Lactate Reimagined as an Exerkine: Emerging Evidence, Physiological Benefits, Controversies, and Clinical Applications

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Abstract

Misconceptions surrounding lactate have persisted for centuries; once dismissed as a mere by-product of anaerobic metabolism and a culprit of fatigue, lactate is now recognized as a powerful exerkine with broad physiological influence across multiple systems. This shift in understanding redefines lactate as more than a waste product, recognizing its critical role in inter-organ communication and physiological regulation during and after exercise. This narrative review explores the multifaceted functions of lactate, highlighting its impact on metabolic regulation, neuroplasticity, immune modulation, muscle adaptation, and angiogenesis. Lactate's interaction with the G-protein-coupled receptor 81 (GPR81) mediates numerous beneficial processes, including anti-inflammatory responses, upregulation of brain-derived neurotrophic factor (BDNF), mitochondrial biogenesis through PGC-1α activation, and vascular endothelial growth factor (VEGF) expression, which supports angiogenesis. While the majority of scientists acknowledge lactate’s vital role in energy homeostasis and systemic signaling, controversies persist concerning the extent of its effects and their dependence on exercise context, intensity, and individual variability. Future research directions include the development of lactate-based therapeutic applications, personalized exercise prescriptions, and integrative approaches with other exerkines. The potential of lactate to enhance patient care, from neurorehabilitation to chronic disease management, underscores its promise as a powerful target for health optimization and performance enhancement. This narrative review aims to deepen our understanding of lactate’s complex roles and guide innovative strategies in health sciences, exercise physiology, and clinical care

Keywords : Lactate, Exerkine, Exercise physiology, Exercise medicine

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แลคเตทมุมมองใหม่ในฐานะเอ็กเซอร์ไคน์: หลักฐานใหม่ ประโยชน์ทางสรีรวิทยา ข้อโต้แย้ง และการประยุกต์ทางคลินิก

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บทคัดย่อ

ความเข้าใจผิดเกี่ยวกับแลคเตทมีมาอย่างยาวนานหลายศตวรรษ จากเดิมที่เคยถูกมองว่าเป็นเพียงผลพลอยได้จากกระบวนการเมแทบอลิซึมแบบไม่ใช้ออกซิเจนและเป็นสาเหตุของความเหนื่อยล้า แต่ปัจจุบันแลคเตทได้รับการยอมรับว่าเป็นเอ็กเซอร์ไคน์ที่สำคัญ ที่ส่งผลทางสรีรวิทยาต่อระบบต่างๆ ในร่างกายอย่างมาก ความเข้าใจที่เปลี่ยนแปลงไปดังกล่าว ทำให้แลคเตทไม่ได้ถูกมองว่าเป็นของเสียอีกต่อไป แต่เป็นตัวกลางสำคัญในการสื่อสารระหว่างอวัยวะและการควบคุมทางสรีรวิทยา ระหว่างการออกกำลังกายและหลังการออกกำลังกาย บทความนี้เป็นการทบทวนวรรณกรรมเชิงพรรณนา ที่ได้รวบรวมบทบาทต่างๆ ของแลคเตท โดยเฉพาะผลกระทบต่อการควบคุมกระบวนการเผาผลาญพลังงาน ความยืดหยุ่นของระบบประสาท การควบคุมระบบภูมิคุ้มกัน การปรับตัวของกล้ามเนื้อ และการสร้างเส้นเลือดใหม่ การทำงานของแลคเตทผ่านตัวรับ G-protein-coupled receptor 81 (GPR81) ช่วยกระตุ้นกระบวนการที่เป็นประโยชน์หลายประการ เช่น การลดการอักเสบ การเพิ่มการแสดงออกของ Brain-Derived Neurotrophic Factor (BDNF) การสร้างไมโตคอนเดรียผ่านการกระตุ้น PGC-1α และการแสดงออกของ Vascular Endothelial Growth Factor (VEGF) ซึ่งช่วยสร้างเส้นเลือดใหม่ แม้ว่านักวิทยาศาสตร์ส่วนใหญ่จะยอมรับบทบาทสำคัญของแลคเตทในการรักษาสมดุลพลังงานและการสื่อสาร แต่ยังมีข้อโต้แย้งเกี่ยวกับขนาดของผลกระทบรวมทั้งความสัมพันธ์ของแลคเตทกับรูปแบบการออกกำลังกาย ความเข้มข้น และความแปรปรวนในแต่ละบุคคล ทิศทางการวิจัยในอนาคตได้แก่ การพัฒนาการประยุกต์ใช้แลคเตทเชิงการรักษา การออกแบบการออกกำลังกายเฉพาะบุคคล และการศึกษาเชิงบูรณาการระหว่างแลคเตทกับเอ็กเซอร์ไคน์อื่นๆ เป็นต้น แลคเตทมีศักยภาพในการเพิ่มประสิทธิภาพการดูแลผู้ป่วย ตั้งแต่การฟื้นฟูสมรรถภาพทางระบบประสาทไปจนถึงการจัดการโรคเรื้อรัง ซึ่งเป็นเป้าหมายสำคัญในการดูแลสุขภาพและส่งเสริมสมรรถภาพทางกาย บทความทบทวนวรรณกรรมเชิงพรรณนานี้มีเป้าหมายเพื่อพัฒนาความเข้าใจบทบาทที่ซับซ้อนของแลคเตทให้ลึกซึ้งมากขึ้น รวมถึงการประยุกต์ใช้เชิงนวัตกรรมสุขภาพ สรีรวิทยาการออกกำลังกาย และการดูแลผู้ป่วย

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Introduction

Lactate has long been a topic of debate in the field of exercise physiology, initially dismissed as a waste product responsible for muscle fatigue and discomfort following intense physical activity (Gladden, 2020). Historically, lactate was associated with anaerobic glycolysis and perceived as a marker of metabolic stress during high-intensity exercise (Hargreaves & Spriet, 2020). As a by-product of glucose metabolism under anaerobic conditions, lactate accumulates when the rate of production surpasses its clearance, traditionally signaling exhaustion (Gladden, 2004). However, it is now recognized that lactate is not exclusively produced during exercise. Even at rest, tissues such as red blood cells, brain, skin, and adipose tissue contribute to basal lactate production, highlighting its fundamental role in intermediary metabolism (Van Hall, 2010). What distinguishes lactate as an exerkine is the surge in its concentration and signaling activity in response to physical activity, particularly from contracting skeletal muscle.

This traditional view shifted with the development of the "lactate shuttle" hypothesis proposed by George Brooks, which posited that lactate serves as an essential intermediary in cellular metabolism rather than a mere waste product (Brooks, 2020). The hypothesis illustrates that lactate is produced by glycolytic tissues and then transported to oxidative tissues, where it is utilized as an energy substrate. In addition to oxidation, lactate is also cleared through gluconeogenesis in the liver (Cori cycle), contributing to blood glucose regulation and overall lactate homeostasis. Recent advances in molecular exercise physiology have highlighted lactate’s role beyond intermediary metabolism, identifying it as an exerkine - a class of bioactive molecules secreted into circulation in response to physical activity, capable of exerting autocrine, paracrine, and endocrine effects on multiple organ systems. Exerkines are released from skeletal muscle and other organs during exercise and serve as molecular messengers that mediate many of the health-promoting effects of physical activity, including metabolic regulation, neuroplasticity, cardiovascular adaptation, and immune modulation (Brooks et al., 2023; Liu et al., 2024).

Within this framework, lactate has emerged as a prototypical exerkine due to its ability to communicate metabolic status from active muscle to distant tissues. Through its interaction with the G-protein-coupled receptor 81 (GPR81), lactate influences gene expression, immune cell activity, and intracellular signaling cascades involved in adaptation and repair (Shang et al., 2023). This signaling capacity elevates lactate from a perceived metabolic by-product to a critical regulator of exercise-induced systemic adaptations. Recognizing lactate’s systemic roles reveals important clinical implications, extending beyond exercise performance to potential therapies for neurological, inflammatory, and metabolic diseases. This signaling function bridges exercise physiology and translational medicine, offering new paths for health and patient care.

The objectives of this article are to provide a comprehensive overview of lactate's evolving role as an exerkine, explore its benefits and applications within exercise science and patient care, delve into existing controversies, and outline potential future research directions. This synthesis aims to deepen understanding and foster innovative approaches to enhancing human health and performance through exercise-derived molecular signaling.

Table 1 Classification, releasing tissue, and physiological functions of key exerkines

Exerkine	Classification	Releasing Tissue	Physiological Function	Key References
Lactate	Myometabolite or Metabolite exerkine	Skeletal muscle	Metabolic regulation, mitochondrial biogenesis, BDNF-mediated neuroplasticity, angiogenesis	Brooks et al., 2023; El Hayek et al., 2019
IL-6	Myokine	Skeletal muscle, immune cells	Glucose metabolism, lipolysis, immune modulation	Hargreaves & Spriet, 2020; Pedersen & Febbraio, 2012
BDNF	Myokine, Cerebrokine	Skeletal muscle, brain	Neurogenesis, learning, memory, cognitive function	Wrann et al., 2013
Irisin	Myokine	Skeletal muscle	White-to-brown fat conversion, energy expenditure	Boström et al., 2012; Huh, 2018
Myostatin	Myokine	Skeletal muscle	Negative regulator of muscle growth	Lee et al., 2001; Rodgers & Garikipati, 2021
FGF21	Hepatokine, Myokine	Liver, skeletal muscle	Metabolic adaptation to exercise, insulin sensitivity	Kim et al., 2013; Fisher & Maratos-Flier, 2016
VEGF	Angiokine, Myokine	Skeletal muscle, endothelial cells	Angiogenesis, vascular remodeling	Hoier & Hellsten, 2014; Olfert et al., 2016
Cathepsin B	Myokine	Skeletal muscle	Neuroprotection, hippocampal neurogenesis	Moon et al., 2016; Wrann et al., 2013
Klotho	Cerebrokine, Anti-aging protein	Kidney, brain, skeletal muscle	Anti-aging, neuroprotection, vascular health	Kuro-o et al., 1997; Sahu et al., 2018

Note: While the term "myometabolite" refers to metabolites produced specifically by skeletal muscle (e.g., lactate), the broader and more widely understood term "metabolite exerkine" is used to emphasize both their origin and systemic signaling function induced by exercise. IL-6 = Interleukin-6; BDNF = Brain-Derived Neurotrophic Factor, FGF21= Fibroblast Growth Factor 21, VEGF = Vascular Endothelial Growth Factor

The concept of lactate as an exerkine represents a paradigm shift in exercise physiology. Traditionally considered merely a by-product of anaerobic glycolysis, lactate's role has now expanded significantly as new evidence reveals its capacity to act as a signaling molecule that communicates with various tissues throughout the body (Brooks, 2020). This recognition has been supported by discoveries showing that lactate is produced in response to exercise and travels via the bloodstream to exert effects on organs such as the brain, liver, adipose tissue, and immune cells (Brooks et al., 2023).

Lactate's role as an exerkine is largely mediated through its binding to GPR81, also known as hydroxycarboxylic acid receptor 1 (HCAR1). This receptor is expressed in multiple tissues, including adipose tissue, liver, and skeletal muscle, where it modulates numerous metabolic and signaling pathways (Liu et al., 2024). For instance, lactate binding to GPR81 in adipose tissue has been shown to inhibit lipolysis, suggesting its role in energy conservation and metabolic regulation during exercise (Hargreaves & Spriet, 2020). Similarly, lactate signaling through GPR81 in immune cells exerts anti-inflammatory effects by reducing the production of pro-inflammatory cytokines, which highlights its potential application in inflammatory diseases and exercise recovery (Llibre et al., 2025).

Lactate also plays a critical role in the brain, where it crosses the blood-brain barrier and acts as an energy substrate during prolonged exercise (Shang et al., 2023). Additionally, lactate can stimulate the expression of brain-derived neurotrophic factor (BDNF), thereby promoting neuroplasticity, cognitive enhancement, and neuroprotection (El Hayek et al., 2019). These findings suggest that lactate-mediated signaling extends far beyond metabolism and muscle physiology, positioning it as a central mediator in exercise-induced systemic adaptations.

Recent discoveries have also expanded the mechanistic understanding of lactate's signaling functions. One such mechanism is histone lactylation, an epigenetic modification in which lactate serves as a substrate for the addition of lactyl groups to histone lysine residues. This process influences gene expression profiles, particularly in macrophages and muscle cells, and may play an important role in regulating inflammatory resolution, immune tolerance, and skeletal muscle remodeling during post-exercise recovery (Zhang et al., 2019).

In parallel, the Astrocyte–Neuron Lactate Shuttle (ANLS) has refined the classic lactate shuttle hypothesis by emphasizing the interplay between astrocytes and neurons. During intense neuronal activity, astrocytes metabolize glucose to lactate, which is then exported via MCT1 or MCT4 and taken up by neurons through MCT2. This shuttling process provides neurons with a rapidly available energy source and supports synaptic transmission, long-term potentiation (LTP), and cognitive resilience (Pellerin & Magistretti, 2012; Magistretti & Allaman, 2015).

The lactate shuttle hypothesis, first proposed by George Brooks, has undergone significant expansion, with recent studies confirming that lactate functions as an energy carrier between glycolytic and oxidative tissues (Brooks, 2020). Moreover, the metabolic and signaling roles of lactate have led to its classification as a key exerkine. Exercise-induced lactate production and subsequent signaling are critical for adaptations such as improved mitochondrial biogenesis, enhanced muscle hypertrophy, and immune modulation (Bartoloni et al., 2024). This has significant implications for optimizing exercise training protocols, enhancing athletic performance, and developing therapeutic interventions for chronic diseases.

Despite these advances, some controversies persist regarding the precise mechanisms through which lactate exerts its systemic effects. The influence of individual factors such as exercise intensity, duration, and training status on lactate signaling remains an area of active investigation (Hargreaves & Spriet, 2020). Continued research is needed to elucidate the full spectrum of lactate's exerkine functions and harness its potential benefits in health and disease management.

Benefits of lactate as an exerkine

1. Metabolic regulation and energy homeostasis

Lactate serves a crucial role in maintaining metabolic regulation and energy homeostasis, especially during and after exercise (Figure 1). As a by-product of glycolysis, lactate accumulates in muscles during intense exercise and is subsequently released into the bloodstream. This circulating lactate is taken up by organs such as the liver, heart, and brain, where it serves as a fuel source, either being oxidized directly for energy or converted back to glucose through gluconeogenesis in the liver (Brooks, 2020; Brooks et al., 2023). This process, known as the Cori cycle (Figure 2), underscores lactate's importance in maintaining energy balance by recycling lactate into usable energy substrates. Additionally, lactate's role as an energy carrier between glycolytic and oxidative tissues allows for enhanced endurance performance by sustaining energy supply under high metabolic demands (Hargreaves & Spriet, 2020).

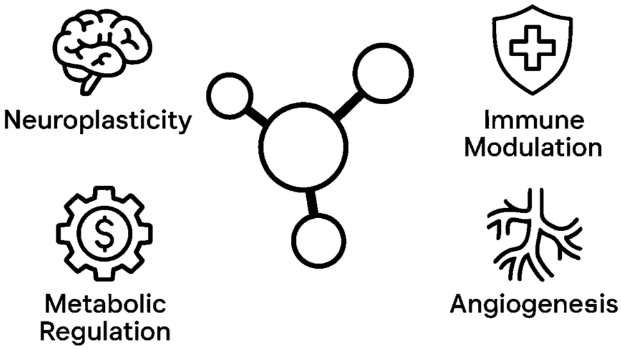

Figure 1 Summary of benefits of lactate as an exerkine
(Adapted from Brooks, 2020; Brooks et al., 2023)

Beyond its role as a substrate, lactate contributes to mitochondrial biogenesis, a key adaptation to endurance training. Lactate acts upstream of several regulatory pathways involving AMP-activated protein kinase (AMPK), reactive oxygen species (ROS), sirtuin 1 (SIRT1), and sirtuin 3 (SIRT3), all of which converge on peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α), the master regulator of mitochondrial biogenesis (Brooks et al., 2023). Activation of PGC-1α promotes the generation of new mitochondria, enhancing the oxidative capacity of muscle cells and improving endurance, energy metabolism, and overall cellular health.

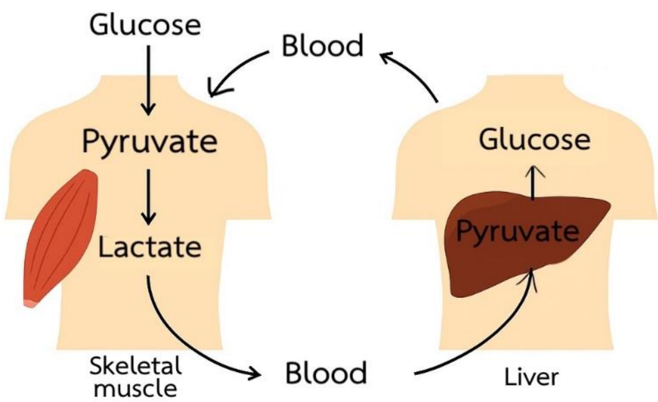

Figure 2 Cori cycle
(Adapted from van Hall, G., 2010)

2. Neuroplasticity and cognitive function

The benefits of lactate extend beyond skeletal muscle metabolism to influence brain function and neuroplasticity. During exercise, lactate crosses the blood–brain barrier via monocarboxylate transporters (MCTs), especially MCT1 and MCT2, and serves as an alternative energy substrate for neurons and astrocytes, thereby supporting cerebral metabolism during periods of elevated energy demand (Shang et al., 2023). This concept is further supported by the ANLS, which describes how astrocytes convert glucose to lactate and supply it to neurons via MCT transporters. This mechanism ensures neurons have rapid access to energy during synaptic activity and is critical for maintaining neurotransmission and neuroplasticity (Pellerin & Magistretti, 2012).

Beyond its metabolic role, lactate acts as a signaling molecule that modulates neuroplasticity. One of the key mechanisms involves the lactate-induced upregulation of brain-derived neurotrophic factor (BDNF), a neurotrophin critically involved in synaptic plasticity, LTP, neurogenesis, and memory consolidation. Lactate stimulates BDNF expression through activation of signaling pathways such as SIRT1, PGC-1α, and the NMDA receptor–dependent CREB (cAMP response element-binding protein) pathway, which are essential for activity-dependent gene transcription in neurons (El Hayek et al., 2019).

Furthermore, lactate may exert its neuroprotective effects via GPR81 (also known as HCAR1), which is expressed on brain endothelial and glial cells. Activation of GPR81 influences neurovascular coupling and modulates inflammatory signaling, contributing to an anti-inflammatory milieu that supports neuronal survival. This receptor-mediated signaling is believed to help reduce neuroinflammation and oxidative stress, factors implicated in neurodegenerative diseases and cognitive decline (Shang et al., 2023). Thus, exercise-induced elevations in circulating lactate promote a multi-faceted neurobiological response that includes enhanced BDNF signaling, improved mitochondrial function, modulation of synaptic plasticity, and reduced neuroinflammation. The integration of ANLS into this framework emphasizes lactate's role not only as a systemic exerkine but also as a local metabolic intermediary supporting neuron-glia interactions and brain energy dynamics.

These effects may underlie the observed cognitive improvements following regular physical activity and position lactate as a potential therapeutic target in conditions such as Alzheimer’s disease, depression, and age-related cognitive impairment. Lactate’s dual role as an energy substrate and exerkine underscores its significance in enhancing brain resilience, learning, and mental health.

3. Anti-inflammatory and immune-modulatory effects

Lactate also exhibits potent anti-inflammatory and immune-modulatory properties, primarily mediated through its interaction with GPR81 (Llibre et al., 2025). When lactate binds to GPR81, it downregulates the expression of pro-inflammatory cytokines, such as TNF-α and IL-6, reducing systemic inflammation. This regulatory effect is particularly beneficial for recovery from exercise-induced inflammation, minimizing muscle damage and facilitating tissue repair (Liu et al., 2024). However, lactate’s immunomodulatory effects appear to be context-dependent. Under certain pathological conditions, such as in tumor microenvironments or during chronic hypoxia, elevated lactate concentrations may instead promote pro-inflammatory or immunosuppressive pathways. For instance, high lactate levels can impair cytotoxic T-cell and NK cell function, contributing to immune evasion in cancer (Brand et al., 2016). Additionally, lactate may upregulate the expression of IL-17 and other pro-inflammatory mediators via HIF-1α–dependent signaling in specific immune cell subsets (Colegio et al., 2014).

These findings highlight the dual role of lactate: while it suppresses excessive inflammation in the context of acute exercise and tissue regeneration, it may also contribute to immune dysregulation in chronically inflamed or hypoxic tissues. Furthermore, lactate-mediated modulation of immune function may offer therapeutic value in chronic inflammatory diseases, where controlling excessive inflammation is paramount.

4. Muscle adaptation, hypertrophy, and angiogenesis

Lactate accumulation during high-intensity exercise plays a significant role in muscle adaptation and hypertrophy. The presence of lactate within muscle fibers creates an acidic intracellular environment, which triggers a cascade of signaling events, including the activation of the mammalian target of rapamycin (mTOR) pathway, a key regulator of protein synthesis and muscle growth (Bartoloni et al., 2024). Lactate also promotes the secretion of anabolic hormones, such as growth hormone, further contributing to muscle hypertrophy and tissue remodeling (Brooks, 2020). Moreover, lactate-induced signaling has been linked to the upregulation of VEGF, a key factor in angiogenesis—the formation of new blood vessels (Brooks et al., 2023). This process enhances blood flow, nutrient delivery, and oxygen transport to exercising muscles, further supporting endurance and recovery. The angiogenic response to exercise training, mediated by lactate, highlights its role in vascular adaptation and overall cardiovascular health.

Types of exercises that provide benefits

1. High-intensity interval training (HIIT)

HIIT involves repeated bouts of vigorous exercise (≥80% VO_{2max}), interspersed with recovery periods. Sessions typically last 20–30 minutes and induce considerable physiological stress, prominently activating anaerobic glycolysis and elevating lactate levels (Hargreaves & Spriet, 2020).

Lactate generated during HIIT acts as a potent exerkine, engaging GPR81 receptors and triggering signaling pathways including PGC-1α, AMPK, SIRT1/3, and ROS, which support mitochondrial biogenesis, oxidative metabolism, and glucose regulation (San-Millán & Brooks, 2019). Lactate also crosses the blood–brain barrier, stimulating BDNF expression, thereby enhancing neuroplasticity and offering neuroprotective benefits (El Hayek et al., 2019). Additionally, it promotes an anti-inflammatory response by downregulating cytokines such as TNF-α and IL-6 through immune cell GPR81 activation (Llibre et al., 2025).

From a musculoskeletal perspective, HIIT supports both endurance and hypertrophy via pathways like mTOR, and enhances angiogenesis through VEGF upregulation, improving capillarization and tissue perfusion (Bartoloni et al., 2024). Clinically, HIIT is time-efficient and effective for improving aerobic/anaerobic fitness, insulin sensitivity, and VO_{2max}, making it suitable for individuals with metabolic syndrome, type 2 diabetes, and cardiovascular conditions, when appropriately supervised.

2. Strength and resistance training

Strength and resistance training utilizes external loads, such as free weights, machines, or bodyweight, to promote muscle strength, hypertrophy, endurance, and power. Protocols typically involve moderate to high intensities (60–90% 1RM), multiple sets, and short rest intervals (30–90 seconds), especially in hypertrophy-focused regimens. These parameters facilitate substantial lactate accumulation, particularly during high-rep sets and advanced techniques like supersets or drop sets (Bartoloni et al., 2024; Brooks, 2020).

Unlike aerobic exercise, resistance training frequently exceeds the anaerobic threshold, activating glycolysis and generating lactate. This intracellular acidification stimulates mTOR signaling, enhancing protein synthesis and muscle growth, and is reinforced by hormonal responses including growth hormone and IGF-1 (Brooks, 2020).

Beyond muscle anabolism, lactate functions as an exerkine, influencing systemic adaptations. It upregulates PGC-1α, supporting mitochondrial biogenesis and endurance; binds to GPR81 receptors on immune cells, reducing inflammation and enhancing tissue recovery; and increases VEGF expression, promoting angiogenesis and nutrient delivery (San-Millán & Brooks, 2019; Llibre et al., 2025).

Lactate may also cross the blood–brain barrier to stimulate BDNF, improving neuroplasticity and cognitive function, particularly beneficial for aging populations (El Hayek et al., 2019). To maximize lactate-mediated benefits, training should include:

1) 8–15 reps with moderate loads

2) 30–60 sec rest intervals

3) Compound movements (e.g., squats, deadlifts)

4) Metabolic strategies (e.g., supersets, circuit-style sets)

Resistance training is clinically valuable for managing sarcopenia, osteoporosis, metabolic syndrome, and improving glucose metabolism, mobility, and quality of life, especially in older adults. The combined musculoskeletal and neurocognitive benefits highlight its importance in both performance and rehabilitation contexts.

3. Endurance training at lactate threshold

Endurance training near the lactate threshold (LT), the intensity at which lactate production exceeds clearance (60–80% VO_{2max}), is a highly effective strategy to stimulate both central and peripheral adaptations (San-Millán & Brooks, 2019). This “sweet spot” intensity promotes metabolic stress while allowing recovery, maximizing aerobic gains.

Sustained aerobic efforts (e.g., tempo runs, steady-state cycling, or rowing) at or just below LT increase the body's ability to utilize lactate as both a fuel and signaling molecule. Lactate at this level enhances mitochondrial biogenesis via AMPK, SIRT1/3, and PGC-1α activation, improving fat oxidation, metabolic flexibility, and lactate clearance capacity. Cardiovascular adaptations include improved stroke volume and plasma volume expansion, which augment oxygen delivery. Simultaneously, lactate promotes angiogenesis through VEGF upregulation, enhancing capillarization and muscle perfusion (Bartoloni et al., 2024).

Lactate also crosses the blood–brain barrier, where it fuels neurons and upregulates BDNF, supporting cognitive resilience, mood regulation, and neuroplasticity - particularly beneficial for aging populations (El Hayek et al., 2019). Immunologically, LT training supports anti-inflammatory signaling via GPR81, stabilizing immune function without the suppressive effects sometimes seen in high-intensity exercise (Llibre et al., 2025). Muscular adaptations include improved oxidative capacity in Type I and IIa fibers and more efficient lactate shuttling, key to fatigue resistance during prolonged activity. Training guidelines for LT adaptations involve:

1) Intensity: ~65–80% VO_{2max} or 75–85% HR_{max}

2) Duration: 20–60 minutes per session

3) Frequency: 2–4 sessions per week

4) Progression: Gradual increases in duration or controlled heart rate drift

LT training is ideal for endurance athletes aiming to improve race pace and delay fatigue, and for clinical populations (e.g., cardiac rehab, type 2 diabetes) due to its low orthopedic strain and high safety profile. Intensity can be monitored via blood lactate, ventilatory threshold, or RPE (6–7/10).

4. Circuit training

Circuit training combines resistance and aerobic modalities in a continuous or near-continuous format, with minimal rest between exercises. This approach targets both muscular strength and cardiovascular endurance, while generating substantial metabolic stress. Formats may include time-based intervals, repetition-based sets, or alternating upper/lower body movements, using modalities such as bodyweight, free weights, or mixed equipment, making it highly adaptable for various populations.

The high-intensity, low-rest structure of circuit training rapidly activates anaerobic glycolysis, resulting in elevated lactate production. Circulating lactate acts as a systemic exerkine, stimulating PGC-1α, which drives mitochondrial biogenesis, aerobic capacity, and fat metabolism (Brooks et al., 2023). These effects are amplified with compound exercises (e.g., squats, kettlebell swings, burpees) and integrated aerobic elements.

Lactate also improves glucose uptake and insulin sensitivity, supporting applications for individuals with type 2 diabetes, obesity, and metabolic syndrome (Hargreaves & Spriet, 2020). On an immunological level, lactate activates GPR81 receptors, reducing TNF-α and IL-6 production, contributing to an anti-inflammatory environment that promotes recovery and immune homeostasis (Llibre et al., 2025).

Muscle adaptations are driven by lactate-induced mTOR signaling, leading to muscle protein synthesis, growth hormone and IGF-1 release, and hypertrophy (Bartoloni et al., 2024). Lactate also crosses the blood–brain barrier, enhancing BDNF expression, with benefits for neuroplasticity, learning, and emotional regulation (El Hayek et al., 2019). Additionally, lactate stimulates VEGF, promoting angiogenesis and improved vascular perfusion.

Additionally, circuit training enhances vascular adaptation through lactate-stimulated VEGF expression, promoting angiogenesis and improving muscle perfusion and oxygen delivery (Brooks et al., 2023). Circuit training is highly adaptable and effective for:

1) General populations seeking full-body, time-efficient workouts

2) Older adults or individuals in rehabilitation, particularly with low-impact modalities

3) Athletes aiming to improve muscular endurance and metabolic efficiency

4) Clinical populations targeting weight loss, blood glucose control, and mobility enhancement

Training parameters to optimize lactate accumulation and systemic benefits include:

1) Intensity: Moderate to high (70–90% HRmax)

2) Work-to-rest ratio: 2:1 or 3:1 (e.g., 30 sec work:10 sec rest)

3) Duration: 20–40 minutes per session

4) Exercise selection: 5–10 multi-joint movements per round

5) Progression: Increase number of rounds, exercise complexity, or external load

5. Sprint interval training (SIT)

SIT involves repeated, short bursts of near-maximal to supramaximal effort (typically >90–95% of VO_{2max}), interspersed with longer recovery intervals. Common protocols include 20–30 second all-out sprints followed by 2–4 minutes of rest, as well as Tabata-style sessions and maximal hill sprints. Unlike traditional HIIT, SIT emphasizes explosive performance, producing profound metabolic and neuromuscular stress in minimal time.

SIT elicits exceptionally high lactate levels due to intense anaerobic glycolysis, fast-twitch fiber recruitment, and limited lactate clearance (Shang et al., 2023). This positions lactate as a potent exerkine, triggering widespread adaptations across organ systems. Lactate generated during SIT activates PGC-1α and oxidative enzymes, supporting mitochondrial biogenesis, metabolic flexibility, and insulin sensitivity, making SIT effective for managing metabolic syndrome and prediabetes (Brooks et al., 2023; Hargreaves & Spriet, 2020).
Crossing the blood–brain barrier, lactate also stimulates BDNF expression, enhancing cognitive performance, memory, and emotional resilience (El Hayek et al., 2019). Immunologically, SIT-mediated GPR81 activation reduces pro-inflammatory cytokine activity, fostering immune recovery and resilience post-exercise (Llibre et al., 2025).

At the muscular level, SIT promotes both mTOR and AMPK activation, facilitating remodeling in type II fibers and enhancing anaerobic power (Bartoloni et al., 2024). Additionally, lactate stimulates VEGF, driving angiogenesis, improving stroke volume, capillary density, and oxygen delivery (Brooks et al., 2023).

Training guidelines to maximize lactate-driven benefits include:

1) Sprint duration: 20–30 seconds

2) Recovery: 2–4 minutes (active or passive)

3) Repetitions: 4–6 per session

4) Frequency: 2–3 sessions per week

5) Progression: Gradual increase in sprint volume, reduced rest intervals, or intensity progression

Despite its intensity, SIT is a time-efficient strategy yielding substantial cardiometabolic, cognitive, and vascular benefits. It is applicable for both athletes and clinical populations when properly monitored. Gradual progression, adequate warm-up/cooldown, and fatigue management are essential to prevent overtraining and ensure safety. However, caution is warranted when applying SIT in certain populations such as the frail elderly, individuals with uncontrolled hypertension, or patients with cardiovascular disease. In these cases, medical screening, individualized exercise prescription, and close supervision by qualified professionals are strongly recommended. Modified or submaximal SIT protocols may be more appropriate to reduce risks while still promoting beneficial adaptations.

6. Functional fitness / CrossFit-style training

Functional fitness, exemplified by CrossFit-style training, is a high-intensity, multimodal approach involving varied, functional movements performed at moderate to high intensities. Sessions typically integrate resistance exercises (e.g., squats, deadlifts), cardiovascular tasks (e.g., rowing, running), gymnastics (e.g., pull-ups, burpees), and metabolic conditioning circuits (e.g., AMRAPs, EMOMs, “For Time”).

Due to large muscle recruitment, short rest intervals, and sustained glycolytic effort, functional fitness elicits significant lactate accumulation, triggering both local muscular and systemic exerkine responses. Lactate stimulates PGC-1α, AMPK, and SIRT1/3, enhancing mitochondrial biogenesis, oxidative capacity, and metabolic flexibility (Brooks et al., 2023).

Functionally driven training improves glucose uptake, insulin sensitivity, and resting metabolic rate, making it effective for preventing obesity and metabolic syndrome (Hargreaves & Spriet, 2020). High-repetition resistance work under fatigue activates mTOR, elevating GH and IGF-1, and supporting hypertrophy and endurance in type II fibers (Bartoloni et al., 2024). Lactate also crosses the blood–brain barrier, enhancing BDNF expression, which supports cognitive function, emotional regulation, and neuroplasticity (El Hayek et al., 2019). The complex motor demands of functional fitness further enhance executive function, motor learning, and exercise adherence.

Immunologically, lactate-GPR81 signaling contributes to anti-inflammatory effects and may mitigate post-exercise immunosuppression, supporting immune resilience (Llibre et al., 2025). Lactate also induces VEGF expression, enhancing angiogenesis, capillary density, and cardiovascular function (Brooks et al., 2023).

Functional fitness is highly scalable, suitable for general fitness, rehabilitation, occupational readiness, and clinical prevention. Its variety and engagement promote long-term adherence and psychological well-being.

Programming recommendations for lactate-driven adaptations involve:

1) Workout duration: 10–30 minutes at high effort (e.g., AMRAPs, EMOMs, "For Time")

2) Rest structure: Minimal or active recovery

3) Movement selection: Emphasize compound, multi-joint lifts and varied task modalities

4) Progression: Increase volume, intensity, complexity, or density over time

While functional fitness is scalable and adaptable, caution is necessary when applying it to certain populations such as frail older adults, individuals with musculoskeletal impairments, or those with cardiovascular conditions. These groups may require medical clearance, modified exercise protocols, and close supervision from trained professionals to ensure safety and appropriateness. Low-impact variations, extended rest periods, reduced volume, and emphasis on technique over intensity are recommended in such cases. Personalized assessment and gradual progression are essential to minimize injury risk and optimize long-term functional gains.

Given its intensity, technical supervision, periodization, and recovery strategies (e.g., sleep, hydration, nutrition) are essential. Monitoring RPE, HR, and lactate response can optimize outcomes and mitigate overtraining risk.

Controversies surrounding lactate

Despite its emerging recognition as an exerkine, lactate remains a subject of debate within the scientific community. The primary controversy revolves around its precise role in metabolism and its effects on systemic physiology. While proponents of lactate's signaling role highlight its diverse benefits, some researchers question the extent and universality of these effects.

The majority of scientists currently support the view that lactate plays a central role in energy metabolism and acts as a signaling molecule with wide-ranging physiological effects (Brooks, 2020). This consensus has been reinforced by mounting evidence demonstrating that lactate is a key intermediary in the lactate shuttle, facilitating communication between glycolytic and oxidative tissues (Brooks et al., 2023). Many researchers, including George Brooks, have emphasized that lactate's function extends far beyond being a metabolic by-product and serves critical roles in energy homeostasis, immune regulation, and neuroplasticity (Brooks, 2020).

However, some scientists remain skeptical about lactate's broader systemic impact and question whether its effects are as significant and universal as described in certain studies. Some researchers argue that lactate's influence is highly context-dependent, varying based on exercise intensity, duration, individual fitness levels, and other factors. Gladden (2004) notes that while lactate plays important metabolic roles, its effects must be understood within a broader network of physiological interactions rather than in isolation. These critics caution against oversimplifying lactate’s roles or attributing systemic adaptations solely to lactate without considering complex interactions with other metabolites. Furthermore, challenges in accurately measuring and interpreting lactate’s systemic effects in human studies remain a major limitation. Factors such as timing of blood sampling, individual lactate kinetics, tissue-specific responses, and the influence of confounding variables (e.g., hydration, diet, stress) can complicate assessments. These methodological constraints may lead to inconsistencies across studies and hinder the translation of mechanistic findings into clinical applications. One widely accepted view, even among skeptics, is that lactate itself is not the cause of exercise-induced acidosis, as it was once believed. The scientific consensus now acknowledges that muscle acidosis is primarily driven by the accumulation of hydrogen ions, not lactate. This shift in understanding has been championed by researchers such as Hargreaves and Spriet (2020), who emphasize the need for clear public and scientific communication regarding lactate’s true role in performance and recovery.

Overall, while a majority of scientists recognize lactate’s importance as a metabolic and signaling molecule, ongoing debate centers on the nuances and mechanisms of its systemic effects, as well as the methodological challenges in capturing these effects in vivo. This underscores the need for continued research to clarify lactate’s roles across different physiological and clinical contexts.

Future directions in lactate research

Research on lactate as an exerkine is expanding rapidly, with several promising directions for future study, particularly in applications aimed at improving human health and performance. One of the most compelling areas is the development of targeted therapeutic applications. Lactate’s ability to modulate immune responses and reduce inflammation offers significant potential in treating chronic inflammatory diseases, neurodegenerative disorders, and metabolic syndromes (Liu et al., 2024). Designing lactate-based therapies, such as controlled lactate infusions or exercise mimetics that simulate lactate's effects, could provide non-pharmacological interventions for conditions like Alzheimer’s disease, rheumatoid arthritis, and type 2 diabetes (Shang et al., 2023).

Personalized exercise prescriptions based on individual lactate kinetics represent another critical research direction. Exercise protocols tailored to optimize lactate production and clearance may enhance training outcomes for athletes and therapeutic interventions for patients with chronic diseases (Brooks, 2020). The use of lactate threshold testing, combined with wearable technology that monitors real-time lactate levels, can enable precision exercise medicine that maximizes metabolic benefits and minimizes adverse responses (Hargreaves & Spriet, 2020).

The integration of lactate signaling with other exerkines, such as irisin and myokines, is also of growing interest. Unraveling the interactions between these molecules could reveal synergistic or antagonistic effects, offering a holistic view of how exercise induces systemic adaptations (Brooks et al., 2023). This integrative approach may lead to innovative strategies for enhancing health and mitigating disease progression.

Further research is needed to explore context-specific lactate effects, considering variables such as exercise intensity, age, sex, and metabolic health. Understanding these nuances will help refine interventions and maximize the efficacy of lactate-targeted therapies. Importantly, deeper investigation into the mechanisms of lactate receptor signaling - particularly GPR81 and emerging candidates - is essential. This includes exploring tissue-specific expression patterns, receptor sensitivity, and intracellular signaling cascades that differ across organs such as brain, muscle, liver, and immune cells. Clarifying how lactate receptor activation cross-talks with pathways like AMPK, mTOR, BDNF, and inflammatory networks will be key to understanding the full therapeutic potential and limitations of lactate signaling. This will also help differentiate its role under physiological versus pathological conditions.

The continued exploration of these areas will deepen the understanding of lactate's multifaceted roles, paving the way for novel applications that extend beyond traditional exercise physiology and into clinical and personalized health strategies.

Applications in patient care

Lactate's emerging role as a systemic signaling molecule offers significant opportunities for enhancing patient care across a variety of health conditions. One of the most promising applications is in neurorehabilitation and neuroprotection. During exercise, lactate crosses the blood-brain barrier and can be utilized as an alternative fuel source for neurons, which is particularly beneficial in patients recovering from brain injuries such as stroke or traumatic brain injury (Shang et al., 2023). Moreover, lactate's ability to upregulate BDNF suggests potential for improving cognitive function, memory, and neuroplasticity, thereby supporting recovery and slowing the progression of neurodegenerative diseases such as Alzheimer's (El Hayek et al., 2019).

In the context of chronic inflammatory and metabolic diseases, lactate's anti-inflammatory properties can be leveraged to regulate immune responses. Binding to its receptor GPR81, lactate has been shown to suppress the production of pro-inflammatory cytokines, making it a potential target for therapies aimed at mitigating chronic inflammation in diseases such as rheumatoid arthritis and metabolic syndrome (Liu et al., 2024). Exercise-based interventions tailored to optimize lactate production can enhance metabolic health, reduce insulin resistance, and improve cardiovascular outcomes (Brooks et al., 2023).

Lactate also plays a critical role in muscle recovery and adaptation, making it valuable in rehabilitation settings. Physical therapy protocols designed to induce controlled lactate production can stimulate anabolic signaling pathways, promoting muscle repair, hypertrophy, and strength gains in patients with muscle wasting or weakness due to injury or chronic conditions (Bartoloni et al., 2024). Additionally, lactate's impact on mitochondrial biogenesis supports improved muscle endurance and function, which is particularly relevant in patients with chronic fatigue or mitochondrial disorders (Brooks, 2020).

The application of personalized exercise medicine using lactate profiling holds further promise. By tailoring exercise prescriptions based on individual lactate kinetics, healthcare providers can maximize therapeutic benefits while minimizing risks, optimizing interventions for diverse patient populations, including those with cardiovascular disease, metabolic disorders, or neurological conditions (Hargreaves & Spriet, 2020). Importantly, individual responses to lactate production and signaling can vary considerably due to factors such as age, sex, fitness level, metabolic health, and genetic differences in lactate transporters or receptor expression. For example, patients with impaired mitochondrial function or metabolic inflexibility may experience altered lactate clearance and utilization. This variability highlights the need for personalized approaches when using lactate as a therapeutic target. Monitoring lactate thresholds, kinetics, and recovery patterns through exercise testing or blood lactate profiling can guide clinicians in designing safe and effective interventions tailored to each patient's physiological profile. These applications underscore the potential for integrating lactate-focused strategies into holistic patient care, enhancing quality of life and functional outcomes.

List of Abbreviations

AMPK AMP-Activated Protein Kinase

ANLS Astrocyte–Neuron Lactate Shuttle

ATP Adenosine Triphosphate

BDNF Brain-Derived Neurotrophic Factor

CREB cAMP Response Element-Binding Protein

GH Growth Hormone

GPR81 G-Protein-Coupled Receptor 81 (also known as Hydroxycarboxylic Acid Receptor 1 – HCAR1)

HR_{max} Maximum Heart Rate

IGF-1 Insulin-Like Growth Factor 1

IL-6 Interleukin-6

LT Lactate Threshold

LTP Long-Term Potentiation

MCT Monocarboxylate Transporter

mTOR Mammalian Target of Rapamycin

NMDA N-Methyl-D-Aspartate

PGC-1α Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha

ROS Reactive Oxygen Species

RPE Rating of Perceived Exertion

SIRT1/3 Sirtuins 1 and 3

SIT Sprint Interval Training

TNF-α Tumor Necrosis Factor Alpha

VEGF Vascular Endothelial Growth Factor

VO_{2max} Maximal Oxygen Uptake

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