of the isoenergetic carbohydrate drink.^[17] Furthermore, in the same study, high-protein dairy milk ingestion was associated with increased insulin-like growth factor-1 (IGF-1), growth hormone, testosterone, follistatin, and follistatin-myostatin ratio, and decreased myostatin and cortisol.^[17] In a double-blind isoenergetic carbohydrate placebo-controlled study, the ingestion of a formulated milk product containing 9 g of milk protein was able to potentiate the anabolic signaling response to a single bout of resistance exercise in healthy male subjects.^[18] Hartman et al. compared the effects of fat-free milk, fat-free soy protein (isoenergetic, isonitrogenous, and macronutrient ratio matched), and isoenergetic maltodextrin on training-induced lean mass accretion in healthy young men on a 12-week split-body resistance exercise program and found that the ingestion of milk was associated with the greatest increase in fat- and bone-free mass, and type I

and type II muscle fiber area.^[10] Importantly, dairy products increase SMM and promote physical performance in older subjects at risk of sarcopenia.^[19] In a single-blind randomized clinical trial, the ingestion of 210 g of ricotta cheese (protein-rich dairy product) per day for 3 months increased appendicular SMM and attenuated the loss of muscle strength in men and women above the age of 60.^[16] The results from a 12-year-long prospective cohort in Korea suggested that a high intake of dairy protein was associated with a decreased risk of developing low weight-adjusted SMM in men (although the association was absent in women).^[20] A meta-analysis by Hanach et al. analyzed 1424 (61–81 years old) participants from 14 studies and confirmed the potential of dairy protein to increase the appendicular SMM in the elderly.^[15]

A number of human studies have shown that milk is superior to other protein sources when it comes to stimulating MPS,^[9,11,21–24] even in comparison to other animal protein sources that generally outperform plant protein (possibly due to the amino acid content, digestion, and absorption kinetics^[9,24,25]). The most common explanation for the efficacy of milk and milk proteins when it comes to stimulating MPS is the presence of fast-digestible whey proteins (β -lactoglobulins, α -lactalbumins, lactoferrins, and immunoglobulins) that represent approximately 20% of the total protein content of whole bovine milk.^[26] Whey proteins contain all the essential amino acids, demonstrate rapid digestion and absorption kinetics, and achieve pronounced post-prandial hyperaminoacidemia.^[9,26] Furthermore, whey proteins have a high proportion of the branched-chain amino acid leucine proposed as a key regulator of amino acid-induced MPS and anabolic response through the mammalian target of rapamycin (mTOR) (e.g., see the “leucine trigger” hypothesis).^[9,26–28] When compared to the residual protein fraction of whole milk consisting mainly of casein (making up approximately 80% of the total protein content of whole bovine milk), it has been consistently shown that whey proteins elicit a greater increment in MPS, show faster digestion and absorption kinetics, and induce greater post-prandial hyperaminoacidemia and hyperleucinemia in humans.^[21,29–31] Nevertheless, beyond protein, milk contains a range of nutrients and bioactive compounds that may have beneficial health effects,^[26,32,33] and that may be responsible for at least some of the unique properties of milk in the context of SMM optimization. More specifically, milk contains vitamins (e.g., B, A, E), minerals (e.g., calcium, magnesium, phosphorus, iodine, selenium, zinc), saturated (70%), and mono- and polyunsaturated (30%) fatty acids, and carbohydrates (oligosaccharides and lactose).^[26,32,33] Furthermore, milk contains bioactive peptides with a wide variety of biological effects; for example, antihypertensive, antithrombotic, opioid, antimicrobial, and cyto- and immunomodulatory peptides, and even peptides that “improve athletic performance and muscle recovery”.^[34]

At least some of the well-documented favorable effects of milk and milk-derived protein supplements (which cannot be completely purified) on the skeletal muscle may be mediated by nonprotein milk constituents and/or their synergistic effects with milk protein. For example, whole milk has been shown to stimulate net MPS (assessed indirectly by amino acid uptake) following resistance exercise more potently than fat-free milk, or isocaloric fat-free milk in

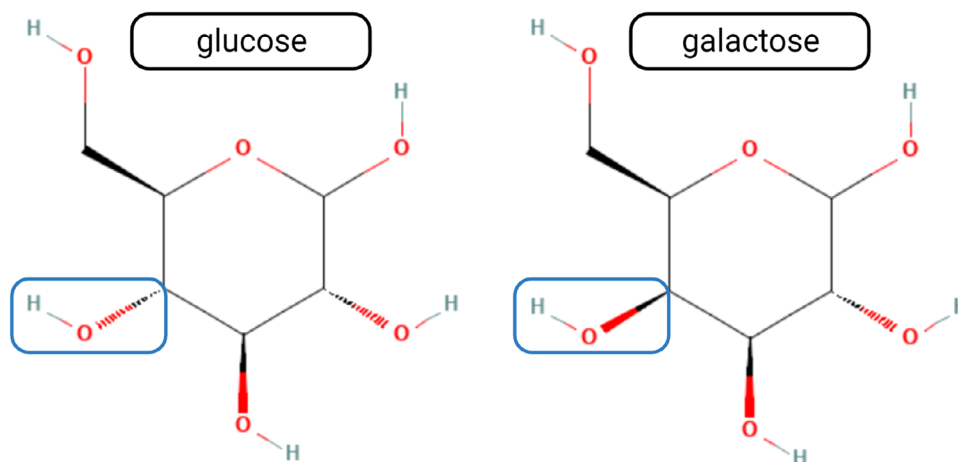


FIGURE 1 Structural difference between glucose and galactose.

human subjects^[35] indicating possible synergistic effects of milk proteins and fats. Consequently, recognition of the potential of milk as a complex food (rather than its protein derivatives) in the context of sports performance and recovery,^[36–38] maintenance of SMM, and the prevention of sarcopenia,^[15,26,39–41] as well as exploration of the effects of nonprotein milk constituents on SMM may result in exciting new developments in the field. Considering the increasing interest in bioactive substances derived from milk, it is reasonable to anticipate that forthcoming research will clarify the specific bioactive elements in milk, whether individual or in combinations, responsible for the diverse biological effects of dairy products. A pivotal step in this endeavor involves designing experiments that discern between the impacts of whole milk and purified, isolated milk components, all while maintaining impartiality by incorporating appropriate control conditions. A pertinent illustration of this approach entails conducting experiments that investigate the effects of a single isolated bioactive compound (e.g., comparison of the effects of lactose with a control condition such as sucrose) and supplementing them with experiments in which only that particular molecule is removed from the complex milk matrix (e.g., milk vs. lactose-free milk). By adopting this methodology, researchers can refrain from prematurely drawing conclusions regarding the bioactive potential of the substances under scrutiny, in the broader context of their significance in mediating the biological consequences of milk.

HYPOTHESIS: D-GALACTOSE PLAYS A ROLE IN SKELETAL MUSCLE HYPERTROPHY-PROMOTING EFFECTS OF MILK

This manuscript aims to draw attention to D-galactose, a monosaccharide present in large quantities in milk in the form of the disaccharide lactose (milk sugar), and propose its potential biological role in the well-documented skeletal muscle hypertrophy-promoting effects of milk.

D-galactose is a hexose monosaccharide different from glucose only concerning the position of the hydroxyl group on the C4 car-

bon (Figure 1). This slight structural modification seems to have been encouraged by evolution as galactose is found throughout the living world both in its free form and bound to macromolecules forming glycoconjugates.^[42–45] Galactose seems to be particularly important for mammals as the principal carbohydrate in milk (lactose) is comprised of one molecule of galactose bound to one molecule of glucose via the β -1 \rightarrow 4 glycosidic bond. Interestingly, in exceptional cases where lactose is not the main milk carbohydrate (e.g., in sea lions and marsupials), the principal milk sugar is still comprised of galactose suggesting that it is essential for early postnatal development.^[42,44,45]

In humans, diet is a major source of galactose, although it is also produced endogenously in gram quantities each day.^[46,47] The majority of exogenous galactose is provided by the consumption of dairy products and milk, although it can also be found in cereals, fruits, vegetables, or honey.^[43,47] Milk and dairy products contain galactose in the form of disaccharide lactose, which is hydrolyzed by β -D-galactosidases on the apical surface of microvilli in the intestine following oral ingestion. Free galactose, liberated by lactose hydrolysis, is then absorbed via the apical sodium-glucose linked transporter type I (SGLT1) and released into the portal circulation through the glucose transporter type 2 (GLUT-2).^[42,43] A substantial amount (88%^[42]) of the galactose absorbed from the intestinal tract is internalized by GLUT-2 and metabolized in the liver, while the rest reaches other organs such as the brain and skeletal muscles. In target organs, galactose is metabolized by three main metabolic pathways: (i) the Leloir pathway which directs galactose towards biochemical pathways responsible for glycosylation, glycogen synthesis, and glycolysis; (ii) conversion to galactonate and replenishment of the pentose phosphate pathway (PPP); (iii) reduction to the alcohol galactitol (for a detailed overview of galactose metabolism please see Conte et al.^[43]). The “alternative” pathways (conversion to galactonate and galactitol) are usually only activated in the presence of an excessive amount of galactose, which cannot be taken up by the Leloir pathway.^[43] In humans, this is typically caused by galactosemia, a group of inborn disorders characterized by reduced galactose metabolic capacity.^[43] In experimental animals, overload of the Leloir pathway (and the activation of alternative metabolic routes)

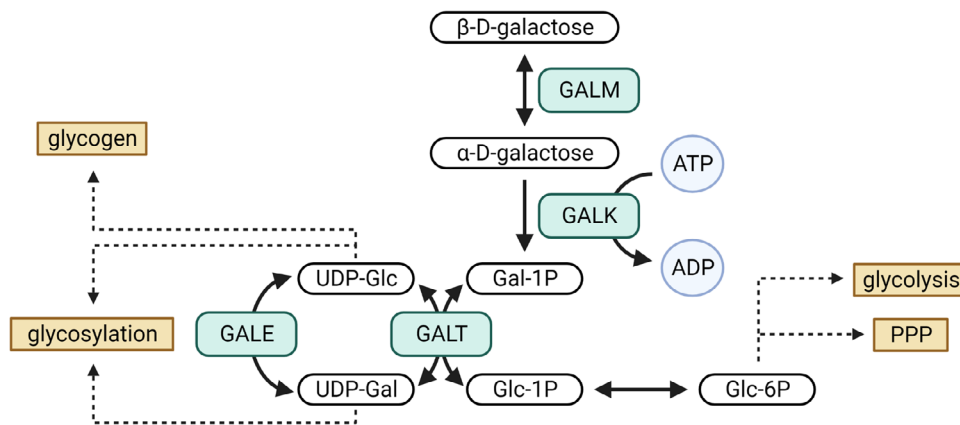


FIGURE 2 Leloir pathway. β -D-galactose is first metabolized to α -D-galactose by galactose mutarotase (GALM). α -D-galactose is converted to α -D-galactose 1-phosphate (Gal-1P) in the only unidirectional reaction of the Leloir pathway catalyzed by galactokinase (GALK). Galactose 1-phosphate uridylyltransferase (GALT) catalyzed the reaction in which Gal-1P and uridine diphosphate glucose (UDP-Glc) give α -D-glucose 1-phosphate (Glc-1P) and uridine diphosphate galactose (UDP-Gal). Finally, UDP-galactose 4-epimerase (GALE) converts UDP-Gal to UDP-Glc. Both UDP-Glc and UDP-Gal are used as glycosylation substrates. UDP-Glc is utilized for glycogenesis, and Glc-1P is metabolized into glucose 6-phosphate (Glc-6P) in the reaction catalyzed by phosphoglucomutase. Glc-6P is directed toward glycolysis or pentose phosphate pathway (PPP).

is standardly induced by chronic parenteral administration of galactose in large quantities—a procedure utilized for modeling oxidative stress and aging-related pathology.^[44,45,48–50]

Considering that (i) the ingestion of dairy products and milk introduces relatively modest amounts of galactose into the organism (~2.5 g of galactose/100 g of milk^[51]), and (ii) the liver removes most of the portal galactose before it reaches other organs (including skeletal muscles) following administration via the physiological (oral) route—potential effects of D-galactose from dairy products on skeletal muscles most likely depend on its metabolism via the main metabolic route—the Leloir pathway.

The Leloir pathway is comprised of the four main enzymatic steps in which (i) β -D-galactose is converted to α -D-galactose in a reaction catalyzed by galactose mutarotase (GALM; EC 5.1.3.3); (ii) α -D-galactose is phosphorylated into α -D-galactose 1-phosphate (Gal-1P) by galactokinase (GALK; EC 2.7.1.6); (iii) Galactose 1-phosphate uridylyltransferase (GALT; EC 2.7.7.12) catalyzes the reaction in which Gal-1P and uridine diphosphate glucose (UDP-Glc) give α -D-glucose 1-phosphate (Glc-1P) and uridine diphosphate galactose (UDP-Gal); (iv) UDP-galactose 4-epimerase (GALE; EC 5.1.3.2) converts UDP-Gal to UDP-Glc (and vice versa).^[43] Both UDP-Gal and UDP-Glc can be used as precursors for glycosylation. Additionally, UDP-Glc can be utilized for glycogenesis or glycolysis^[43] (Figure 2).

We propose that galactose (in quantities metabolized primarily via the Leloir pathway) has the potential to promote muscle homeostasis and hypertrophy by (i) promoting anabolic signaling via restoration/maintenance of mature protein glycosylation patterns; (ii) providing energy substrates for short (glycolysis) and long-term (restoration of glycogen, increased muscle lipid content) energy production and optimizing metabolic function (promoting glucose and fatty acid utilization, increasing mitochondrial content/activity).

Galactose maintains mature glycosylation of growth factor receptors and promotes anabolic signaling

Accumulating evidence supports the hypothesis that evolutionary forces selected galactose as a monosaccharide, which helps cells maintain growth factor-related signaling during fluctuations in the availability of energy substrates.^[44,52] As emphasized in Homolak et al.,^[44] the ability of galactose to antagonize potentially detrimental effects of energy fluctuations might be particularly important in vulnerable and highly energy-dependent periods of life (e.g., in the suckling period, but also old age) and in vulnerable and energy-dependent cells (e.g., neurons) although this remains to be confirmed experimentally. Sasaoka et al. have elegantly demonstrated that galactose is the preferred monosaccharide substrate (10 times more effective than glucose or mannose) for the maintenance of mature glycosylation patterns during sugar deprivation in different mammalian cell lines (e.g., HEK293, HepG2, PC12).^[52] Importantly, the maintenance of mature glycosylation patterns with trace amounts of galactose was associated with reduced endoplasmic reticulum stress and diminished cell death.^[52] The function of growth factor receptors heavily depends on their glycosylation patterns due to their effects on receptor sorting, ligand binding, oligomerization, downstream signaling, galectin binding, intramicrodomain interactions, and so forth.^[53–55] Sasaoka et al. demonstrated that even trace amounts of galactose (0.3 mM) can rescue the maturation of growth factor receptors (e.g., IGF-1 receptors [IGF-1R]) and promote growth signal transduction in sugar starvation conditions *in vitro*.^[52]

Growth factors play an essential role in skeletal muscle regeneration and growth and in skeletal muscle stem (satellite) cell proliferation and differentiation.^[56,57] IGFs (notably IGF-1) are particularly important and their potential to induce and sustain muscle growth has been repeatedly demonstrated in a number of studies.^[56–63] The

major role of IGF-1 signaling in muscle hypertrophy is beyond the scope and has been reviewed elsewhere (e.g., Refs.[57, 63–65]); however, several key points will be emphasized for clarity. In a simplified view, IGF-1 facilitates muscle development by tilting the equilibrium in favor of MPS over MPB upon binding to IGF-1 receptors (IGF-1Rs), provided that there are ample nutrients and essential molecular constituents like amino acids. IGF-1R is a receptor with tyrosine kinase activity, composed of two external alpha subunits containing ligand-binding domains and two transmembrane beta subunits responsible for transmitting intracellular signaling following alpha subunit-mediated beta subunit phosphorylation. It is important to highlight that IGF-1Rs exhibit substantial glycosylation, featuring 11 potential N-glycosylation sites and at least 6 mucin-type O-glycosylation sites on the α and insulin receptor ectodomain, respectively.^[66] The proper glycosylation patterns play a critical role in governing the correct folding, activity, and functionality of these receptors, which, in turn, underlie their physiological signaling. Upon ligand binding, IGF-1Rs activate the phosphoinositide 3-kinase (PI3K)/Akt/mTOR and PI3K/Akt/glycogen synthase kinase-3 β (GSK-3 β) pathways.^[64] The aforementioned pathways stimulate MPS (by promoting mTOR), but also inhibit MPB (by antagonizing proteasomal degradation, autophagy, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) and Smad catabolic pathways).^[64] The result of IGF-1-induced activation of MPS and inhibition of MPB is an increment in SMM proportional to time spent in anabolic conditions. Several stimuli can promote IGF-1 anabolic signaling pathways. For example, exercise causes a large transient increase in circulating IGF-1, but also promotes its secretion and paracrine action in the human skeletal muscle extracellular matrix.^[65]

Conditions that result in low general and/or temporal availability and responsiveness of IGF-1Rs (including inadequate IGF-1R glycosylation patterns), and/or nutrients (e.g., malnutrition, caloric deficit) all have the potential to abolish the effects of IGF-1 and impair hypertrophy or promote muscle wasting. Inversely, potentiating the actions of IGF-1 in the old age has the potential to prevent and/or alleviate sarcopenia in experimental animals.^[67,68] In this context, glycosylation patterns hold particular significance. Research has demonstrated that branched N-glycans located on the extracellular domain of IGF-1Rs enhance their interaction with galectins, leading to the formation of a molecular lattice. This lattice effectively hinders the endocytosis of glycoprotein receptors, thereby extending anabolic signaling and promoting increased cell proliferation.^[69]

Considering that aging is associated with a reduction in availability and responsiveness of growth factor receptors,^[70] altered N-glycosylation patterns,^[71] and progressive reduction in food intake resulting in energy-protein malnutrition,^[72,73] the ability of galactose to prevent nutrient-sensitive reduction in IGF-1R availability and IGF-1 signaling^[52] might be an important mechanism by which the exposure to trace amounts of galactose (e.g., provided by the consumption of dairy products and milk) might prolong the time spent in anabolic conditions to increase SMM. While Sasaoka et al. provided evidence that, in an *in vitro* setting, galactose can enhance anabolic signaling and cell survival by increasing the presence of growth factor receptors on the cell surface during periods of starvation, it remains unexplored whether galactose can support anabolic

signaling through this mechanism *in vivo*. Furthermore, the impact of age-related changes in glycosylation patterns of growth factor receptors in relation to factors such as sex, comorbidities, and nutritional status has yet to be investigated. Future studies are needed to comprehensively unravel the potential of galactose in this context. Considering that D-galactose plays a major role in glycosylation and that ~50% of all human proteins are glycosylated,^[43] it is reasonable to assume that glycosylation of growth factor receptors is not the only mechanism by which the replenishment of glycosylation substrates can promote muscle homeostasis and hypertrophy. For example, structural support, tensile strength, and elasticity of skeletal muscles depend on collagens which, in turn, depend on glycosylation for the correct folding of collagen fibers.^[43] The indirect regulation of muscle homeostasis *in vivo* may also involve the modulation of glycosylation in various other cell types. For instance, inadequate galactosylation of the Fc fragment of immunoglobulin G has been linked to ageing and inflammatory conditions that impact muscle function, such as myositis.^[74] Unfortunately, it is still not understood whether the absence of galactose is causally related to age-related and inflammatory processes or how endogenous and exogenous galactose might play a role in this context. Future mechanistic studies might elucidate the biological importance of the observed associations and provide the foundations for understanding the indirect effects of orally administered galactose on muscle function in humans.

Galactose can promote long-term anabolic signaling by providing short- and long-term extracellular and intracellular energy substrates

Anabolic signaling, responsible for the maintenance of MPS and SMM, relies on the availability of extracellular and intracellular energy substrates. Long-term nutrient availability (critical for the maintenance of skeletal muscles in the anabolic state) is to a large extent controlled by the liver via glycogenolysis, glyconeogenesis, and gluconeogenesis. In fact, although the role of liver glycogen stores received much less attention than muscle glycogen in the context of exercise performance and recovery,^[75] recent evidence suggests that it plays a substantial role in regulating exercise capacity in mice.^[76] Interestingly, in humans, liver glycogen was replenished two times faster when 1/3 of glucose was substituted with galactose in a post-exercise drink.^[77] In the 6-h post-exercise period, 56 ± 6 g of liver glycogen was synthesized in the group treated with a galactose-supplemented drink, while only 23 ± 3 g of liver glycogen was present in individuals treated with a drink containing glucose.^[77] The aforementioned results might be particularly important for milk (lactose)-derived galactose as galactose alone does not seem to be able to reproduce the effects of the drink containing both glucose and galactose as shown both in humans and rodents.^[77,78] The synergistic effects of glucose and galactose are still not fully understood; however, glucose might promote galactose-induced glyconeogenesis by stimulating insulin secretion (because galactose provides a weaker stimulus for insulin secretion in rodents and humans).^[77,78] Furthermore, *in vitro* experiments with human skeletal muscle cells have shown that D-galactose can promote the uptake and oxidation

of glucose,^[79] suggesting that sufficient glucose availability might be required for some of its effects. Preferential utilization of galactose for liver glycogen synthesis in rats^[80] suggests that galactose ingestion might promote the capacity for systemic nutrient availability between meals, and, thus, prolong muscle anabolic signaling. The latter is further supported by studies in trained male cyclists demonstrating that galactose ingestion is associated with increased total carbohydrate oxidation rates during prolonged exercise.^[81]

In addition to indirect effects, galactose can also act directly on skeletal muscles by providing short- and long-term energy substrates and altering metabolism. Primary human muscle cells grown in a D-galactose medium demonstrate an increased number of mitochondria,^[79] basal mitochondrial oxygen consumption rate (~40%) and cytochrome c oxidase activity (~+85%), and decreased lactate production (>5-fold).^[82] Furthermore, proliferation and differentiation in the D-galactose medium increased fatty acid oxidation.^[79] D-galactose also increased metabolic switching in human skeletal muscle cells (transition from fatty acid to glucose oxidation upon acute glucose exposure).^[79] Importantly, D-galactose pretreatment increased glucose uptake (1.8-fold), oxidation (2.6-fold), and oxidative reserve (3-fold)^[79] suggesting that D-galactose has the potential to promote utilization of glucose. Overall, the results suggest that D-galactose does not only act as a substrate for glycolysis and glycogenesis to provide short- and long-term intracellular energy supply but also promotes metabolism by potentiating glucose utilization.

Intramyocellular lipids serve as another important intracellular source of energy, which is, analogously to muscle glycogen, utilized during prolonged exercise and increased by repeated muscle contractions.^[83] D-galactose treatment of primary human muscle cells increases intramyocellular stores of neutral lipids^[79] possibly in parallel with promoting fatty acid oxidative capacity (Figure 3).

Regrettably, comprehensively grasping all the implications of the aforementioned discoveries within the realm of human health poses a challenge. The primary reason for this lies in the observation that the effects of galactose appear to vary contingent upon the concurrent presence of other endogenous or exogenously administered nutrients. Upcoming research endeavors could shed light on the role of galactose by extending experiments comparing galactose to appropriate control conditions (e.g., equimolar glucose) to include additional experiments conducted within a more intricate biochemical milieu. For instance, in the context of milk, investigating the effects of galactose-free milk preparations, in which galactose is substituted with glucose, may yield valuable insights into the physiological impacts of milk-derived galactose.

IMPLICATIONS OF THE HYPOTHESIS

The potential of D-galactose muscle hypertrophy-promoting effects in sarcopenia

The ability of D-galactose to promote MPS by counteracting catabolic signaling via several complementary mechanisms (Figure 3) might be

particularly important in the context of sarcopenia. In fact, some of the beneficial effects of milk and dairy products in sarcopenia^[20,34–36] may be at least partially mediated by D-galactose. Sarcopenia is characterized by a chronic catabolic state in which the intracellular and extracellular environment promotes long-lasting activation of MPB-related processes.^[84–87] There are two mutually interdependent etiopathogenic clusters (EPCs)^[88] driving sarcopenia: (i) inflammation-related processes, which trigger muscle catabolism (direct catabolic effects) and inhibit growth factor signaling (indirect catabolic effects)^[86]; and (ii) pathophysiological processes, which reduce nutrient availability (e.g., reduced intake and absorption of micro- and macronutrients).^[89] D-galactose has the potential to counteract both EPCs. Orally administered D-galactose can alleviate inflammation^[90] and reduce oxidative stress^[45,91] in rodents. Additionally, even trace amounts of galactose can rescue growth factor (IGF-1) signaling *in vitro*.^[52] The latter might be exceptionally important in the context of sarcopenia as accumulating evidence shows that muscle atrophy in the elderly (and in many chronic diseases) might be mediated by reduced IGF-1 and IGF-1R availability and signaling.^[64,65] Furthermore, D-galactose can also counteract mechanisms responsible for low nutrient availability. At the organismic level, D-galactose might promote gastrointestinal homeostasis^[45,90–93] and improve the malabsorption of nutrients recognized as some of the causes of malnutrition in old age.^[94,95] Additionally, galactose can replenish liver glycogen stores and provide a reserve for the maintenance of constant energy supply between meals, which are less frequent and provide fewer nutrients in the elderly.^[95,96] The ability of galactose to replenish muscle energy stores (muscle glycogen and intramyocellular lipids) might provide an additional intracellular energy reserve and postpone catabolic signaling.^[79]

There is some preclinical evidence suggesting that galactose might also provide additional benefits in the elderly at high risk of sarcopenia and malnutrition. For example, oral galactose treatment can prevent and alleviate cognitive decline in a rat model of sporadic Alzheimer's disease^[97–99] suggesting that it might be able to promote homeostasis of multiple tissues simultaneously.

D-galactose and skeletal muscle fiber types?

One interesting question that remains to be resolved is related to the potential muscle fiber type-specific effects of D-galactose. In general, individual muscle fibers contain different isoforms of myosin heavy chain (MHC) proteins based on which they can be classified as (i) type I (slow-twitch/small force fibers with predominant oxidative metabolism); type IIA (fast-twitch/medium force fibers with a combined oxidative and glycolytic metabolic profile); and type IIB (fast-twitch/large force fibers with predominant glycolytic metabolism) (please note that this simplified classification does not fully reflect reality as there seems to be a spectrum of muscle fiber types and some muscle fibers can coexpress multiple MHCs (e.g., see a comprehensive review by Schiaffino and Reggiani^[100])).

On one hand, the ability of galactose to rescue growth factor signaling may stimulate glycolytic metabolism and predominantly promote

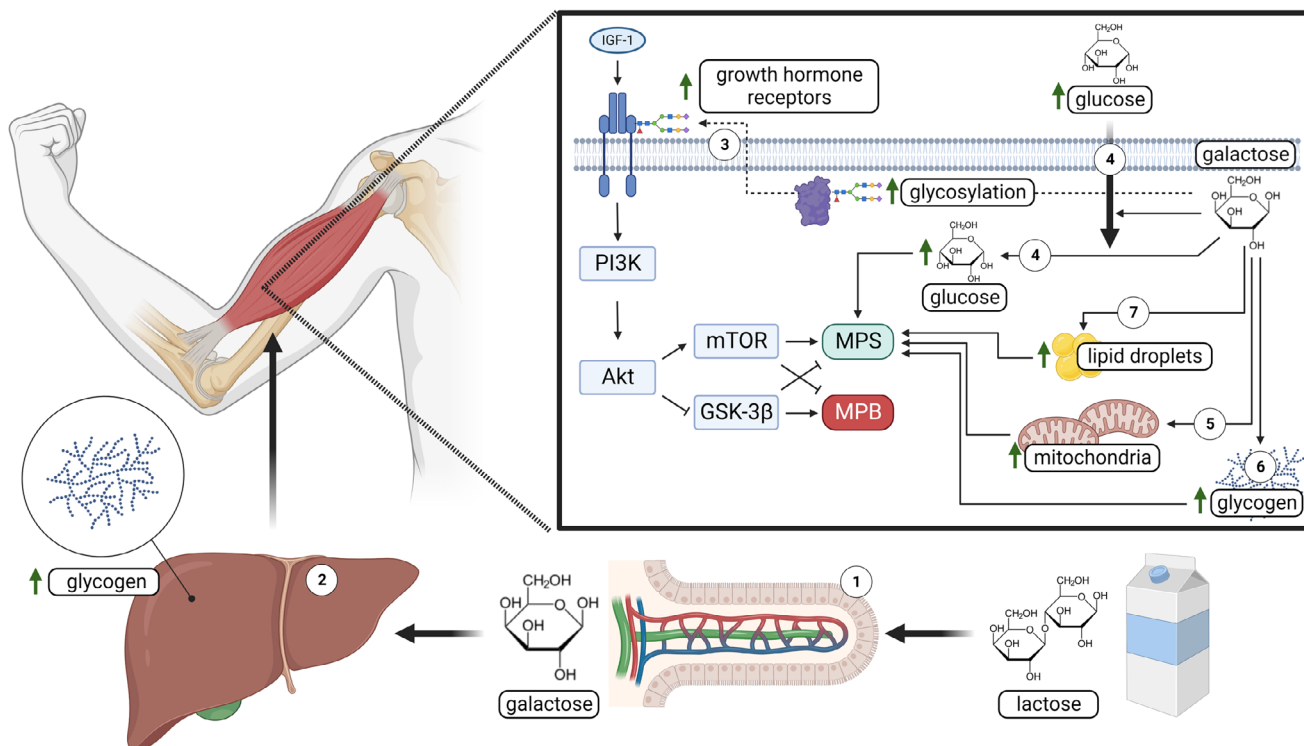


FIGURE 3 The hypertrophy-promoting effects of milk-derived D-galactose on skeletal muscles. D-galactose is liberated from the milk sugar lactose by β -D-galactosidases on the apical surface of intestinal microvilli (1). A substantial amount of portal D-galactose (~88%) is internalized by glucose transporter 2 and metabolized in the liver, while the rest reaches skeletal muscles and other organs. Hepatic metabolism of D-galactose replenishes liver glycogen stores ensuring long-term energy supply to other organs via glycogenolysis (2). The remaining D-galactose (~12%) reaches skeletal muscles where it is metabolized primarily via the Leloir pathway. Metabolism of D-galactose in skeletal muscles provides glycosylation substrates that rescue maturation of growth factor receptors (e.g., insulin-like growth factor 1 [IGF-1]) and promote growth signal transduction in the conditions of suboptimal nutrient supply (3). Remaining D-galactose can replenish cellular stores of glucose (providing short-term energy substrates) by (i) biochemical conversion via the Leloir pathway; and (ii) increasing glucose uptake. Increased glucose uptake (4) is accompanied by increased metabolic capacity (5). Additionally, D-galactose increases muscle glycogen (6) and intramyocellular lipid stores (7) (providing long-term energy substrates). Rescue of growth factor signaling, the replenishment of extracellular (liver glycogen) and intracellular stores of energy substrates, and stimulation of the metabolic activity of skeletal muscles together promote muscle protein synthesis (MPS) and decreases muscle protein breakdown (MPB) resulting in muscle hypertrophy. GSK-3 β , glycogen synthase kinase-3 β ; PI3K, phosphoinositide 3-kinase.

the function (and hypertrophy) of fast-twitch glycolytic fibers. For example, Christoffolete et al. reported that genetic induction of skeletal muscle IGF-1 signaling results in muscle hypertrophy accompanied by a metabolic shift towards increased insulin sensitivity, utilization of glucose, and expression of glucose transporter 4 in mice.^[101] Interestingly, at the same time, muscle IGF-1 reduced the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) suggesting reduced reliance on mitochondrial oxidative metabolism (i.e., predominant hypertrophy of glycolytic fibers).^[101] In the context of the effects of D-galactose on the glycosylation of growth factor receptors and growth factor signaling,^[52] the administration of D-galactose might preferentially promote the growth of fast-twitch glycolytic fibers.

On the other hand, D-galactose has the potential to stimulate oxidative metabolism. Current evidence indicates that interventions promoting metabolic transition (e.g. genetic ablation of carnitine palmitoyltransferase 2 in mice^[102]) can alter the metabolic profile of muscle fibers, but does not change the composition of MHC isoforms and it

is, therefore, reasonable to assume that galactose will not alter muscle fiber type regardless of its effects on muscle fiber metabolism. Most studies on skeletal muscle hypertrophy focus on heavier loads and hypertrophy of type II fibers; however, increasing evidence indicates that type I muscle fibers also demonstrate a substantial hypertrophic potential under appropriate conditions (e.g., aerobic training^[103,104] or training to achieve momentary muscular failure with low loads (e.g., 30% of 1 repetition maximum)^[105,106]). Physiological mechanisms responsible for the hypertrophy of type I muscle fibers are not completely understood^[105]; however, at least during aerobic exercise in humans, hypertrophy of type I muscle fibers was associated with an increased oxidative (aerobic) capacity,^[103,104] suggesting that contrary to the muscle fiber type-fiber size paradox,^[107] hypertrophy of type I muscle fibers can occur simultaneously with increased oxidative capacity (as also confirmed experimentally by Scheffler et al. in pigs^[108]). In this context, it is possible that galactose might promote hypertrophy of type I muscle fibers by promoting their oxidative capacity. Even if the oxidative capacity-promoting effects of galactose limit the

hypertrophic potential of some muscle fibers (due to the fiber type–fiber size paradox^[107]), the overall beneficial effect in sarcopenia should not be ruled out considering that increased aerobic capacity has the potential to alleviate sarcopenia-related pathophysiological processes.^[109]

LIMITATIONS

Reports suggesting that galactose can also exert detrimental effects on skeletal muscles should not be neglected nor overlooked. For example, Chang et al. reported that chronic parenteral administration of D-galactose to mice (8 weeks; 125 mg/kg) causes skeletal muscle mitochondrial complex I deficiency accompanied by grip strength impairments.^[110] Chronic subcutaneous administration of D-galactose (600 mg/kg) can reduce the expression of IGF-1 and antioxidant enzymes catalase and superoxide dismutase, as well as increase the expression of myoblast determination protein 1 (MyoD) and tumor necrosis factor α (TNF- α) in skeletal muscles of rats.^[111] Wu et al. demonstrated that chronic intraperitoneal administration of D-galactose (200 mg/kg) causes muscle fibrosis, senescence, and oxidative stress in mice.^[112] Yanar et al. were able to mimic slow twitch muscle fiber aging-related redox dyshomeostasis by chronic intraperitoneal administration of D-galactose (60 mg/kg) in Sprague–Dawley rats.^[113]

The reported detrimental effects of D-galactose on skeletal muscles in rodent studies can be explained by tissue exposure. Large doses of D-galactose and/or parenteral administration often result in D-galactose exposure, which exceeds tissue metabolic capacity (i.e., the capacity of the Leloir pathway) and leads to the activation of alternative routes (conversion to galactonate and galactitol), which promote redox dyshomeostasis in rodents.^[44,45,93] In all of the abovementioned studies, which reported detrimental effects of D-galactose on skeletal muscles, relatively large doses (60–600 mg/kg) were repeatedly administered via the parenteral route (bypassing intestinal absorption and liver metabolism) likely resulting in concentrations of D-galactose, which surpass the capacity of the Leloir pathway. In contrast, chronic administration of D-galactose to rodents does not seem to be associated with detrimental health effects when supplied orally (with the administration spread throughout the day).^[44,45,93,97–99] In fact, even when very large doses of galactose (~7.5 g/day) were administered for 12 weeks to Sprague–Dawley rats (via the oral route), there were no changes in inflammatory markers (TNF- α , interleukin-1 β , interleukin-6, zonulin, C-reactive protein) and the treatment was associated with reduced plasma endotoxin concentration (suggesting improved rather than diminished function of the gastrointestinal barrier).^[45,114] The latter suggests that the administration of galactose via the physiological (oral) route has limited potential to exceed tissue metabolic capacity due to buffering effects of the gastrointestinal tract and the liver. The potential of D-galactose to promote rather than undermine skeletal muscle function when administered via the oral route is indirectly supported by studies reporting the beneficial effects of milk. For example, Liu et al. reported that the consumption of goat milk promotes glucose

metabolism in the skeletal muscles of rats on a high-fat diet, possibly via the AMP-activated protein kinase (AMPK) pathway.^[115]

Consequently, rodent studies reporting detrimental effects of parenterally administered D-galactose on skeletal muscle provide poor foundations for inference about the potential impact of milk-derived D-galactose on skeletal muscle function. Animal studies focused on the effects of chronic oral (ad libitum) administration of D-galactose on skeletal muscle function might provide some evidence to support or reject the proposed hypothesis. Additionally, studies on the effects of orally administered milk on skeletal muscles might provide some insight; however, given the complex biochemical constitution of milk, it might be challenging to discriminate between the effects of D-galactose and the effects of other bioactive constituents. A good approach might be to compare the effects of milk with the effects of galactose-free milk as a control condition.

Finally, the proposed hypothesis is in part based on evidence from *in vitro* studies (e.g., the effects of trace amounts of galactose on glycosylation of growth factor receptors^[52]; the effects of galactose on the accumulation of intramyocellular lipids^[82]). While *in vitro* experiments may provide some useful information, the absence of physiological conditions (e.g., replacing glucose with galactose in differentiation medium^[82]) limits the possibility of fully understanding the results of *in vitro* studies in the context of potential effects of D-galactose *in vivo*. *In vivo* studies demonstrating the ability of D-galactose to promote IGF-1R signaling during periods of limited nutrient availability (or lack thereof) might provide the evidence necessary for contextualization of the muscle hypertrophy-promoting potential of D-galactose. Furthermore, to fully understand the effects of milk-derived galactose, future studies should focus on the combined effects of galactose and glucose, as it can be assumed that the galactose-mediated effects of milk take place in the presence of isomolar concentrations of glucose. The importance of the latter is reflected in studies that reported the potential of galactose to promote the restoration of liver glycogen only in the presence of glucose.^[77,78]

CONCLUSION

A unique biochemical fate of D-galactose might be responsible for some of the skeletal muscle hypertrophy-promoting effects of milk. D-galactose might increase MPS by (i) promoting anabolic signaling via maintenance of growth factor receptor mature glycosylation patterns; and (ii) providing extracellular (liver glycogen) and intracellular substrates for short (muscle glycolysis) and long-term (muscle glycogen, intramyocellular lipids) energy availability. Additionally, D-galactose might optimize the metabolic function of skeletal muscles by increasing mitochondrial content and promoting glucose and fatty acid utilization. The hypertrophy-promoting potential of D-galactose should be further explored in the context of sarcopenia.

AUTHOR CONTRIBUTIONS

Jan Homolak conceived the hypothesis and wrote the first draft of the manuscript. Ana B. Perhoc, Davor Virag, Ana Knezovic,

Jelena O. Barilar, and Melita Salkovic-Petrisic provided critical feedback. All authors agreed to the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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