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N-lactoyl phenylalanine suppresses appetite and obesity with important implications for aging and age-related diseases

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LacPhe as a new paradigm in aging research:

Recently, glucagon-like peptide-1 receptor agonists such as Ozempic®, have gained traction within the news for their promise in not only improving blood sugar but generally reducing weight through modulation of appetite (see https://www.nytimes.com/2024/06/24/briefing/ozempic-weight-loss-drugs.html). Nascent research has continuously sought to find other therapeutics that may reduce obesity, which represents a major risk factor for a myriad of diseases, including cardiovascular and heart diseases. It is well established that exercise helps to downregulate appetite.[1] Through promoting appetite control and modulating energy intake, exercise serves an important role beyond only weight loss, such as reducing disease burden, especially among older adults.[1] Conversely, anorexia of aging occurs antecedent to

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fragility, sarcopenia, and weight loss.[2] Yet, research has consistently suggested that exercise can serve fundamentally different roles in the aging process, by slowing down molecular cascades that drive aging and modulate appetite.[2] Thus, the role of appetite in the aging process needs further elucidation. While the persistent loss of appetite as a hallmark of aging may confer an increased risk of muscle dystrophy, transient exercise-induced loss of appetite via distinct age-independent regulators of appetite may serve to increase longevity.[2] New research has emerged discovering a key exercise-induced regulator of appetite, which is promising as a potential target for obesity, yet its role in aging remains unclear.

Recent findings show that exercise stimulates the production of N-lactoyl-phenylalanine (LacPhe), a bloodborne signaling metabolite that suppresses feeding to ameliorate obesity.[3] As an “exerkine”, LacPhe is synthesized from the fusion lactate and phenylalanine, an essential metabolite, activated through the action of carnosine dipeptidase 2 (CNDP2)-expressing cells including macrophages and epithelial cells.[3, 4] These seminal studies also show that the benefits of improved glucose homeostasis and reduced weight of LacPhe occurs only in diet-induced obese mice, and not necessarily lean mice.[3] Since an increase in lactate or phenylalanine alone does not produce similar effects as LacPhe, the conjugated form of LacPhe is assumed to be responsible for modulating the exercise-dependent response.[3] While LacPhe is directly related to exercise through lactate, a by-product of anaerobic glycolysis that accumulates in muscle tissues during intense exercise, alternative pathways can also activate LacPhe. Metformin, in addition to its role in increasing insulin sensitivity and reducing glucose uptake, causes reductions in fat mass through the production of LacPhe (Figure 1).[4] Beyond metformin and intense exercise, emergent research also has shown LacPhe generation in conditions of phenylketonuria and mitochondrial disease.[5] Together, LacPhe represents a promising signaling molecule to reduce fat mass through its appetite-suppressing and energy-balancing effects across mammalian species, including humans.[3]

Of particular interest to aging research is LacPhe’s role in modulating glycolytic flux. Within the context of metformin treatment LacPhe is generated via inhibition of mitochondrial electron transport chain complex I (Complex 1), and subsequent lactate-producing increased glycolytic flux.[4] While complex I inhibition can also represent a negative state of induced oxidative stress, in the context of metformin treatment, this generally provides anti-tumoral activity, and LacPhe generation. Interestingly, many studies have shown that natural complex I activity diminishes with aging (as previous reviewed by Signorile and De Rasmo[6]). Indeed, other studies have confirmed by showing that the efficiency of ATP production via oxidative phosphorylation diminishes across human aging, leading to increased lactate dehydrogenase and oxidative stress.[7] These all are suggestive of increased glycolytic flux in older individuals and greater lactate production, which would suggest increased LacPhe levels. Interestingly, lower glycolytic flux is observed in the contracting muscle of older humans,[8] implicating that exercise-inducible glycolytic flux may have a blunted effect. However, it remains unclear if there is a physiological difference between chronic changes in glycolytic flux and acute exercise-inducible changes, especially as it pertains to the positive effects of LacPhe signaling.

Notably, this commonality in the mechanism of LacPhe in both the regulation of exercise and metformin-induced body mass regulation may explain the anti-aging effects of exercise and metformin.[9] While metformin is well-understood to decrease weight, in part through the action of LacPhe, some studies have shown that metformin protects against age-associated weight loss, thus promoting longevity (as previously reviewed by Novelle et al.[9]). Thus, despite the potential for dangerously lowered food intake among geriatric patients, generally, metformin has shown to be safe, and even beneficial, through improving glycaemic control. Similarly, it may be that life-long exercise results in higher baseline levels of LacPhe, mitigating age-induced glycolytic imbalances, for improved longevity. However, while it has been found that acute elevated LacPhe levels are normalized more slowly than lactate after intense exercise,[3] it is unclear whether LacPhe serum levels undergo chronic changes. Thus, while both metformin[9] and regular exercise[1] are known to extend lifespan, it remains unclear the role LacPhe has in mediating this extension, if any. Beyond these fundamental studies of LacPhe levels across aged samples, several other avenues must be pursued.

Areas of developing research for understanding LacPhe:

Metformin's association with LacPhe emerged from researchers finding correlations between LacPhe and type 2 diabetes presence, then determining LacPhe as the causality.[5] In the future, it will be of interest to study LacPhe's association with other anorexigenic, type 2 diabetes, and metabolic control regulating drugs, such as amylin analogs, monoamine reuptake inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, dual glucose-dependent insulinotropic polypeptide (GIP)-GLP-1 receptor agonists, and triple agonists that target glucagon, GIP, and GLP-1 receptors.[5] Regulators that cause gluconeogenesis, such as glucagon, are known to decrease LacPhe by virtue of their usage of lactate as a substrate.[5] Since GLP-1 helps regulate blood sugar by reducing gluconeogenesis, it is plausible that akin to metformin, GLP-1 receptor agonists may also reduce body weight in a LacPhe-dependent manner. While research remains controversial, it has been suggested that GLPs can extend overall lifespan (see https://www.nytimes.com/2024/06/24/briefing/ozempic-weight-loss-drugs.html; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10186594/). Thus, if LacPhe is associated with the mechanism of action of GLPs, this again highlights the potential of LacPhe as a potential extender of life expectancy. Another promising avenue is looking at differences in LacPhe dynamics between monotherapy (e.g., GLP-1 agonists alone) and combination therapies (e.g., metformin plus GLP-1 agonists).

Beyond studying LacPhe, further studies must explicate the role of CNDP2. Xiao et al.[4] found that LacPhe biosynthesis is driven by the inhibition of Complex I and dependent on CNDP2 intestinal epithelial cells, with CNDP2-knockout greatly reducing LacPhe production. Similarly, CNDP2 is also the biosynthetic enzyme responsible for exercise-inducible LacPhe.[3] Given this central role of CNDP2, the influence of CNDP2 in the process of aging and age-related diseases is an important area of future research. Notably, one recent *in silico* study has found that aging decreases CNDP2 expression in white adipose tissue in rats.[10] Therefore, this age-related loss of CNDP2 may be responsible for age-related appetite dysregulation. Yet, it remains unclear whether decreased expression of CNDP2 directly translates to increased fat mass or disrupted glycolytic regulation through lower LacPhe levels. Similarly, it is unclear if regular exercise throughout one's life affects

CNDP2 expression in old age, or if exercise-induced LacPhe production is only acute, without lasting effects. Equally, the secondary roles of CNDP2, if any are related to LacPhe, remain unclear. For example, recent studies have shown that CNDP2 is crucial in maintaining metabolic balance and transport functions in human proximal tubule cells.[11] Additionally, variants in the CNDP2 gene have been linked to an increased risk of diabetic nephropathy, tumor disease, and aggravated kidney damage in *Cndp2*-KO mice, potentially due to increased ferroptosis.[11] Given the necessity of gut epithelial $CNDP2^{+}$ in producing LacPhe, this evinces that the lack of CNDP2 increases the risk of other age-related diseases. An age-related loss of CNDP2 *in vivo* would suggest that the loss of LacPhe is a driver of age-related metabolic and kidney disease.

Additionally, the tissue-dependent effects of LacPhe are yet to be understood. Our understanding of tissue dependency with aging is undergoing rapid transformations, and recent studies underscore that traditional models of system-wide longevity may be inaccurate.[12] Rather, lifespan is determined by the accelerated aging of a single, or multiple single, organs, which predicts future disease states and mortality.[12] Thus, the role of exercise in modifying the relative accelerated aging phenotypes in organ-specific decline, may differ between individuals. However, it is unknown if this inter-individual or intra-individual organ heterogeneity may be attributed to LacPhe. Berkel and Cacan[10] have found that *in silico* CNDP2 expression, in response to caloric restriction, is elevated in murine white adipose tissue, but not in heart tissue Additionally, loss of CNDP2, which affects LacPhe, is associated with altered kidney function.[11] Yet, LacPhe presence in other tissues has not been well-explored. It may be that LacPhe can slow down accelerated aging in certain organs, in part due to its improved glycolytic handling. Since the receptors and neural circuits involved with LacPhe remain unclear,[3] this is a promising area of future research. It may be that estrogen and its receptors, particularly estrogen receptor alpha, may be involved in the action of LacPhe. This is a promising area of research since recent studies have found that estrogen receptor alpha is involved in both blood pressure as well as regulation of body weight through the medial amygdala.[13-16] In any case, these and other neural circuits must be examined.

Interestingly, while the bulk of the studies on LacPhe have considered its systematic energy-balancing effects, LacPhe may be related other disease states through oxidative stress. Significantly higher LacPhe levels are associated with Phenylketonuria, an inborn error of Phe metabolism that affects neurocognitive functioning.[17] van Wegberg et al.[17], using an untargeted metabolomics approach, found that LacPhe showed a positive association with reaction times. Unexpectedly, this study also showed that mental health issues are negatively associated with LacPhe, which may be a by-product of social burdens caused by dietary restrictions of Phe.[17] While LacPhe has primarily been studied in the context of Phenylketonuria, it has also been shown to be implicated in other disease states including mitochondrial encephalopathy lactate acidosis syndrome (as discussed in van Wegberg et al.[17]) and myocardial infarction.[18] Notably, both of these studies reflect potential mitochondrial overload, with LacPhe potentially arising with greater mortality risk in myocardial infarction as a response to oxidative stress and to restore long-term glycemic control.[18] Since working memory may also be related to oxidative stress,[17] this suggests a poorly elucidated role of LacPhe in modulating cellular responses to oxidative stress and

other signs of mitochondrial dysfunction.[19] As an increased burden of oxidative stress is a hallmark of the aging process, the role of LacPhe oxidative stress, especially in disease states such as Alzheimer's disease, remains unclear.

Finally, in the future, while LacPhe has increasingly been studied, tangential modulators must also be studied. Notably, metformin is associated with increases of several N-lactoyl amino acids beside LacPhe.[5] This reflects a study that suggested type 2 diabetes diabetic retinopathy is associated with several N-lactoyl amino acids, including N-lactoyl isoleucine, N-lactoyl valine, N-lactoyl tyrosine, N-lactoyl phenylalanine, and N-(2-furoyl) glycine.[20] Similarly, CNDP2 is known to mediate the reverse proteolysis of other N-lactoyl-amino acids.[21] Mechanistically, growth differentiation factor 15 (GDF15) is also released as an exercine. Notably, CNDP2-KO mice remain fully sensitive to the anorexigenic effects of recombinant GDF15 and semaglutide.[4] Interestingly, GDF15 has recently been observed to modulate glucose homeostasis in the loss of the mitochondrial fusion protein OPA1.[22] However, the relation between GDF15, Lac-Phe, and metformin in energy balance currently remains unknown.[4] Recent studies have also shown SLC17A1 and SLC17A3, which are part of a family of transporters for amino acids, act as physiologic urine transporters for Lac-Phe (see https://www.biorxiv.org/content/10.1101/2024.04.18.589815v1.abstract). While all of these topics have provided insights in elucidating the regulators of LacPhe and other N-lactoyl amino acids, their relevance in aging research remains limited.

Conclusion:

The potential benefits of LacPhe in the context of aging are promising, yet few studies have adequately studied them. A withstanding question in the field of aging research is the seemingly deleterious effects of metformin and exercise with aging. Recent findings have shown that metformin abrogated exercise-mediated increases in elder human skeletal muscle mitochondrial respiration.[23] Thus, while it may be tempting to treat LacPhe as a miracle compound, especially with the rise of gluconeogenesis-based weight-loss treatments that may rely upon LacPhe, the therapeutic potential of LacPhe remains unclear. Given that LacPhe may be associated with certain disease states through oxidative stress,[17] the interdependence of aging, exercise, mitochondrial dysfunction, and LacPhe remain of central interest. Otherwise, it may be that inflammatory mediators mediate the relationship of LacPhe arising in disease states (e.g., glioma[24]) and in response to intense exercise. Research using aging models will be vital to determine the long-term impact of LacPhe on aging processes and age-related diseases, especially in the context of its broader mechanisms within the regulators discussed here. Together, these advances in the understanding of LacPhe in aging may yield the ability to therapeutical utilize it for improving overall health and longevity.

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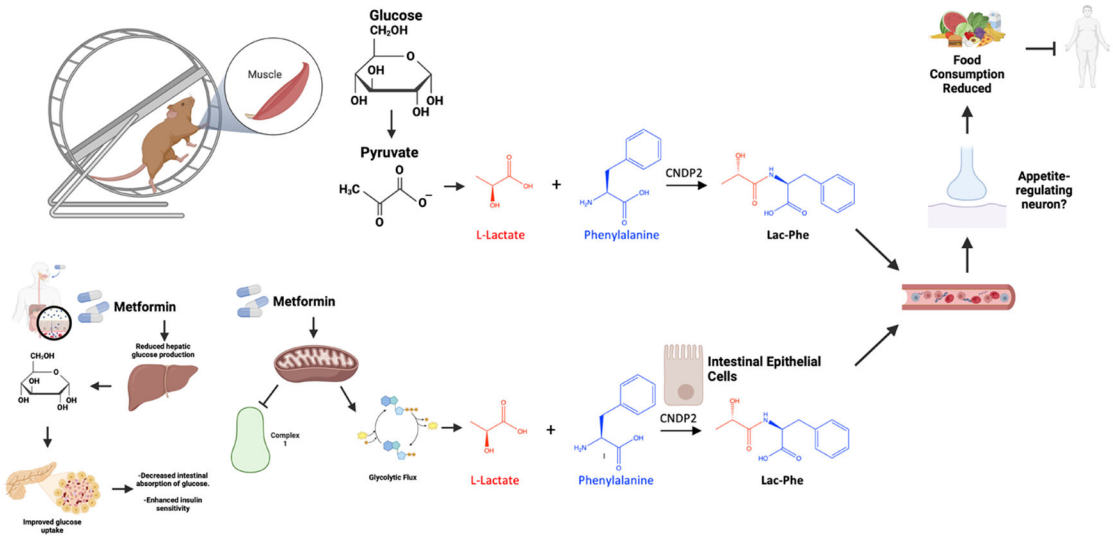

Figure 1: LacPhe contributing to weight loss and appetite mitigating effects of exercise (top) and metformin (bottom) through CNDP2.

The exact mechanisms of regulation of appetite neurons remain unclear, the end result is reduced food consumption, leading to lower fat mass and body weight. Created with BioRender.com. CNDP2: Carnosine dipeptidase 2.