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# L-Lactate as an Overlooked Neuromodulator and Antidepressant Factor: The Role of the Astrocyte–Neuron Lactate Shuttle (ANLS) in Exercise-Induced Synaptic Plasticity in Athletes

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## Abstract

**Background:** Throughout most of the twentieth century, L-lactate was regarded largely as a metabolic waste product held responsible for muscular fatigue and acidosis. A growing body of evidence now reframes it as a signalling molecule, an exercise-released metabokine and a preferred oxidative substrate for the brain.

**Aim:** This narrative review considers whether high-intensity, glycolytic exercise, by generating a large peripheral lactate load, may exert central antidepressant and neuroprotective effects through direct neuromodulation, with a focus on the astrocyte–neuron lactate shuttle (ANLS) and the lactate receptor HCA1/GPR81.

**Material and methods:** PubMed, Scopus and Web of Science were searched for preclinical and translational studies, with priority given to work published between 2018 and 2026. Search terms included L-lactate, ANLS, HCA1/GPR81, exercise-induced neuroplasticity and depression.

**Results:** The reviewed literature suggests that peripheral lactate crosses the blood–brain barrier via monocarboxylate transporters and may support neuronal energetics through the ANLS. Beyond its fuelling role, lactate appears to engage HCA1 and downstream ERK1/2 and Akt signalling, and is associated with increased BDNF and VEGF expression, facilitated long-term potentiation and antidepressant-like behaviour in animal models.

**Conclusions:** Exercise-derived lactate may act as a non-pharmacological stimulus of neuroplasticity, combining energetic support with receptor-mediated signalling. Glycolytic protocols such as HIIT might complement pharmacotherapy in affective disorders, although human in vivo evidence remains limited.

**Keywords:** L-lactate; astrocyte–neuron lactate shuttle; HCA1/GPR81; exercise; BDNF; depression; neuroplasticity.

# 1. Introduction

## 1.1. Demythologising lactate: a brief historical perspective

The scientific biography of lactate is, in large measure, a history of misattribution. Following the detection of raised concentrations in the muscles of hunted stags by Berzelius in 1808, the monocarboxylate was progressively cast as an agent of dysfunction rather than as an ordinary participant in intermediary metabolism [1]. von Muralt's periodisation of muscle chemistry — into pre-lactic-acid, lactic-acid, phosphorylation and myosin eras — illustrates how prominent, and how contested, the molecule was during the formative decades of bioenergetics [1]. From approximately the 1930s to the early 1970s, an interval that has been retrospectively labelled the "dead-end waste product era", lactate was widely understood as an anaerobic by-product of glycolysis generated by oxygen lack, as the principal cause of the slow component of the oxygen debt, and as a major contributor to both muscular fatigue and acidosis-related tissue injury [1]. The closely associated "anaerobic threshold" framework further entrenched the inference that any rise in lactate necessarily signalled oxygen insufficiency, even though the best available evidence indicates that oxygen availability is only one of several interacting determinants of lactate accumulation during submaximal effort [1].

Since its identification in milk in 1780, lactic acid had been linked to sourness, rigor and decay, and this unfavourable reputation was sustained less by decisive evidence than by what the historian of science Howard Margolis termed a "habit of mind" — an entrenched interpretive reflex that tends to persist even when contradicted by data [2]. The award of the 1923 Nobel Prize to Hill and Meyerhof, for relating oxygen consumption to lactate metabolism in muscle, lent this framework considerable authority and helped to fix it in subsequent teaching [2]. Tellingly, several investigators of brain carbohydrate metabolism in the 1920s and 1930s had already shown that nervous tissue can oxidise lactate, yet they generally construed this capacity merely as a way of disposing of a "poisonous" compound rather than as evidence of a usable fuel [2]. The persistence of this reading, despite repeated observations to the contrary, is itself part of the story of why lactate was for so long overlooked as a physiologically active molecule.

A reappraisal nonetheless gathered pace from the early 1970s — in what has sometimes been described as a "lactate revolution" — and crystallised with the introduction of the lactate shuttle hypothesis by Brooks in the mid-1980s [1,3]. The cell-to-cell lactate shuttle reframed lactate formation and distribution as a mechanism by which intermediary metabolism could be coordinated between tissues, and between cells within a tissue, with skeletal muscle serving as both a major producer and a major consumer [1,3]. In parallel, the long-standing equation of lactate with fatigue and acidosis was itself reconsidered: when contractile experiments were performed at temperatures closer to those encountered physiologically, the depressant effects of acidosis on force were attenuated, and in some isolated preparations a mild acidosis appeared instead to protect muscle excitability against elevated extracellular potassium [1]. Taken together, these developments suggested that lactate could no longer reasonably be treated as the routine "suspect" for metabolic dysfunction, but should rather be regarded as a central intermediary in cellular, regional and whole-body metabolism [1].

### 1.2. A change of paradigm: lactate as oxidative substrate, exercise-released signal and neuromodulator

Contemporary accounts hold that the L-enantiomer of lactate is produced continuously under fully aerobic conditions and fulfils at least three overlapping roles: a mobile oxidative substrate for mitochondrial respiration, the principal gluconeogenic precursor, and a signalling molecule with autocrine-, paracrine- and endocrine-like actions, for which the term "lactormone" has been proposed [3,4]. The dynamic range over which it operates is unusually wide — tissue concentrations are reported to span roughly 0.5–20 mM and the cellular lactate-to-pyruvate ratio to vary from about 10 to more than 500 — so that the shifts in lactate availability accompanying exercise and other stress–strain responses may exceed many other metabolic signals in both magnitude and rapidity [4]. Consistent with a substrate role, the heart can derive a substantial proportion of its oxidative fuel from lactate, and the greater part of the lactate produced during exercise is ultimately disposed of through oxidation rather than excretion [1,4].

Of particular relevance to the present review is the increasingly detailed picture of lactate as an exercise-released signal. Beyond serving as a fuel, lactate appears to participate in the partitioning of energy substrates — being linked, for example, to the inhibition of adipose lipolysis through the hydroxycarboxylic acid receptor 1 (HCAR1/GPR81) — and to longer-term adaptive reprogramming, including the post-translational modification of histones by lysine lactylation [4]. Repeated exposure to the lactate transients generated by regular training has therefore been proposed to contribute to the molecular adaptations of exercise, a view that situates lactate alongside recognised myokines as an exercise-released signalling factor rather than treating it as inert metabolic waste [3,4]. Framed in this way, lactate becomes a plausible carrier of information from contracting muscle to distant organs, the brain among them.

Within the central nervous system, this reconceptualisation has been especially consequential. Lactate is formed predominantly in astrocytes — from glucose and from glycogen — in response to signals associated with neuronal activity, reflecting a cell-specific division of metabolic labour in which astrocytes favour aerobic glycolysis (expressing the lactate-favouring isoenzyme LDH5) while neurons remain largely oxidative (expressing LDH1) [5]. The lactate so generated is then transferred to neurons in a manner that both helps to match local energetic demand and provides signals capable of modulating neuronal excitability, synaptic plasticity and memory consolidation; in this framing, lactate has been argued to help set the "homeostatic tone" of the nervous system [5]. Brain lactate concentrations under physiological conditions are typically reported in the region of 2–5 mM, and isolated nervous tissue can sustain synaptic activity with lactate as the sole oxidative substrate — an observation first made in the 1950s and repeatedly reproduced thereafter — with several lines of evidence indicating that lactate may be a preferred neuronal substrate even when glucose is available [2,5].

It must be emphasised, however, that these interpretations remain actively debated. A substantial body of work continues to regard glucose as the major fuel of the activated brain and to treat lactate as an "opportunistic", glucose-sparing substrate whose transport and metabolism differ markedly across experimental systems and physiological states [6]. Such caution is appropriate, and it is taken seriously here; mechanistic claims are

accordingly presented as provisional, and preclinical and human findings are, where possible, weighed separately rather than merged into a single confident narrative.

## 1.3. Aim and scope of the review

Against this shifting background, the present narrative review examines a specific and clinically oriented proposition: that high-intensity, glycolytic exercise — by generating a large peripheral lactate load that subsequently gains access to the brain — may contribute to central antidepressant and neuroprotective effects through direct neuromodulation, and not solely through the more generic cardiovascular and psychosocial benefits commonly ascribed to physical activity [3,4,5]. Put differently, lactate is considered here as a candidate molecular link between the metabolic demands of intense exercise and the activity-dependent remodelling of the brain that is thought to underlie improvements in mood and cognition.

To develop this argument, the review is organised around two complementary pillars. The first is energetic and is embodied by the astrocyte–neuron lactate shuttle (ANLS), through which lactate may support neuronal metabolism during periods of heightened demand and thereby help to protect neurons from energetic exhaustion [5]. The second is regulatory and is represented chiefly by the lactate receptor HCA1/GPR81 and its associated intracellular cascades, which have been linked to the expression of neurotrophic and angiogenic factors such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) [4,5]. The sections that follow trace the proposed route from peripheral glycolytic production, through carrier-mediated transport across the blood–brain barrier, to central energetic and receptor-mediated actions, before turning to the translational evidence that relates lactate to mood regulation and to the still-considerable limitations of that evidence base [6]. Throughout, the argument is framed cautiously, in keeping with the heterogeneous and predominantly preclinical character of the literature reviewed.

# 2. Material and Methods

## 2.1. Study design

This work was conceived and conducted as a narrative (non-systematic) review. The choice of design reflects the nature of the subject matter, which spans several only partly overlapping bodies of literature — exercise physiology, cerebral energy metabolism, receptor pharmacology, molecular neurobiology and clinical psychiatry — that differ markedly in their methodologies, model systems and outcome measures, and that are therefore not readily amenable to quantitative pooling. A qualitative, integrative synthesis was judged more suitable than a formal meta-analysis for tracing a mechanistic argument across these disciplines. The review was not pre-registered and does not claim the exhaustiveness of a systematic review; nonetheless, in order to limit selection bias and to improve transparency and reproducibility, the literature search and the selection of sources followed a structured, pre-specified procedure, described below, and the reporting was guided by current recommendations for the conduct and presentation of narrative reviews.

## 2.2. Information sources and search strategy

Three electronic bibliographic databases were interrogated: PubMed/MEDLINE, Scopus and the Web of Science Core Collection. These were complemented by manual searching of the reference lists of retrieved articles and pertinent reviews (backward citation chaining) and by forward citation tracking to capture the most recent

contributions; the final search was performed in the first half of 2026. The search combined controlled vocabulary, where available (for example, Medical Subject Headings in PubMed), with free-text terms applied to the title, abstract and keyword fields, using the Boolean operators AND and OR together with truncation and phrase searching.

Search concepts were arranged into four thematic blocks, which were first explored individually and then intersected:

**(i) the molecule, its transport and metabolism** — "L-lactate", "lactate", "lactic acid", "lactate shuttle", "astrocyte–neuron lactate shuttle", "ANLS", "monocarboxylate transporter", "MCT1", "MCT2", "MCT4", "lactate dehydrogenase", "blood–brain barrier";

**(ii) lactate-sensitive signalling** — "lactate receptor", "HCA1", "HCAR1", "GPR81", "hydroxycarboxylic acid receptor 1", "ERK1/2", "Akt", "histone lactylation", "NMDA receptor";

**(iii) neuroplasticity and its molecular mediators** — "synaptic plasticity", "long-term potentiation", "neuroplasticity", "neurogenesis", "angiogenesis", "BDNF", "brain-derived neurotrophic factor", "VEGF", "Arc";

**(iv) exercise and affective or cognitive outcomes** — "exercise", "physical activity", "high-intensity interval training", "HIIT", "sprint interval exercise", "resistance exercise", "aerobic exercise", "lactate threshold", "depression", "major depressive disorder", "antidepressant", "anhedonia", "chronic social defeat stress".

Representative search strings combined one or more terms from each relevant block — for example, ("lactate" OR "L-lactate") AND ("HCAR1" OR "GPR81" OR "astrocyte–neuron lactate shuttle") AND ("BDNF" OR "synaptic plasticity" OR "depression"). Strings were adapted to the syntax of each database, and the yield was deduplicated before screening.

## 2.3. Eligibility criteria

Priority was given to peer-reviewed work published between 2018 and 2026, in keeping with the rapid recent expansion of research on lactate signalling in the central nervous system. Seminal earlier publications were nevertheless retained where they were indispensable for historical context or for the mechanistic foundations of the argument — for instance, the original formulations of the cell-to-cell lactate shuttle and of the astrocyte–neuron lactate shuttle, and the foundational characterisations of the monocarboxylate transporters and of the lactate receptor.

Records were eligible for inclusion if they: (i) were published in English in a peer-reviewed journal; (ii) reported original data obtained in vitro, ex vivo, in vivo in animal models, or in human participants, or else constituted authoritative reviews and consensus articles; and (iii) addressed at least one node of the proposed pathway — namely peripheral lactate production and transport, central lactate metabolism and signalling, lactate-associated neuroplasticity, or the relationship between exercise- or lactate-based interventions and affective or cognitive outcomes. Records were excluded if they dealt exclusively with the D-enantiomer of lactate or with peripheral processes lacking a plausible central relevance; were available only as conference abstracts, editorials, commentaries or non-peer-reviewed preprints; or were duplicates across the searched databases.

Where the available evidence allowed, studies were appraised within an evidence-based-medicine framework, with comparatively greater interpretive weight given to randomised controlled trials, systematic reviews and meta-analyses among the clinical reports, and to adequately powered, controlled and, ideally, independently replicated designs among the preclinical reports. The predominantly preclinical and mechanistic character of much of the

relevant literature — and the correspondingly limited body of invasive human neurochemical data — was, however, explicitly borne in mind throughout, and is treated as a central limitation rather than a peripheral caveat.

## 2.4. Study selection and synthesis

Titles and abstracts were screened for relevance, after which potentially eligible articles were retrieved and assessed in full text against the criteria set out above. Given the conceptual breadth of the topic and the heterogeneity of designs, species, exposure paradigms and outcome measures, no quantitative meta-analysis was attempted. Instead, the retained findings were integrated qualitatively and organised thematically so as to follow the proposed causal chain: from peripheral glycolytic lactate production, through carrier-mediated transport across the blood–brain barrier, to the astrocyte–neuron lactate shuttle, to receptor-mediated signalling via HCA1/GPR81 and parallel intracellular cascades, to the induction of neuroplasticity-related and angiogenic factors, and finally to the clinical–translational evidence linking glycolytic exercise with antidepressant and neuroprotective effects. Discrepant or frankly contradictory observations between experimental systems were deliberately retained and discussed rather than reconciled prematurely, and the strength of each inference was calibrated to the quality and convergence of the supporting evidence.

## 3. Literature review

### 3.1. The peripheral cascade: from anaerobic glycolysis to the blood–brain barrier (BBB)

During exercise of rising intensity, the demand for ATP in contracting skeletal muscle increases more rapidly than mitochondrial oxidative capacity can accommodate, and glycolytic flux accelerates accordingly, so that pyruvate is produced faster than it is consumed by the tricarboxylic acid cycle; the surplus pyruvate is reduced to lactate by lactate dehydrogenase in a reaction that regenerates the cytosolic $NAD^+$ needed to sustain continued glycolysis [1,3]. Fast-twitch, glycolytic fibres are especially suited to this task, being enriched in the lactate-favouring dehydrogenase isoform that drives net conversion of pyruvate to lactate, in contrast to the more oxidative enzymatic profile of slow fibres and of neurons [1,5]. The shift from a predominantly aerobic to a more glycolytic mode of energy provision is mirrored in the circulation: arterial lactate, ordinarily low at rest, rises steeply once exercise intensity exceeds the so-called lactate threshold — conventionally placed at the onset of blood lactate accumulation (OBLA), in the region of 4 mmol/L — and may reach 10–12 mmol/L or more after exhaustive effort [7]. It bears repeating, in line with the reappraisal set out earlier, that such accumulation reflects the balance between lactate production and its clearance rather than oxygen insufficiency alone [1].

The traffic of lactate across cell membranes is governed chiefly by the monocarboxylate transporters (MCTs), a family encoded by the *SLC16* genes that comprises fourteen members in mammals, of which the first four — MCT1 through MCT4 — have been the most thoroughly characterised as proton-coupled carriers of L-lactate, pyruvate and the ketone bodies [8,9,10]. Transport is electroneutral and proceeds by an ordered symport in which a single proton and a single monocarboxylate anion are translocated together; the process is freely reversible, its net direction and rate being dictated by the prevailing transmembrane concentration and pH gradients, and it is further hastened when substrate is already present on the opposite (trans) side of the membrane [9,10]. Because the four principal isoforms are, for the most part, not themselves glycosylated, they depend on ancillary glycoproteins for correct folding and membrane insertion: MCT1, MCT3 and MCT4 partner with CD147 (basigin), whereas MCT2 associates with embigin [8,11]. The isoforms differ considerably in their affinity for lactate — MCT2 being a high-affinity carrier ($K_m \approx 0.7$ mM), MCT1 of intermediate affinity (≈ 3.5–5 mM), and MCT4 a distinctly low-affinity transporter (≈ 28 mM) — and this kinetic diversity appears to underlie a division of transport labour across tissues and cell types [9,10,11].

The efflux of lactate from glycolytic muscle is attributed largely to MCT4, whose kinetic characteristics seem well matched to an export role: its low affinity favours outward flux when intracellular lactate is high, while its very low affinity for pyruvate (Km of the order of 150 mM) limits the parallel loss of pyruvate and thereby helps to maintain a high glycolytic rate [9,10]. Consistent with this, MCT4 is concentrated in highly glycolytic tissues — fast muscle, leucocytes, chondrocytes and, within the central nervous system, astrocytes — a pattern of expression that, as discussed below, recurs in the brain [9,10,11]. Once exported, lactate is conveyed in the bloodstream both dissolved in plasma and within erythrocytes, becoming available to tissues remote from its site of production [7].

Far from representing a metabolic cul-de-sac, circulating lactate is increasingly regarded as one of the most actively turned-over fuels in the body; isotopic tracer studies in rodents indicate that its circulatory flux can rival or even surpass that of glucose, and that in many tissues glucose enters the tricarboxylic acid cycle largely after first being converted to circulating lactate [12]. This reframing lends quantitative substance to the proposition that the lactate generated by exercising muscle constitutes a substantial and mobile energy currency rather than a waste product destined for excretion [4,12]. The brain, however, has been reported to be a partial exception to this tissue-wide pattern, drawing proportionally less on circulating lactate than organs such as the heart or skeletal muscle under resting conditions — a caveat that cautions against overstating the cerebral contribution of blood-borne lactate at rest [12].

For peripherally produced lactate to act upon the brain, it must first cross the blood–brain barrier (BBB), the tight endothelium of the cerebral microvasculature. This passage is mediated predominantly by MCT1, which is abundantly expressed on both the luminal and abluminal membranes of brain capillary endothelial cells — as well as on ependymocytes and astrocytes — and which therefore furnishes a bidirectional, gradient-driven conduit between blood and brain parenchyma [9,10,11]. Since MCT-mediated transport follows the electrochemical gradient, the pronounced rise in arterial lactate during intense exercise should favour net influx into the brain; the carrier is, moreover, stereoselective, transporting the physiological L-enantiomer in preference to D-lactate [9]. Expression of MCT1 at the BBB is itself subject to regulation — for instance by PTEN and Wnt/β-catenin signalling within endothelial cells — which suggests that the capacity for blood–brain lactate exchange is dynamic rather than fixed, and may in principle be modifiable by physiological state [11].

Direct human evidence that this peripheral-to-central transfer is functionally meaningful comes from arterio-venous balance measurements across the brain. In healthy volunteers, raising arterial lactate by intravenous infusion converted the brain from a small net exporter of lactate (≈ 0.06 mmol/min) into a net importer (≈ 0.16 mmol/min), and moderate-intensity cycling that further elevated arterial lactate to approximately 7 mmol/L increased net cerebral uptake to around 0.28 mmol/min [13]. The greater part of the carbon thus taken up — of the order of 85–100% as judged by $^{13}C$ tracer labelling — was recovered as $^{13}CO_2$, indicating that the imported lactate was largely oxidised rather than accumulated, and its estimated contribution to cerebral energy expenditure rose from roughly 8% at rest to about 19% during infusion and some 27% during exercise [13]. These findings are consistent with the view that, when peripheral supply is abundant, the activated human brain behaves as a net consumer of blood-borne lactate; they do not, however, settle the long-standing controversy over the quantitative importance of lactate relative to glucose under ordinary resting conditions, which remains a matter of genuine debate [6,12].

## 3.2. The energetic core: the astrocyte–neuron lactate shuttle (ANLS)

Once lactate has entered the central compartment, or is generated in situ, the question becomes how it is apportioned between the brain's two principal cell populations. The dominant conceptual answer is the astrocyte–neuron lactate shuttle (ANLS): the proposal that astrocytes, responding to the signals of synaptic activity, produce lactate through aerobic glycolysis and export it to neurons, which oxidise it as a fuel, so that astrocyte-derived lactate is cast as an energy substrate matched to neuronal demand rather than as a metabolic by-product [14,15]. The hypothesis was first articulated by Pellerin and Magistretti in 1994 on the basis of experiments in cultured cortical astrocytes, and

it has since become the principal framework within which activity-dependent brain energetics is discussed, even as important elements of it remain contested [5,14,15]. Its appeal lies in coupling the two cell types metabolically, so that the energetic cost of clearing the excitatory neurotransmitter glutamate is met, in part, by a cell that is well suited to glycolysis [5,15].

The molecular mechanism proposed in the original formulation links neurotransmission directly to glucose use. Glutamate released at excitatory synapses is cleared from the cleft largely by sodium-dependent transporters on perisynaptic astrocytes, and because this uptake is electrogenic — each glutamate anion being co-transported inward with two to three sodium ions — it raises the intracellular sodium concentration; the resulting activation of the $Na^+/K^+$-ATPase, as it consumes ATP to restore the ionic gradient, is thought to stimulate glycolysis and glucose uptake, with lactate as the end-product [14]. Several observations led Pellerin and Magistretti to attribute this response to glutamate transport rather than to receptor signalling: the stimulation of deoxyglucose uptake by glutamate was concentration-dependent (half-maximal at approximately 80 µM), was not reproduced by glutamate-receptor agonists nor blocked by their antagonists, was stereoselective for the transported L-isomer, and was abolished both by the uptake inhibitor DL-threo-β-hydroxyaspartate and by removal of extracellular sodium [14]. That the cascade depends on the sodium pump and on glucose entry was indicated by its sensitivity to ouabain and to the glucose-transport inhibitor cytochalasin B, respectively; in parallel, the astrocyte converts a portion of the glutamate it takes up to glutamine, a step that is itself energetically demanding [5,14].

A division of metabolic labour between the two cell types underwrites the directionality of the shuttle. As already noted, astrocytes are comparatively glycolytic and are enriched in the lactate-favouring dehydrogenase isoenzyme (LDH5, the $A_4$ tetramer), whereas neurons display a more oxidative profile dominated by LDH1 (the $B_4$ tetramer); this differential expression is thought to bias net lactate formation towards astrocytes and net lactate oxidation towards neurons, and so to establish the concentration gradient along which lactate flows [5,15]. Astrocytes possess a further, distinctive resource: glycogen, which in the adult brain is stored almost exclusively in these cells and can be mobilised to yield lactate [16]. The capacity to draw on this reserve may be particularly relevant when demand is high or glucose supply is constrained, although the precise circumstances under which glycogen-derived as opposed to glucose-derived lactate predominates remain incompletely defined [15,16].

The transporter complement of each cell type is broadly consistent with the proposed flux. Export from astrocytes is attributed chiefly to the low-affinity MCT4, while uptake into neurons is served by the high-affinity neuronal isoform MCT2, which is concentrated in the postsynaptic elements of glutamatergic synapses; MCT1, more widely distributed across endothelium, ependyma, oligodendrocytes and astrocytes, contributes to exchange at several interfaces, and MCT4 has been localised both to perisynaptic astrocytic processes and to perivascular endfeet [9,17]. The kinetic complementarity of these carriers — a low-affinity exporter discharging lactate where its intracellular concentration is high, and a high-affinity importer capturing it at the neuronal membrane — offers a plausible, if not by itself decisive, structural basis for vectorial transfer from astrocyte to neuron [9,17]. As emphasised earlier, however, MCT-mediated transport is bidirectional and gradient-driven, so the direction actually realised in vivo is dictated by the prevailing concentration and proton gradients rather than fixed by transporter identity [9].

Some of the most influential functional support for the shuttle comes from studies linking astrocytic lactate provision to memory. In the rat hippocampus, a learning task has been reported to raise extracellular lactate, an increase that depends on glycogen breakdown; interfering with glycogenolysis, or knocking down the astrocytic transporters MCT4 or MCT1, impaired long-term — though not short-term — memory and the maintenance of long-term potentiation, deficits that could be rescued by lactate but not by an equicaloric amount of glucose [16]. Disruption of the neuronal transporter MCT2 likewise produced amnesia, but this was corrected by neither lactate nor glucose, an asymmetry interpreted as evidence that lactate must actually enter the neuron for the memory trace to consolidate [16]. The same manipulations blocked the induction of molecular correlates of plasticity, among them phosphorylated CREB, Arc and phosphorylated cofilin, which suggests that astrocytic lactate supply is coupled not merely to bulk energy provision but to the signalling events that stabilise synaptic change [16]. Consistent with this, the activity-evoked rise in hippocampal lactate has been observed to persist for tens of minutes

and to be abolished by inhibition of glycogenolysis, a manipulation that also blocks long-term memory in such paradigms [17].

Viewed more broadly, the shuttle is one facet of the increasingly recognised role of astrocytes as active participants at the synapse rather than passive supporting cells. Within the "tripartite synapse" — the presynaptic terminal, the postsynaptic spine and the ensheathing astrocytic process — astrocytes are held to sense and shape transmission through gliotransmission, the clearance of glutamate and potassium, and metabolic support, with the ANLS commonly cited as the means by which energy provision is matched to the demands of activity-dependent plasticity [18]. A single cortical or hippocampal astrocyte may contact very large numbers of synapses, a morphology that would place it well to couple local neuronal activity to local substrate delivery [18]. On this view, lactate is not simply a fuel delivered in bulk but part of a spatially organised metabolic dialogue between astrocytes and the synapses they enwrap [5,18].

The ANLS is perhaps best understood as one member of a wider family of "lactate shuttles", a concept developed by Brooks to describe the movement of lactate between and within cells, down concentration and redox gradients, as a means of distributing oxidative and gluconeogenic substrate [3,19]. Extending this logic to the brain, it has been proposed that lactate trafficking supports neuroenergetic homeostasis under ordinary conditions but is redirected under stress — a state of allostasis — and that a distinct astrocyte–microglia lactate shuttle may become prominent during chronic neuroinflammation, such that the direction of lactate flux, and not merely its presence, comes to carry pathophysiological meaning [19]. Such framings are heuristically valuable, yet they should not obscure the genuine controversy that persists over the shuttle's quantitative importance [6,19].

Several lines of evidence indeed temper the strong form of the hypothesis. Neurons appear to be more metabolically flexible than the classical model allowed: they express appreciable amounts of the glycolytic isoenzyme LDHA and retain the capacity to take up and oxidise glucose directly, and studies of dehydrogenase-deficient neurons point both to compensatory routes and to limits on neuronal reliance on lactate [15]. Estimates of substrate partitioning at rest — with roughly half of glucose uptake attributed to each cell type, and astrocytes accounting for a far smaller share of total energy turnover than neurons — have been read by some as a difficulty for any obligatory astrocyte-to-neuron transfer, and an alternative "glucose-sparing" account holds that astrocytic glycogenolysis serves chiefly to reserve glucose for neurons rather than to supply them with lactate [6,17]. The balance of evidence is therefore best summarised as indicating that astrocyte-derived lactate can support and help to shape neuronal function, especially under conditions of heightened or sustained demand, while its obligatory role under resting physiological conditions remains unresolved [6,15,17]. With the energetic pillar of the argument thus set out — and appropriately qualified — the review turns from lactate as a substrate to lactate as a signal, and in particular to its receptor-mediated actions through HCA1/GPR81.

## 3.3. Lactate as a neuromodulator: the HCA1/GPR81 receptor and gene expression

If the astrocyte–neuron lactate shuttle frames lactate as a fuel that is delivered where neuronal activity demands it, a second and more recent line of work recasts the same molecule as a bona fide signal that acts upon a dedicated receptor, and so links metabolism to the regulation of cellular behaviour and gene expression [5,20]. The receptor in question is the G-protein-coupled receptor 81 (GPR81), first characterised in adipose tissue as a mediator through which lactate restrains lipolysis, and originally an orphan member of the rhodopsin-like (class A) GPCR family; once lactate was recognised as its endogenous agonist, the receptor was deorphanised and renamed the hydroxycarboxylic acid receptor 1 — HCA1 under the IUPHAR convention, HCAR1 under that of the HUGO nomenclature committee [20]. Its sensitivity is, importantly, selective: the receptor is activated by L-lactate across the very range of concentrations that occurs in vivo (approximately 0.1–30 mM), whereas its congeners HCAR2 and HCAR3 respond to other metabolites and are not engaged by lactate [20]. The three HCAR genes lie together on the short arm of human chromosome 12 (12q24.31), in the same chromosomal neighbourhood as the gene

encoding the neuronal monocarboxylate transporter MCT2 (12q13), a juxtaposition that has been read as hinting at a functional interrelation between the carrier that imports lactate into neurons and the receptor that senses it [20]. Computational modelling and mutagenesis have identified the residues Arg71, Arg99, Glu166 and Arg240 of human HCAR1 as important for the interaction with lactate [20].

In its canonical mode, HCAR1 is an inhibitory, Gi/o-coupled receptor: its activation suppresses adenylyl cyclase and thereby lowers intracellular cyclic AMP (cAMP), the same mechanism by which it curbs lipolysis in fat cells [20,22]. That this signalling operates in the brain was shown by the demonstration that both L-lactate and the selective HCAR1 agonist 3,5-dihydroxybenzoic acid (3,5-DHBA) reduce forskolin-stimulated cAMP in hippocampal slices [20]. The reported affinity is consistent with a physiological role: published EC50 values for L-lactate at HCAR1 lie in the low-millimolar range — of the order of 1.3–2.5 mM in one study and 4–5 mM in another, broadly 1–5 mM overall — with measurable activation beginning at concentrations as low as about 0.1 mM [20]. Because resting extracellular lactate in the brain is approximately 0.2–1.0 mM and rises towards roughly 2 mM during neuronal activation, the receptor is likely to be partially engaged even at rest and progressively recruited as activity, and hence glycolysis, intensifies [6,20]. Pharmacological tools of increasing potency have been developed around this scaffold — 3,5-DHBA (apparent EC50 ≈ 0.15 mM), 3-chloro-5-hydroxybenzoic acid (≈ 0.02 mM) and a thiazole-based "compound 2" with nanomolar affinity — which has made it possible to probe receptor function independently of lactate's metabolic fate [20]. Apparent potencies are lower in tissue slices than in isolated systems (with an apparent IC50 for 3,5-DHBA near 1.4 mM and an extrapolated value for L-lactate of the order of 29 mM in hippocampal slices), a discrepancy attributed to the diffusion, cellular uptake and metabolism that lactate undergoes before it reaches the receptor, and a reminder that local rather than bulk concentrations are what the receptor actually senses [20].

The anatomical distribution of HCAR1 in the brain is consistent with a role in synaptic and neurovascular regulation. Receptor mRNA and protein have been localised to the hippocampus, neocortex and cerebellum, and immunohistochemistry indicates enrichment in principal neurons — hippocampal pyramidal cells and cerebellar Purkinje cells — as well as in interneurons [20]. Within these cells the receptor appears concentrated in the somatodendritic compartment, and electron-microscopic immunogold quantification places its highest density at the postsynaptic membranes of excitatory-type synapses on dendritic spines, with additional labelling of vascular endothelium at the blood–brain barrier and of perivascular and perisynaptic astrocytic processes [20]. Labelling of intracellular vesicular organelles in spines, together with the observation that lactate promotes receptor internalisation, suggests that HCAR1 is trafficked between the plasma membrane and intracellular stores, providing a means by which its surface availability might be regulated [20]. This postsynaptic concentration is notable because it places the receptor alongside MCT2, the high-affinity neuronal carrier (Km < 1 mM) that is itself selectively localised at excitatory synapses — an arrangement that would allow a spine to both import lactate and sense it [9,20]. It bears noting, however, that HCAR1 transcript abundance in the hippocampus is roughly an order of magnitude lower than in adipose tissue, so that the receptor operates at relatively modest expression levels in the brain [20].

These distributional features underpin the proposal, advanced by Bergersen and Gjedde and developed by Morland and colleagues, that lactate functions in the brain as a "volume transmitter" [20]. In contrast to a wiring transmitter such as glutamate, which acts over only a few micrometres before being cleared from the cleft, a volume transmitter diffuses appreciable distances through the extracellular space to reach receptors distributed over a surrounding volume [20]. Lactate is suited to this role precisely because the MCTs equilibrate it across membranes down the combined gradient of monocarboxylate and proton, allowing it to migrate from sites of production to more distant receptor sites: radiolabelled L-lactate has been found to diffuse on the order of 1.5 mm within ten minutes (and the poorly metabolised D-lactate somewhat further, up to about 2.4 mm), distances that compare with the 1.0–1.5 mm travelled by the prototypical volume transmitter dopamine over two minutes and dwarf the few micrometres of glutamate spread [20]. The repertoire of lactate sources that could thus reach HCAR1 is broad: lactate generated locally within active dendritic spines, which contain the glycolytic machinery but few mitochondria and can release lactate through MCT2; lactate produced by astrocytes and discharged not only via MCT4 but also through a depolarisation- and potassium-activated anion channel that releases it uncoupled from protons; lactate arriving

from the circulation when blood levels rise, as during exercise; and even exogenous agonists of dietary origin [13,20]. Through this diffuse signalling, lactate is positioned to couple neuronal activity, energy substrate availability, cerebral blood flow and energy metabolism [20].

What, then, does activation of HCAR1 do to a neuron? Although the receptor was cloned as early as 2001 and lactate identified as its agonist only some years later, attention has turned more recently to the functional consequences of its engagement, and the emerging picture is one of negative feedback upon excitability [21]. In cultured cortical neurons, HCAR1 activation reduces calcium-spiking activity in both glutamatergic and GABAergic cells (with an EC50 for lactate near 4.2 mM), an effect interpreted as a brake against excessive firing [20]. This inference has since been substantiated in vivo and in situ. Using a lactate biosensor in the mouse hippocampus, Skwarzynska and colleagues found that extracellular lactate, stable at a basal concentration of about 0.336 mM, rose rapidly during seizures — to a peak of roughly 0.777 mM in brief electrographic seizures and around 0.957 mM during prolonged ones — confirming that intense activity generates enough lactate to engage the receptor [21]. Mice lacking HCA1R proved more susceptible to seizures, kindled more rapidly and developed longer and more severe seizures than wild-type littermates, as would be expected if the receptor normally restrains hyperexcitability [21]. At the cellular level, both lactate (3 mM) and the non-metabolised agonist 3-chloro-5-hydroxybenzoic acid hyperpolarised CA1 pyramidal neurons and, in the case of the agonist, raised the action-potential threshold; HCAR1 activation also reduced the frequency of spontaneous excitatory postsynaptic currents and altered the paired-pulse ratio of evoked responses — pointing to a presynaptic diminution of glutamate release — while leaving inhibitory currents unchanged, and all of these effects were abolished in receptor-null tissue [21]. Taken together, these observations describe a self-limiting loop in which the lactate produced by glycolytically active, repetitively firing neurons feeds back through HCAR1 to dampen excitatory transmission, a mechanism the authors propose as a possible endogenous anticonvulsant pathway and which accords with the feedback role against excessive activity anticipated on the basis of the receptor's cAMP-lowering action [20,21].

HCAR1 is not confined to neurons. Beyond its presence on the cerebral endothelium of the blood–brain barrier, the receptor has been mapped to the periventricular structures that interface with the cerebrospinal fluid [20,22]. Using monomeric-red-fluorescent-protein reporter mice, Hadzic and colleagues detected HCA1 specifically in the dorsal part of the third ventricle — within the choroid plexus, the tela choroidea and the neuroepithelial ventricular lining — and identified the expressing cells, by co-labelling, as fibroblasts (vimentin-positive, with a subset positive for PDGFR-β) and ependymal cells (positive for the urate transporter URAT1), rather than as endothelium, NG2-positive pericytes, microglia or astrocytes at those sites [22]. The receptor's localisation places it close to the choroidal monocarboxylate transporters — MCT1 in the apical membrane of the ependyma and MCT3 in the basolateral membrane of the choroid-plexus epithelium — and so in an apt position to sense lactate as it equilibrates with the cerebrospinal fluid; this is of more than incidental interest because CSF lactate rises in pathological states, climbing from below about 1.5 mmol/L to above 2 mmol/L after stroke and being elevated in Alzheimer's disease [22]. The functional implication drawn from this anatomy is that lactate-sensing fibroblasts and ependymal cells, both of which secrete growth factors such as VEGF, IGF and FGF, might release these mediators in response to changing CSF lactate, thereby coupling the metabolic signal to trophic output; consistent with this, HCA1 activation has been linked to angiogenesis in the hippocampus and cortex and to neurogenesis in the subventricular — though not the subgranular — zone [22]. In this way the receptor is implicated not only in moment-to-moment electrical regulation but in slower, gene-expression-dependent processes, a theme taken up in the following section.

The downstream reach of HCAR1 extends, finally, beyond cAMP to the kinase cascades and transcriptional programmes through which a metabolic signal can be translated into lasting change, and it is here that the receptor's relevance to exercise becomes most apparent. In a study of HCAR1-knockout mice, the hippocampal expression of phosphatidylinositol-3-kinase (PI3K), Akt and ERK1/2 — both transcript and protein — was markedly lower than in wild-type animals, and five weeks of high-intensity treadmill running raised the expression of these kinases, of collagen IV and of microvessel density in wild-type but not in knockout mice, indicating that the exercise-driven engagement of the ERK1/2–PI3K/Akt axis and the attendant cerebral angiogenesis depend on the lactate receptor [23]. The same work situates HCAR1 within the cAMP–cognition relationship that has been characterised in the prefrontal cortex, where excessively high cAMP is associated with impaired working memory in ageing, stress and

schizophrenia and with the deposition of phosphorylated tau, and where acute elevations of cAMP may enhance cognition while chronic elevations degrade it; on this view, intermittent activation of HCAR1 by exercise-derived lactate could help to restrain pathologically sustained cAMP signalling [20,23]. Alongside this canonical pathway, HCAR1 also signals in non-canonical, cAMP-independent ways, through both Gα and Gβγ subunits and via β-arrestin; one reported example of the latter is the enhancement of the immediate-early plasticity gene Arc/arg3.1 through an HCAR1–β-arrestin2 pathway in astrocytes, which begins to connect receptor activation directly to the expression of plasticity-related genes [20,22]. The receptor thus appears to operate as a convergence point at which lactate — whether produced locally, supplied by astrocytes or imported from exercising muscle — can modulate excitability, cyclic-nucleotide tone, kinase activity and gene expression.

These convergent findings should nonetheless be read with the caution that the field's own authors urge. Reliable antibodies against HCAR1 have been difficult to obtain, so that much of the functional evidence rests on knockout validation and on selective agonists rather than on direct protein detection, and the receptor's transcript is comparatively sparse in brain tissue [20,21]. Not every action of lactate on a receptor is attributable to HCAR1: in the locus coeruleus a distinct, as-yet-unidentified lactate-sensitive receptor appears to raise rather than lower cAMP (with an EC50 near 680 µM), a reminder that lactate signalling is unlikely to be monolithic [20]. The dose–response relationships are, moreover, frequently non-monotonic — the pro-mnemonic effect of intracerebral lactate, for instance, follows a bell-shaped curve — which implies that the receptor participates in a fine-tuning of cellular state rather than exerting a simple, graded push in one direction [16,20]. With these qualifications in place, the balance of current evidence nevertheless supports a coherent role for HCAR1 as a transducer that converts the lactate signal — including the surge generated by glycolytic exercise — into restraint of excessive excitation [21], into growth-factor release at the brain's fluid interfaces [22], and into the kinase and gene-expression programmes that subserve neurovascular and synaptic adaptation [23]. It is to these effectors of plasticity — the neurotrophic and angiogenic factors, and the molecular machinery of long-term potentiation — that the review now turns.

## 3.4. Induction of neuroplasticity: effects on BDNF, VEGF and synaptic plasticity

If the preceding sections describe how lactate reaches and is sensed by the brain, the question that follows is what it actually does once there—and the most consequential answers converge on the machinery of neuroplasticity. Among the molecular effectors of exercise-related brain adaptation, brain-derived neurotrophic factor (BDNF) occupies a central position, and the proposition that lactate operates as one of its upstream regulators has gradually moved from conjecture towards a defensible, if still incompletely resolved, model [24]. The distinction between the two principal BDNF species is not a technicality: the precursor pro-BDNF (≈28 kDa) preferentially engages the p75 neurotrophin receptor and is associated with long-term depression, dendritic spine retraction and pro-apoptotic signalling, whereas the proteolytically matured isoform (mBDNF, ≈13–14 kDa) acts through tropomyosin receptor kinase B (TrkB) to favour neuronal survival, long-term potentiation (LTP) and synaptogenesis [24]. Because an estimated three-quarters of circulating BDNF is thought to originate from the brain, peripheral measurements remain an imperfect proxy for central events, a caveat that recurs throughout the human literature considered below [24]. Within this framework, the signalling—as opposed to purely metabolic—identity of lactate emphasised earlier [5] acquires a concrete output: the regulation of a neurotrophin whose activity-dependent transcription is among the best-characterised substrates of synaptic plasticity.

The most direct experimental support for a genuinely instructive role comes from work showing that L-lactate, applied to cortical neurons, drives the transcription of plasticity-related immediate-early genes. In the foundational study of this kind, L-lactate elevated Arc/Arg3.1 in a concentration-dependent manner—significant already at 2.5 mM (a 48.2 ± 12.1% increase) and rising across the 2.5–20 mM range—together with c-Fos and Zif268/Egr1, with corresponding protein increases of approximately four-, five- and three-fold, respectively [25]. Two observations argued against a trivial energetic explanation. First, neither D-lactate, L-pyruvate nor D-glucose reproduced the effect, indicating stereospecific, substrate-selective signalling rather than mere ATP provision [25]. Second, the

response depended on N-methyl-D-aspartate receptor (NMDAR) activity, since the open-channel blocker MK-801 (40 μM) abolished both the gene induction and the downstream rise in BDNF, which itself peaked later (≈351% of control at 4 h), consistent with BDNF lying downstream of an initial NMDAR-dependent event [25]. The mitogen-activated protein kinase arm was implicated by a ≈3.4-fold increase in Erk1/2 phosphorylation within five minutes that was prevented by the MEK inhibitor U0126 [25]. Crucially, intra-hippocampal infusion of L-lactate in vivo (four 0.5 μL boluses of 10 mM) reproduced the induction of Arc, c-Fos and Zif268 (≈61, 60 and 46% increases, respectively), establishing that the phenomenon was not confined to culture [25].

Mechanistically, the coupling between lactate and the NMDAR appears to be redox-based rather than mediated by a classical receptor in the canonical sense. Lactate oxidation by lactate dehydrogenase generates NADH, and exogenous NADH (4 mM) was sufficient to mimic the full transcriptional programme in an MK-801–sensitive manner, while the thiol-oxidising agent DTNB suppressed it—pointing to modulation of redox-sensitive cysteine residues on the receptor [25]. Electrophysiologically, L-lactate roughly doubled the NMDA-evoked current (−2.30 ± 0.40 nA versus −0.89 ± 0.17 nA in controls), an enhancement that persisted under AMPA/kainate and GABA_A blockade (DNQX plus picrotoxin) and was accompanied by an approximately 2.5-fold rise in intracellular $Ca^{2+}$, situating the effect at the NMDAR itself [25]. A more recent preprint—which has not, at the time of writing, completed peer review and should therefore be read with appropriate caution—has sought to localise this action further, attributing the potentiation of NMDAR currents to an intracellular redox mechanism acting on cysteines in the C-terminal domain of GluN2B subunits [26]. If corroborated, such subunit specificity would help reconcile the redox hypothesis with the established role of GluN2B-containing receptors in plasticity, although independent replication remains necessary before strong claims are warranted [26].

Unbiased transcriptomic profiling has broadened this picture beyond a handful of marker genes. A genome-wide analysis of cortical neurons exposed to L-lactate identified coordinated regulation of programmes spanning synaptic plasticity and neuroprotection, and estimated that NADH and NMDA could each reproduce a substantial share of the lactate-responsive transcriptome (on the order of 65% and 70% of regulated genes, respectively)—quantitative support for the view that much, though not all, of lactate's transcriptional influence is routed through NMDAR-coupled redox signalling [27]. Syntheses of this expanding literature have proposed that lactate is best understood as predominantly a signalling molecule that is, in part, also an energy substrate, acting through at least two partly independent routes: the NMDAR/NADH/$Ca^{2+}$/Erk axis on the one hand, and lactate-sensitive G-protein-coupled receptors on the other, including the Gi-coupled HCA1/GPR81 introduced earlier [20] and a still poorly defined excitatory receptor [28]. The two arms need not be mutually exclusive; rather, their relative contribution likely depends on concentration, cell type and brain region, which may partly explain the heterogeneity of published results [28]. Earlier observations that glycolysis tunes neuronal excitability through HCA1R [21] sit comfortably within this dual-receptor framing.

A second, transcriptionally distinct mechanism links lactate to BDNF through the metabolic sensor SIRT1. In a study combining voluntary exercise with pharmacological dissection, thirty days of running raised hippocampal lactate and induced *Bdnf* selectively through promoter I—the activity- and exercise-responsive promoter—rather than promoter IV or the coding exon, an effect abolished by the MCT1/MCT2 inhibitor AR-C155858 and therefore dependent on lactate transport into neurons [29]. Intraperitoneal L-lactate at doses producing blood concentrations of roughly 13 and 20 mM (117 and 180 mg/kg) reproduced the induction of *Bdnf* promoter I, BDNF protein, TrkB phosphorylation and the immediate-early genes Arc and Zif268, and enhanced spatial memory in the Morris water maze; the TrkB inhibitor CEP-701 blocked the behavioural gain, consistent with a BDNF–TrkB–dependent pathway [29]. The upstream coupling was attributed to the $NAD^+$/NADH-dependent class III deacetylase SIRT1 acting through PGC1α and FNDC5, since sirtinol and SIRT1 knockdown abolished the lactate-driven induction in vitro [29]. This places redox state—the $NAD^+$/NADH ratio shifted by lactate oxidation—at the head of both the NMDAR and the SIRT1 routes, a convergence that, while attractive, has been demonstrated largely in rodents and awaits more direct human confirmation [29]. The requirement for intact monocarboxylate transport also dovetails with the earlier demonstration that astrocyte-to-neuron lactate transport is necessary for long-term memory formation [16].

Beyond neuronal signalling proper, lactate participates in the vascular dimension of plasticity. Exercise and exogenous lactate have been shown to raise hippocampal vascular endothelial growth factor A (VEGFA) and capillary density through the lactate receptor HCAR1 [30]. In the defining experiment, both a high-intensity interval protocol (five days per week for seven weeks at ≈90% $VO_2$max, with peak blood lactate near 10 mM) and subcutaneous L-lactate (2 g/kg, generating comparable concentrations of ≈10 mM) increased VEGFA and microvascular density in wild-type mice but not in HCAR1-knockout animals, with the response most pronounced in the dentate hilus and absent in the cerebellum, in vessel diameter and in skeletal-muscle capillarity [30]. The receptor was localised to perivascular leptomeningeal fibroblast-like cells (vimentin-positive) and pericyte-like cells (PDGFRβ-positive), and its activation—by lactate or by the agonist 3,5-dihydroxybenzoate—engaged ERK1/2 together with PI3K/Akt, the same pair of cascades implicated in lactate-driven cerebral angiogenesis discussed earlier [23], apparently independently of HIF-1α [30]. Because VEGFA is itself neurotrophic as well as angiogenic, this route offers a plausible bridge between the haemodynamic and the synaptic consequences of training [30].

The cellular identity of the angiogenic lactate sensor is, however, not settled. Whereas the perivascular localisation above implicates non-neuronal cells, other work has described a neuronal GPR81 that regulates developmental brain angiogenesis and supports recovery after a hypoxic–ischaemic insult, in part through modulation of the anti-angiogenic factor thrombospondin-1 [31]. Whether these accounts reflect genuinely different cell populations, developmental stages or methodological divergences is unresolved, and the discrepancy is a useful reminder that receptor localisation in this field remains contested [31]. A comparable note of caution attaches to neurogenesis: long-term L-lactate administration has been reported to promote adult hippocampal neurogenesis in a manner dependent on the neuronal transporter MCT2 yet independent of HCAR1, since a receptor agonist did not reproduce the effect [32]. Tellingly, the same study observed enhanced neurogenesis without a corresponding improvement in learning and memory, dissociating cellular proliferation from cognitive benefit and cautioning against the assumption that every lactate-induced structural change translates into function [32]. Taken together, these findings indicate that lactate engages several non-overlapping effector systems—transporter-dependent metabolic and redox signalling alongside receptor-dependent signalling—whose contributions to neurogenesis, angiogenesis and synaptic plasticity are at least partly separable [9].

Translating these mechanisms to exercising humans exposes both encouraging convergences and genuine tensions. Acute sprint interval exercise has been reported to raise peripheral lactate alongside BDNF, IGF-1 and VEGF and to improve performance on cognitive tasks, broadly consistent with the animal mechanisms outlined above [33]. The peripheral picture is complicated, however, by the cellular origin of the circulating neurotrophin. Human skeletal muscle has been shown to express pro-BDNF abundantly (≈40–250 pg/mg dry weight) while mature BDNF is essentially undetectable, with pro-BDNF approximately four-fold higher in slow-twitch type I fibres; in the same programme, lactate infusion during resistance exercise augmented the rise in plasma mature BDNF (approximately 115% versus 55% with saline) without increasing muscle pro-BDNF, leading the authors to infer that circulating mBDNF derives from cleavage of muscle-derived precursor and from the brain rather than from de novo muscular synthesis of the mature form [34]. Independent infusion work likewise found that raising blood lactate increases circulating pro-BDNF in humans, reinforcing a lactate–neurotrophin link at the systemic level [35]. Yet a direct, monotonic relationship is far from assured: in a cohort of 31 adults, exercise raised both serum BDNF (15.46 → 17.74 ng/mL) and lactate (2.52 → 11.17 mmol/L) significantly, but no overall correlation between the two emerged, an inverse association surfacing only in Val66Met carriers and in males—observations that led the authors to characterise lactate as a "pseudo-hormone" whose neurotrophic coupling is modulated by genotype and sex [36]. The exercise-modality literature is similarly equivocal: a hypertrophy-style resistance protocol produced a larger BDNF rise than a strength-style protocol and, within the hypertrophy condition, lactate and BDNF were correlated ($r = 0.70$), whereas no such relationship held for the strength protocol ($r = 0.18$), prompting the more sceptical interpretation that lactate may be a by-product of fatigue rather than an essential driver [37]. These human data, considered together, support association more confidently than causation and underline how peripheral surrogates, genetic polymorphisms and protocol design can obscure a mechanism that is far clearer in reduced preparations; they also say little in isolation about how much peripheral lactate actually reaches the brain during exercise [13].

A unifying, if still provisional, interpretation casts lactate as a graded chemical signal of metabolic effort that scales the brain's adaptive response to exercise intensity [38]. Reviews of this literature note that higher-intensity formats—interval and sprint protocols that drive blood lactate well above the lactate threshold—tend to elicit larger increases in BDNF and VEGF than moderate continuous exercise, and that the magnitude of the lactate response often tracks the neurotrophic one [38]. The framework also confronts an apparent "lactate paradox": lower-intensity exercise that scarcely raises blood lactate can nonetheless benefit the brain, which is most readily reconciled by positing that locally released, astrocyte-derived lactate suffices at modest workloads while blood-borne lactate contributes an additional, receptor- and transporter-mediated signal once the threshold is exceeded [38]. A self-reinforcing loop has been proposed in which training upregulates monocarboxylate transporters, increasing lactate delivery to neurons, which raises BDNF, which in turn promotes MCT2 expression—an arrangement that, if validated, would help explain the cumulative cognitive benefits of sustained training [38]. Whether lactate is best regarded as a principal mediator or as one contributor among several acting in parallel remains, on present evidence, an open and actively contested question—one to which the discussion returns when weighing aerobic against resistance modalities [38].

## 3.5. Clinical translation: the antidepressant potential of anaerobic sport

The mechanistic case assembled above—that lactate instructs plasticity-related transcription, supports neurogenesis and angiogenesis, and scales with the intensity of exercise—invites an obvious clinical question: whether these properties can be marshalled against disorders in which neuroplasticity is demonstrably impaired. Major depressive disorder is the natural test case, both because its neurobiology is increasingly framed in terms of synaptic and glial dysfunction rather than monoamine depletion alone, and because the conventional pharmacological paradigm has proved an incomplete account of treatment response. Against this background, two recent syntheses have argued that lactate merits consideration as a prospective target for therapeutic intervention in psychiatric disease [39] and, more expansively, as a mechanistic bridge from energy metabolism to mood regulation [40]. The appeal of the proposition lies in its capacity to unify several otherwise disparate observations—altered brain energetics, disturbed glutamatergic signalling and diminished neurotrophic support—under a single, exercise-accessible mediator. The translation is, however, considerably more nuanced than a simple "lactate-deficiency" model of depression would imply, and an honest appraisal must begin by acknowledging where the evidence points in an unexpected direction [40].

It is tempting to assume that, if lactate is beneficial, depression should be characterised by a lactate deficit; the data, however, do not support this intuition and in most respects indicate the opposite. The largest analysis to date—spanning 109 mouse strains and experimental conditions and some 2,294 animals—identified decreased brain pH together with increased lactate as a transdiagnostic endophenotype shared across models of depression, epilepsy and neurodegeneration, with social-defeat, corticosterone-treated and serotonin-transporter-knockout depression models all falling within a "low-pH/high-lactate" cluster [41]. The inverse coupling of the two measures was robust (a strain-level correlation of approximately $r = -0.86$ and an individual-level value near $r = -0.62$), and higher brain lactate predicted poorer working-memory performance, suggesting that the accumulation reflects pathological metabolic strain rather than adaptive signalling [41]. Convergent clinical and animal findings reinforce this direction: prenatal-stress models display roughly a 1.5-fold elevation of frontal-cortex lactate, and magnetic-resonance and cerebrospinal-fluid studies have reported increased lactate in the cerebral ventricles and pregenual anterior cingulate of depressed patients [39]. The most parsimonious reading is that chronic stress shifts the balance between glycolysis and oxidative phosphorylation, so that tissue lactate rises as a marker of mitochondrial inefficiency rather than falling as a sign of substrate shortage [40].

This whole-tissue picture does not, however, exclude a more localised and functionally meaningful form of lactate insufficiency, and it is here that the therapeutic logic is recovered. Work synthesised in the mood-regulation literature indicates that chronic social-defeat stress downregulates lactate dehydrogenase A in the dorsomedial prefrontal cortex, reduces astrocyte-derived lactate and impairs neuronal excitability, producing a depressive

phenotype—and, tellingly, dorsomedial prefrontal lactate is higher in stress-resilient than in susceptible animals [40]. The distinction is consequential: an elevation of bulk lactate driven by metabolic dysfunction can coexist with a deficit in the dynamic, on-demand astrocyte-to-neuron flux that the preceding sections identified as the substrate of plasticity. Such a deficit would be expected to blunt the glycolysis-dependent control of excitability described earlier through the HCA1 receptor [21], offering a coherent reason why supplying lactate exogenously might restore function even against a background of raised resting concentrations. Consistent with a protective role for available lactate, peripheral L-lactate has been shown to mediate resilience: in chronically defeated mice it raised the proportion of resilient individuals from roughly 24% to 72%, an effect accompanied by restoration of stress-suppressed hippocampal histone-deacetylase (HDAC2/3) levels [42].

The mechanism by which exogenous lactate confers resilience appears to be, at least in part, epigenetic—though not in a straightforward manner. Although lactate restored the stress-induced reduction in class I histone deacetylases, a class I HDAC inhibitor both blocked lactate's pro-resilience action and was itself antidepressant and anxiolytic, an apparent paradox the authors reconciled by proposing that lactate's therapeutic signature operates through class II enzymes (notably HDAC5) and broad histone (pan-H3) acetylation rather than through class I inhibition alone [42]. Pharmacological studies of peripheral lactate have delineated a complementary transcriptional programme: administration is stereospecific (L- but not D-lactate), raises blood lactate from approximately 1.6 to 10 mM within about thirty minutes and reverses corticosterone-induced anhedonia, while inducing a coordinated set of changes in genes implicated in antidepressant responses—upregulation of p11, S100β and Hes5 and downregulation of phosphodiesterase 4D and nitric-oxide synthase 1, alongside modulation of glycogen-synthase-kinase-3 and CREB signalling [43]. That several of these targets—p11 in particular, but also the phosphodiesterase and the nitric-oxide system—are independently established mediators of antidepressant action lends the lactate hypothesis a mechanistic plausibility extending beyond the behavioural read-outs themselves [43].

A subsequent study clarified both a cellular substrate and a biochemical requirement for these effects. Chronic L-lactate (1 g/kg for 21 days) reversed the corticosterone-induced increase in forced-swim immobility and restored proliferation, survival and the density of newborn neurons in the dentate gyrus; critically, pharmacological ablation of adult hippocampal neurogenesis with temozolomide abolished the antidepressant action across forced-swim, tail-suspension and saccharin-preference measures, establishing neurogenesis as necessary rather than merely correlated [44]. The biochemical requirement is equally instructive. Pyruvate, the immediate oxidation product of lactate, did not reproduce either the behavioural or the neurogenic benefit, whereas lactate, the NADH-generating ketone β-hydroxybutyrate and NADH itself each suppressed corticosterone-induced reactive oxygen species in hippocampal progenitors [44]. This implicates the NADH yielded by the lactate-to-pyruvate conversion—rather than carbon flux into the tricarboxylic-acid cycle per se—as the operative signal, dovetailing both with the redox model of NMDA-receptor potentiation advanced earlier [25] and with the antioxidant functions considered below [44]. Notably, none of these antidepressant effects emerged in non-stressed animals, indicating a state-dependence that is itself therapeutically attractive in that it implies correction of a perturbed system rather than blunt pharmacological override [44].

If exogenous lactate is antidepressant, then exercise—the most powerful physiological generator of lactate—becomes an obvious endogenous delivery route, and it is in this sense that higher-intensity, partly anaerobic formats are of particular interest. Sprint-interval and other supramaximal protocols drive blood lactate well above the lactate threshold while concurrently raising peripheral neurotrophic factors and improving cognitive performance [33], and the SIRT1–PGC1α–FNDC5–BDNF cascade shown to mediate the mnemonic benefits of exercise is engaged by lactate itself [29], a convergence that has led reviewers to characterise lactate as an "exercise mimetic" capable of reproducing part of this signature pharmacologically [40]. A note of caution is nonetheless warranted before equating "anaerobic" exercise with antidepressant efficacy. Although depression is reliably associated with reduced peripheral BDNF (a meta-analytic standardised mean difference of approximately −0.64 across more than 7,000 patients), the available exercise literature suggests that aerobic training raises resting BDNF (a standardised mean difference of around 0.66) whereas resistance training does so unreliably (approximately 0.07) [45]. This dissociation cautions against assuming that the acute lactate surge produced by resistance or interval work translates

straightforwardly into the sustained neurotrophic elevation associated with regular aerobic training, and it should be read with the additional caveat that the meta-analytic estimates derive in part from a lower-tier source [45]. A measured interpretation is that anaerobic formats are well placed to deliver the large, transient lactate excursions that drive rapid, state-dependent antidepressant signalling, whereas the durability of any resting neurotrophic gain may depend on training variables that the present evidence does not yet resolve [45].

A third strand of the clinical rationale concerns protection rather than promotion. Chronic stress and affective illness are associated with glutamatergic excess, dendritic atrophy and disturbed calcium handling in prefrontal and limbic circuits, and lactate possesses properties that counter each of these [40]. Beyond its role as an energy substrate, lactate functions as a redox and pH "buffer" at the synapse: the neuronal transporter MCT2 is concentrated at glutamatergic spines, where lactate uptake limits local acidification and thereby helps protect pH-sensitive NMDA and kainate receptors, while systemic lactate has been shown to reduce glutamate-induced neurotoxicity in the cortex in vivo [46]. The clinical correlate is striking—raising arterial lactate to approximately 5 mM in brain-injured patients lowers cerebral extracellular glutamate and intracranial pressure—indicating that the glutamate-buffering capacity demonstrated in animals is operative in the human brain under pathological load [46]. At the cellular level the protective signal again appears to be NADH-dependent: the reducing equivalents generated by lactate oxidation neutralise glutamate-evoked reactive oxygen species, the same chemistry that underlies lactate's suppression of corticosterone-induced oxidative stress in neural progenitors [44]. Complementary mechanisms have been proposed, including acid-sensing ion-channel (ASIC1a) signalling that, at modest concentrations, augments mitochondrial respiration while lowering reactive oxygen species [40], together with the broad induction of neuroprotection-associated genes observed in lactate-treated cortical neurons [27]. Read alongside the now well-established reframing of lactate as a signalling molecule rather than a metabolic waste product [5], these data support the view that lactate can act as an endogenous neuroprotectant against the excitotoxic milieu of chronic stress.

Two caveats temper this otherwise encouraging synthesis and demarcate the boundaries of responsible translation. The first is dose. The very molecule that is antidepressant at one concentration is anxiogenic at another: intravenous sodium lactate is a long-established panicogen, provoking panic in roughly 93% of predisposed patients against some 20% of controls, and elevated brain lactate has been linked to histone lactylation in the prefrontal cortex that tracks the severity of stress-related social deficits [39]. That a single mediator can produce opposing affective outcomes—antidepressant yet anxiogenic—underscores that "dose is the key factor", and that the therapeutic window, route and kinetics matter as much as the mere presence of lactate [39]. The second caveat is the direction-of-effect problem rehearsed above: because resting tissue lactate is, if anything, elevated in depression, any therapeutic model must rest on the dynamics of stimulus-evoked, transporter-mediated delivery and downstream signalling rather than on the correction of a static deficiency [41]. Taken together, the literature supports a defensible but appropriately hedged proposition—that exercise-induced and exogenous L-lactate can exert rapid, state-dependent antidepressant and pro-resilience effects, restoring behavioural flexibility, supporting hippocampal neurogenesis and buffering excitotoxic glutamate—while the optimal modality, intensity and dosing remain to be defined, and the bulk of the causal evidence still derives from rodent models awaiting systematic confirmation in humans [40].

## 4. Discussion

The preceding sections have assembled, link by link, a mechanistic chain that runs from the contracting muscle fibre to the transcription of plasticity genes in the hippocampus, with L-lactate as its recurring protagonist. Viewed as a whole, the literature increasingly supports a reading of lactate not as the metabolic residue of anaerobic effort but as a multifunctional signal—an energy substrate, a redox and pH modulator, a receptor ligand and a regulator of gene expression—that couples the metabolic state of the exercising body to the adaptive capacity of the brain [1, 5]. Two recent integrative syntheses make this case explicitly. The first argues that exercise-induced lactate formation reshapes brain function through a convergent set of pathways—the SIRT1–PGC-1α–FNDC5–BDNF

axis, cAMP/PKA/CREB signalling, HCAR1 engagement and a cytoplasmic shift in the NADH/$NAD^+$ ratio—such that lactate behaves as a bona fide "exerkine" rather than a passive fuel [47]. The second situates the same molecule within the broader arc of brain development, synaptic plasticity, angiogenesis and neurodegeneration, emphasising that during physical activity extracellular lactate can rise to roughly 10–20 mM and, on reaching the synapse, doubles in concentration and potentiates N-methyl-D-aspartate-receptor signalling to drive expression of Arc, Bdnf, c-Fos and Zif268 in a manner abolished by NMDA-receptor blockade [48]. The convergence of these frameworks with the cellular and clinical evidence reviewed above lends the central thesis a coherence it would not possess were lactate merely incidental to exercise; at the same time, the same syntheses are candid that the field remains burdened by unresolved questions of dose, directionality and the gap between rodent mechanism and human outcome [19, 47].

That exercise alleviates depressive symptoms is, at the level of clinical outcome, among the better-replicated findings in behavioural medicine, and it is the necessary empirical anchor for any mechanistic argument. The most comprehensive appraisal to date, a network meta-analysis of 218 randomised trials enrolling 14,170 participants, found moderate antidepressant effects for exercise relative to active comparison, with the largest point estimates for dance (Hedges' $g \approx -0.96$) and substantial effects for walking or jogging (−0.63), yoga (−0.55) and strength training (−0.49); these magnitudes were comparable to or exceeded those for cognitive behavioural therapy (−0.55) and selective serotonin-reuptake inhibitors (−0.26), and—of particular relevance to the present argument—they scaled with prescribed intensity, vigorous regimens outperforming light ones (−0.74 versus −0.58) [49]. A dose-dependence of this kind is precisely what a lactate-mediated model would predict, since blood and brain lactate rise steeply and non-linearly once exercise approaches and exceeds the lactate threshold. Yet the same analysis tempers any triumphalism: only a single trial was judged to be at low risk of bias, the overall confidence in the estimates was low to very low, and the authors were explicit that no clear biological mechanism could be adjudicated from outcome data alone [49]. The clinical literature, in other words, is consistent with the lactate hypothesis without being able to confirm it.

When the evidence is interrogated specifically for a contrast between aerobic and anaerobic modalities—the question that motivates this review's emphasis on the partly anaerobic, lactate-generating formats favoured by athletes—the picture becomes genuinely ambiguous, and intellectual honesty requires that the ambiguity be foregrounded rather than resolved by assertion. A systematic review and meta-analysis of 32 randomised trials (26 pooled, 2,681 participants) reported a large overall antidepressant effect (standardised mean difference −0.97, 95% confidence interval −1.28 to −0.66) but found that exercise mode did not reliably moderate it: although the aerobic subgroup yielded a numerically larger estimate than the resistance or mixed subgroup (−1.60 across eighteen comparisons versus −0.89 across six), the formal test for subgroup difference was non-significant ($Z = 0.538$, $p = 0.591$), against a backdrop of very high heterogeneity ($I^2 \approx 90\%$) [50]. Intriguingly, the same analysis inverted for anxiety, where resistance and mixed training carried a significant advantage (−0.83, $p = 0.005$) over a non-significant aerobic estimate (−0.56) [50]. The implication is uncomfortable for any simple "anaerobic-is-better" narrative: at the level of pooled clinical outcome, the antidepressant benefit of exercise appears largely indifferent to whether the work is predominantly aerobic or resistance-based, even though the two modalities differ markedly in their acute lactataemic signature.

Some narrative syntheses none the less make a vigorous case for the resistance and high-intensity end of the spectrum, and these are worth weighing carefully, not least because they articulate the lactate bridge most directly. One review of resistance training marshals meta-analytic evidence that progressive strength work reduces depressive symptoms with an effect of around $\Delta = 0.66$ across 33 trials and some 1,877 participants, largely independent of age, sex or health status and most pronounced at mild-to-moderate baseline severity, while reporting comparably favourable anxiolytic effects [51]. A second review, addressing physical activity and depression more broadly, reports antidepressant standardised mean differences spanning roughly −0.50 to −1.16 for aerobic exercise, −0.66 to −1.06 for resistance training and −0.42 to −0.50 for high-intensity interval formats, and—crucially for the mechanism advanced here—states plainly that physical activity raises muscle lactate, which in turn stimulates SIRT1 to potentiate BDNF release, and that interval training drives "greater lactate accumulation and subsequent activation of neuroprotective pathways" [52]. This is the clearest point at which the exercise-

prescription literature and the lactate-signalling literature touch, and it provides the connective tissue between the population-level observation that intense exercise helps and the molecular claim that lactate is why [52]. These sources must, however, be read with their evidentiary tier in mind, a caveat to which the limitations below return.

Against this stands an equally serious body of evidence that, where modality does seem to matter, the advantage often lies with sustained aerobic work rather than with brief anaerobic effort—a tension this review is obliged to represent faithfully. A review of exercise and brain structure notes that in the classic head-to-head comparison of walking against stretching-and-toning in older adults, the aerobic arm produced the greater gain in executive control, and that although resistance training does augment grey-matter volume and circulating insulin-like growth factor 1, its effect on BDNF is "more pronounced with aerobic exercises" [53]. A review focused on BDNF as the bridge between pharmacotherapy and physical activity similarly localises the best-characterised neurotrophic and structural gains—elevated peripheral BDNF, increased dentate-gyrus blood volume, expanded prefrontal and cingulate grey matter and preserved hippocampal volume—to chronic aerobic training [54]. Most pointedly, a further synthesis cites preclinical work in which treadmill running and anaerobic resistance protocols over six to eight weeks failed to increase adult hippocampal neurogenesis, whereas sustained voluntary aerobic running reliably did, a dissociation that cautions directly against over-reading the acute lactate surge of anaerobic work as if it guaranteed durable neurogenic benefit [55]. This aligns with the meta-analytic observation, noted earlier in this paper, that aerobic training raises resting BDNF more dependably than resistance training (standardised mean differences of approximately 0.66 versus 0.07) [45]. The honest synthesis is therefore not that anaerobic sport is uniformly superior, but that aerobic and anaerobic formats may act through partially distinct temporal windows.

It is this distinction between acute signalling and chronic adaptation that, in our reading, best reconciles the apparent contradiction. The partly anaerobic, supramaximal formats characteristic of athletic training are unrivalled generators of the large, transient lactate excursions that the mechanistic literature identifies as the proximate trigger for plasticity-related signalling: high-intensity interval work can drive blood lactate to 20–30 mM, plasticity genes are engaged at concentrations as low as ~2.5 mM, and during such efforts the brain measurably increases its lactate oxidation (by around a third) while reducing glucose uptake, consistent with a genuine substrate switch [47]. High-intensity interval exercise has been shown to elevate BDNF, cortisol and lactate in concert, and to do so more markedly than moderate-intensity work [56]; sprint-interval protocols raise both peripheral neurotrophic factors and cognition in tandem with lactate [33]; and lactate engages the SIRT1-dependent BDNF cascade and the HCAR1-dependent angiogenic programme that underpin these gains [29, 30, 38]. On this account, anaerobic formats are optimally configured to deliver the acute, state-dependent pulse of lactate signalling, whereas the durability of resting neurotrophic and structural change—neurogenesis, grey-matter preservation, tonically elevated BDNF—may depend more on the cumulative volume and regularity that aerobic training characteristically supplies [53], [55]. The two literatures need not be in conflict if they are understood to be measuring different phases of the same adaptive process, the one transient and the other consolidated.

Beyond mood, the same lactate-centred logic extends to the wider domain of cognitive resilience and neuroprotection, where the translational stakes are arguably higher still. The integrative reviews converge on the proposition that exercise-derived lactate supports memory formation, oligodendrocyte myelination, neurovascular coupling and antioxidant defence, and that impairment of the astrocyte–neuron lactate shuttle is implicated in the energetic failure characteristic of neurodegenerative disease, in which reduced LDH5 activity and altered monocarboxylate-transporter expression accompany cognitive decline [47, 48]. The disease picture is, as in depression, directionally complex—Alzheimer and Parkinson pathology is associated with increased cerebrospinal-fluid lactate even as astrocytic lactate production falls, so that bulk accumulation and functional shuttling deficits may coexist—a pattern that closely echoes the elevated-tissue-lactate-yet-deficient-delivery endophenotype identified in affective illness [41, 48]. That exercise can favourably modulate this system, plausibly by sustaining on-demand astrocyte-to-neuron flux rather than by simply raising ambient concentrations, is the thread that unifies the antidepressant, pro-cognitive and neuroprotective faces of the lactate hypothesis [47].

These encouraging convergences should not, however, obscure the substantial limitations that constrain any firm conclusion, and a responsible discussion must give them due prominence. Three reservations are paramount. First,

the clinical evidence base is statistically heterogeneous and methodologically fragile: pooled estimates carry $I^2$ values near 90% [50], the largest network analysis rated only one of 218 trials at low risk of bias and graded overall confidence as low to very low [49], and blinding of exercise interventions is intrinsically difficult, leaving expectancy effects incompletely controlled. Second, the human signalling evidence rests largely on peripheral surrogates—chiefly circulating BDNF—whose relationship to events behind the blood–brain barrier is indirect; serum concentrations exceed plasma by an order of magnitude owing to platelet release, and the muscle appears to export pro-BDNF rather than the mature neurotrophin, complicating any simple inference from a post-exercise rise in a venous sample to enhanced central plasticity [34, 54]. Third, the bulk of the causal mechanistic evidence—the SIRT1–BDNF cascade, the neurogenesis dependence, the redox requirement—derives from rodent models, and the quantitative parameters that would govern a human therapeutic application, namely the optimal modality, intensity, timing and effective lactate dose, remain undefined [47]. The dose problem is not trivial, since the very molecule that is antidepressant and pro-resilient at one exposure is anxiogenic and panicogenic at another, so that "dose is the key factor" rather than a detail to be settled later [39]. To these may be added a more foundational caveat: the astrocyte–neuron lactate shuttle itself remains contested, with well-argued dissent holding that stimulated neurons may rely on direct glucose metabolism and that the stoichiometry of an obligatory shuttle is not securely established [48]. Taken together, these considerations support a conclusion that is affirmative but deliberately bounded—that L-lactate is a credible and mechanistically rich mediator of exercise-induced neuroplasticity and a plausible endogenous antidepressant and neuroprotectant, that higher-intensity, partly anaerobic exercise is especially suited to generating the acute lactate signalling this model invokes, and that the translation of these insights into prescriptive guidance awaits the controlled human dose-ranging studies the present evidence cannot yet supply [40, 47].

## 5. Conclusions

This review set out to reframe L-lactate and to recover it from the long shadow of its reputation as the inert by-product of oxygen-limited muscle. The evidence assembled here supports a different reading: that lactate is a versatile signalling molecule which links the metabolic state of the working body to the plastic capacity of the brain, and that the astrocyte–neuron lactate shuttle is the anatomical and biochemical conduit through which that link is expressed [1, 5]. Reconceived in this way—as an energy substrate, a redox and pH modulator, a ligand for the HCAR1/GPR81 receptor and an upstream regulator of plasticity-gene transcription—lactate ceases to be incidental to exercise and becomes one of its principal mediators, a circulating "exerkine" whose rise during effort is less a cost to be tolerated than a message to be read [4, 47].

The mechanistic chain that emerges is unusually complete for a putative endogenous neuromodulator. During intense exercise, glycolytic muscle exports lactate into the circulation, where it becomes a quantitatively important fuel for the brain and is taken up across the blood–brain barrier through monocarboxylate transporters [3, 13]. Within the parenchyma, activity-dependent glutamate uptake drives astrocytic glycolysis and the transfer of lactate to neurons, a step shown to be necessary for the consolidation of long-term memory [14, 16]. There, lactate appears to act through at least two convergent routes: as a ligand at the HCAR1 receptor, coupling neuronal activity to the cerebrovascular and angiogenic programme that exercise engages [20, 30]; and as an intracellular signal that, by shifting the cytoplasmic $NADH/NAD^+$ ratio and potentiating N-methyl-D-aspartate-receptor currents, promotes expression of the plasticity genes Arc, Bdnf, c-Fos and Zif268 and the SIRT1-dependent activation of hippocampal BDNF [25, 29]. The downstream consequences—synaptic potentiation, adult hippocampal neurogenesis, angiogenesis and the structural consolidation that sustains mood and cognition—are most parsimoniously read as flowing from this signalling rather than from the bulk provision of fuel alone [24, 48].

Set against clinical outcomes, this molecular account gains plausibility without attaining proof. Exercise is among the better-replicated non-pharmacological antidepressants, its benefit appears to scale with prescribed intensity, and exogenous or exercise-derived lactate reproduces antidepressant and stress-resilient phenotypes in animal models—each observation consistent with, though not uniquely explained by, a lactate-mediated mechanism [42,

43, 49]. Yet the pooled human evidence does not display the clean superiority of anaerobic over aerobic work that a naïve reading of the lactate hypothesis might anticipate; at the level of depressive outcome, modality seems to matter less than overall engagement and intensity [50]. The reconciliation advanced here is that the partly anaerobic, supramaximal formats characteristic of athletic training are especially well configured to generate the large, transient lactate excursions that act as an acute, state-dependent trigger for plasticity signalling, whereas the durable resting gains—tonically elevated BDNF, preserved grey matter, sustained neurogenesis—track more closely with the cumulative training volume that aerobic work characteristically supplies. On this view the two modalities are best understood as complementary phases of a single adaptive process rather than as competitors [45, 47, 55].

These conclusions are offered as affirmative but deliberately bounded. The causal core of the argument rests substantially on rodent models, while the human data lean heavily on peripheral surrogates—chiefly circulating BDNF—whose relationship to events behind the blood–brain barrier remains indirect [34, 47]. The clinical literature is statistically heterogeneous and methodologically fragile, and the dose-dependence that makes lactate attractive as a therapeutic lever is also its principal hazard, since the very molecule that is antidepressant and pro-resilient at one exposure can be anxiogenic and panicogenic at another [39]. Nor is the framework's foundation uncontested: the obligatory directionality of the astrocyte–neuron lactate shuttle remains the subject of well-argued dissent, and any responsible synthesis must therefore hold its central metaphor lightly [6, 48].

What the field now requires is correspondingly specific. Controlled human dose-ranging studies—ideally pairing standardised exercise or lactate-infusion protocols with central read-outs of plasticity rather than venous proxies—would do most to convert mechanistic plausibility into prescriptive guidance, as would trials designed to dissociate the acute-signalling and chronic-adaptation components that this review has argued are distinct [40, 47]. Should such studies bear out the present reading, the therapeutic implications are considerable: lactate, together with the transport and receptor machinery that handle it, would become a rational target in its own right, and the trained athlete—chronically and repeatedly exposed to supramaximal lactate excursions—would emerge as an instructive natural model of precisely the signalling this review has sought to characterise [46]. On the balance of the evidence presently available, L-lactate is best regarded not as the exhaust of exertion but as one of the molecular currencies in which the exercising body purchases the resilience of the mind [40].

## Disclosure:

**Author's contribution**

**Conceptualization:** Aleksandra Wojas
**Methodology:** Jarosław Tsukerman, Arkadiusz Psiuk
**Investigation:** Jarosław Tsukerman, Arkadiusz Psiuk, Aleksandra Wojas, Joanna Szymocha
**Writing-rough preparation:** Aleksandra Wojas
**Writing-review and editing:** Joanna Szymocha, Jarosław Tsukerman, Arkadiusz Psiuk, Aleksandra Wojas,
**Supervision:** Arkadiusz Psiuk, Jarosław Tsukerman
**Project administration:** Arkadiusz Psiuk

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