# Neuroimmunological and Neuroenergetic Aspects in Exercise-Induced Fatigue

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**Abbreviations**

| | | |
|---|---|---|
| ADO | – | adenosine |
| ATP | – | adenosine triphosphate |
| BBB | – | blood-brain barrier |
| CNS | – | central nervous system |
| CVO | – | circumventricular organs |
| DAMP | – | danger-associated molecular pattern |
| GABA | – | γ-aminobutyric acid |
| IL-1 | – | Interleukin 1 |
| IL-6 | – | Interleukin 6 |
| LPS | – | lipopolysaccharide |
| PAMP | – | pathogen-associated molecular pattern |
| RNS | – | reactive nitrogen species |
| ROS | – | reactive oxygen species |
| S100 | – | S100 calcium-binding protein |
| TNF | – | tumor necrosis factor-alpha |
| TLR | – | Toll-like receptor |
| $VO_{2max}$ | – | maximal oxygen consumption |
| 5-HT | – | 5-hydroxytryptamine |

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## ABSTRACT

*Feelings of fatigue not only occur in chronic and acute disease states, but also during prolonged strenuous exercise as a symptom of exhaustion. The underlying mechanisms of fatigue in diseases seem to rely on neuroinflammatory pathways. These pathways are interesting to understand exercise-induced fatigue regarding immune system to brain signaling and effects of cerebral cytokines. Activation of the immune system incurs a high-energy cost, also in the brain. In consequence immune cells have high energetic priority over other tissues, such as neurons. A neuronal inactivation and corresponding changes in neurotransmission can also be induced by end products of ATP metabolism and elicit feelings of fatigue in diseases and after intensive and prolonged exercise bouts. Since there are no existing models of exercise-induced fatigue that specifically address interactions between neuroimmunologic mechanisms and neuroenergetics, this article is combining scientific evidence across a broad range of disciplines in order to propose an inflammation- and energy-based model for exercise-induced fatigue.*

**Keywords:** exercise-induced fatigue, neuroinflammation, neuroenergetics, adenosine, cytokines.

## 1. Introduction

To study exercise-induced fatigue for many years, priority was given to muscles over the brain as a regulatory factor. Already in 1915, Alessandro Mosso postulated that both, the will (central component) and the muscular work (peripheral component), have to be taken into account when considering the resulting impairment of exercise performance. Mosso distinguished the diminution of the muscular force and the sensation of fatigue (1). As a result of the upcoming knowledge of the bi- and multidirectionality of biological systems, the paradigm shifted to the inclusion of cerebral processes in order to guarantee homeostasis in all systems during exercise by modulating athlete´s behavior (2,3).

Since proinflammatory cytokines induce changes in behavior during acute infection by provoking feelings of fatigue (4,5), it is reasonable that the remarkable rise in circulating proinflammatory signals during prolonged strenuous exercise (6) may also contribute to exercise-induced fatigue. In this regard, the neuromodulatory properties of myogenic/neuronal Interleukin 6 (IL-6) and cerebral immune cell-derived Interleukin 1 (IL-1) have recently been discussed as major factors in exercise-induced fatigue (7,8).

According to the selfish immune system theory (9), high synthesis rates of cytokines indicate high energy turnover of immune cells and with that, higher energetic needs of those. In the case of an increasing brain macrophage activity, energy substrates may be shifted away from neurons to these immune cells to maintain their activity (8,10). Because decreasing neuronal activity seems to induce feelings of fatigue also during exercise, a compromised energy provision to neurons due to increasing brain immune cell activity could account for the decline in exercise performance (11,12).

The initially increasing neuronal and glial energy turnover during prolonged strenuous exercise (11,12) may favor the generation of the nucleoside adenosine (ADO) (13), which negatively mediates exercise performance in a concentration-dependent manner by modulating dopamine neurotransmission in the basal ganglia (14,15).

Here, we propose that (neuro-)immunological mechanisms influence neuroenergetics, with both proinflammatory signals and end products of energy turnover inducing feelings of fatigue during prolonged strenuous exercise and ultimately provoking exercise termination.

## 2. Peripheral and central fatigue

Already in the late nineteenth century, the physiologist Angelo Mosso postulated that "muscular fatigue also is at bottom an exhaustion of the nervous system" (2). In the context of exercise-induced fatigue, central or supraspinal fatigue appears to originate in regions of the brain and is defined as the inability of the CNS to drive motor neurons efficiently during the performance of intermittent or prolonged aerobic exercise (16), whereas peripheral or muscle fatigue is the result of biochemical changes in the exercising limb muscles (17).

### 2.1 Lactate accumulation

According to the lactate theory of exercise fatigue, the exercising muscles stop working due to a massive intracellular lactate accumulation as a consequence of an insufficient supply of oxygen and the upregulation of the muscle cell´s anaerobic metabolism (17).

However recent findings challenge the correctness of the lactate theory (Robergs, 2004) and emphasize the significance of lactate as energy substrate in other metabolic processes (18,19). Via intracellular monocarboxylate transport proteins, lactate is used as an additional energy substrate both by contracting and adjacent inactive muscle fibers. During strenuous exercise, a reciprocal brain-muscle energy exchange occurs in which the brain favors muscle-derived lactate in order to provide enough circulating glucose to type-2 muscle fibers as its primary energy substrate (20-22).

The energetic capacity of exercising muscles does not decrease significantly to promote peripheral fatigue, since muscles are still capable to generate power at exhaustion (23). Because neither lactate accumulation in exercising muscles nor associated muscle acidification cause peripheral fatigue (23), these findings underline the assumption of exercise termination forced by central mechanisms.

### 2.2 Neurotransmission

Neurotransmission of monoamines plays a crucial role in exercise-induced fatigue. The central fatigue hypothesis postulated by Newsholme et al. (24) states that exercise-induced synthesis of cerebral serotonin (5-HT) provokes the onset of fatigue symptoms. Since 5-HT can not cross the blood-brain barrier (BBB), brain cells rely on the uptake of tryptophan as its precursor. Animal studies (25) have shown that tryptophan injections in the cerebral ventricle of rats were associated with the onset of exercise-induced fatigue, while inhibition of the conversion of tryptophan to 5-HT could improve running time to fatigue. However, others have proven a reduction in plasma tryptophan in humans after exhaustive aerobic exercise (26), which seems contradictory to the aforementioned findings. Strasser et al. conclude that there is limited availability of tryptophan for 5-HT biosynthesis in the brain after the enzymatic conversion to kynurenine in the periphery.

Recent findings provide evidence that dopaminergic neurotransmission in striatopallidal neurons increases exercise performance by maintaining motivation and motor regulation (27,28). A blockage of central dopaminergic D1/D2 receptors results in a significant decrease in endurance performance and maximal oxygen uptake (29).

### 2.3 Cytokines

Many systemic inflammatory and neuroinflammatory disorders, i.e. chronic fatigue syndrome (CFS), depression or multiple sclerosis, are frequently accompanied by high amounts of circulating cytokines and a persistent state of mental and physical fatigue (30). Neuroimaging studies have suggested the presence of neuroinflammation in the midbrain of CFS patients (31). Furthermore, CFS patients achieve volitional exhaustion significantly faster and consistently report a higher rate of perceived exertion during an exercise task, assuming that CFS, in part, is mediated centrally (32). Chronic fatigue in athletes suffering from overtraining/athlete burnout may also result from circulating proinflammatory cytokines and a neuroinflammatory state (33,34).

Vargas & Marino (35) proposed a neuroinflammatory model for acute fatigue during exercise. The authors suppose a potential interaction between cytokine release during prolonged strenuous exercise and their effects on afferent feedback signalling to the brain that might lead to feelings of fatigue. In particular, the extraordinary increase in plasma IL-6 concentration is proposed to be a major fatigue-inducing factor due to its receptor-mediated signal transduction in neuronal afferents and circumventricular organs (CVO).

Already in 2000, the influence of muscle-derived IL-6 was considered to play an important role in the development of central fatigue (36). Subcutaneous administration of a low dose of recombinant IL-6 to athletes increase their sensation of fatigue at rest and significantly impairs athletic performance during a 10-km running time trial (37). Because of its autocrine, paracrine or endocrine effects, muscle-derived IL-6 may also function as an energy sensor and a hormone-like molecule that increases energy substrate mobilization (38-40), possibly by an intensity-dependent upregulation of cortisol (41,42). Therefore, high IL-6 levels could represent the need for energy substrates.

After an eccentric exercise bout, the concentration of IL-1 increases significantly in rat brain regions responsible for movement, coordination, motivation, perception of effort, and pain. Its levels correlate significantly with both post-exercise delayed recovery and decreased performance in a subsequent task (43). Further, intracerebroventricular injection of IL-1 significantly decreased wheel running activity in uphill running mice, whereas IL-1ra improved wheel running in downhill running mice (44). Another study identified perivascular and meningeal macrophages as the major producer of brain IL-1 during exercise (8).

There is vast evidence that microglia, another mononuclear phagocytic cell type in the CNS and the main actor in neuroinflammation, synthesize both IL-1 and TNF in high amounts after activation. Furthermore, the decrease in symptoms of depression and fatigue is accompanied by a reduced TNF secretion in the CNS through modulation of neuroinflammation (31,45,46).

## 3. Systemic inflammatory response during exercise – muscle damage, leukocytosis and endotoxemia

Via the production of IL-6 and reactive oxygen species (ROS), both exercise-induced muscle damage (47,48) and the intensity-dependent rise in circulating T-lymphocytes and neutrophils (49,50) significantly contribute to the exercise-induced systemic inflammation (51,52). The rise in serum neopterin during exhaustive aerobic exercise suggests an increased activation of peripheral macrophages (26). However, results from Ostrowski et al. (53) reveal an increase of the anti-inflammatory cytokines IL-10, IL-1 receptor antagonist and soluble TNF receptors during and after strenuous exercise, possibly due to the massive increase in IL-6 (41,54).

Lymphocyte-derived extracellular heat shock proteins are known to increase during high-load exercise and are further proposed to promote fatigue sensation via marked influence on motor neurons and deeper structures of the CNS (55). These molecules also promote inflammation by acting as a danger signal from the immune system. Bårdsen et al. (56) suggest that the significant increase in extracellular heat shock proteins in CFS patients might signal to the brain and contribute to the state of fatigue.

The observation that prolonged strenuous exercise favors a systemic inflammatory state was discussed by John Marshall, assuming that the exercise-induced increase in intestinal permeability and lipopolysaccharide (LPS)-induced endotoxemia may be the underlying cause (57). LPS is a gut-derived proinflammatory fragment of the outer membrane of gram-negative bacteria and a pathogen-associated molecular pattern (PAMP). Pals et al. (58) showed that the degree of the intestinal permeability depends mainly on exercise intensity and correlates with body core temperature. In fact, human studies show that the severity of endotoxemia seems highly dependent on the environmental temperature (59,60), but also on the composition of the gut microbiota (61). In this regard, the supplementation of probiotics over a period of 4 weeks displays a tendency to decreasing intestinal permeability and reducing LPS in the bloodstream (62).

After an ultramarathon, 81% of the participants showed plasma LPS levels > 0.1 ng/ml (endotoxic), while 2% even had a plasma concentration of 1 ng/ml (potentially lethal) despite moderate environmental temperatures (20,3°C-22,3°C) (63). Both exercise-induced functional splanchnic hypoperfusion and translocation of LPS are damaging the protein-barrier complex between enterocyte membranes via temperature-dependent and immune-mediated mechanisms (64-66). This contributes to an endotoxic state.

## 4. Communication interfaces between periphery and central nervous system

A systemic inflammatory response has been shown to affect the activity of immune cells in the brain. The growing importance of the bidirectionality between the periphery and the central nervous system (CNS) and the impact of neuroimmunomodulatory mechanisms (67) puts the interplay of endocrine, neuronal and immunological mechanisms in the forefront of exercise regulation (3). Due to acute or chronic immune stressors, dysregulation at periphery-CNS interfaces, i.e. the BBB, CVO, and afferent nerve fibres (68), is associated with pathological conditions in which fatigue is a common feature (69). As prolonged strenuous exercise represents a huge physiological stressor accompanied by immune activation, interface-specific cells could get regulated in order to induce systemic adaption and maintain homeostasis in all systems during exercise (2,70).

Some cytokines use specific mechanisms to access the brain parenchyma by bypassing its saturable transport mechanisms (71). The serum level of the S100 calcium-binding protein (S100) which provides information about the severity of the BBB´s permeability, increases during strenuous exercise (72). Both duration and intensity of an exercise bout (73) and game-related activities or events (74) seem to determine the rise in S100 plasma concentration. Furthermore, S100 is the most frequently assessed biomarker in studies investigating sport-related concussion which is known to induce BBB disruption (75). According to the severity of concussion, the post-injury neuroinflammatory state promotes metabolic dysfunction and neuronal impairment (76), often followed by persistent feelings of fatigue, without regard of traumatic brain injury severity (77,78). A correlation between the onset of exercise-induced fatigue and the number or magnitude of impacts to the head is possible, but experimental data are lacking.

Although LPS is able to alter transport rates for many peptides across the BBB (79), LPS acts on receptors outside the BBB rather than directly on BBB´s structures to modulate its integrity (80,81). Peripheral administration of subseptic doses of LPS initiates the synthesis of IL-1 and tumor necrosis factor-alpha (TNF) messenger RNA at the CVO, but not at the BBB (82). Since plasma LPS concentration can rise significantly during prolonged strenuous exercise (63), CVO could play a decisive role in neuroimmunological modulation. Recent studies show that communication between peripheral immune cells and brain structures predominantly occurs at the sensory CVO (83). Their unique structure enables them to

monitor and transmit blood- and cerebrospinal fluid-derived information from circulating substances that do not readily cross the BBB.

During a systemic inflammatory response, concentrations of the IL-6 receptor and the IL-6 signal transducer glycoprotein 130 are highest in the sensory CVO. The synthesis rate of both increase significantly in accordance with circulating IL-6 (84), thereby enforcing its neuroimmunomodulatory properties. The huge rise in serum IL-6 during prolonged strenuous exercise may increase levels of soluble IL-6 receptor and glycoprotein 130 in the sensory CVO. A systemic inflammatory response upregulates IL-1 receptor and TLR (Toll-like receptor) 4 in the sensory CVO as well, both changing the activity of neurons and inducing gene expression of proinflammatory cytokines (85-87). The IL-1 receptor and TLR4 is expressed by microglia and by brain macrophages. After a single systemic administration of LPS, microglia show increased proliferation in the sensory CVO compared with other regions of the brain (88), presumably compensating for the lack of a protecting BBB.

Receptors for cytokines and LPS are also expressed at the terminal nerve endings of the vagus nerve, suggesting a crucial role in immunomodulation and sickness behavior via signalling from nucleus tractus solitarius to brainstem, hypothalamus and higher brain centers (89-91). Once these receptors become activated, the vagus nerve is stimulated in a dose-dependent relationship (92,93).

Since the afferent activity of the hepatic vagus nerve seems to contribute to the orchestration of the metabolic and hormonal responses to exercise, cytokine-induced stimulation of the vagus nerve could influence exercise performance in a dose-dependent manner (94). Similarly, activation of glial cells in the spinal cords of mice during eccentric exercise alters their gene expression due to the emerging skeletal muscle inflammation (95), provoking exercise-induced muscle hyperalgesia by IL-6 signalling on primary afferent nociceptors (96). Enhanced glial cytokine synthesis in the spinal cord is also shown during acute and chronic pain states and in inflammatory muscle disease (97,98) with fatigue and pain pathways being quite similar regarding cytokine signalling (99).

## 5. Neuroinflammation and fatigue

Since the perception of fatigue as a hallmark of sickness behavior seems to be cytokine-driven (4,5), fatigue is widespread in people suffering from neurodegenerative and chronic inflammatory diseases (30). Both direct and indirect measurement methods revealed an increased intestinal permeability, higher circulating LPS levels and a region-specific rise in neuroinflammation (100-104). Therefore, a causal relationship between intestinal permeability, neuroinflammation and the perception of fatigue is reasonable.

Rats exposed to either an immunological or a physical stressor show symptoms of sickness behavior in a time-dependent manner. However, when IL-1 receptor antagonist is injected intracerebroventricularly prior to the physical stress exposure, symptoms do not appear (105). Indeed, IL-1 and IL-6 may function as immunological correlates of human sickness behavior. During infection, levels of IL-1 and IL-6 spontaneously released from peripheral blood mononuclear cell cultures were consistently correlated with reported manifestations of acute sickness behavior including fever, malaise, pain, fatigue, mood and poor concentration (106).

An animal study showed that the administration of anti-inflammatory omega-3 fatty acids significantly inhibit LPS-induced neuroinflammation in the prefrontal cortex, hippocampus and hypothalamus and reverses depression-like behavior (46). Moreover, supplementation of the omega-3 fatty acid eicosapentaenoic acid in the course of 16 weeks promotes symptom remission and structural brain changes in patients with CFS (107).

## 6. Energetic regulation – is there a selfish immune system in the brain?

From an ecoimmunological point of view, an acute inflammatory response is metabolically extremely costly according to its allostatic load (108). As allostasis is an evolutionarily conserved and energy-intensive response to resume local homeostasis, the allostatic load indicates the severity of the homeostatic disruption (109). Based on in vitro O2-consumption rates (24), activated macrophages turn over ATP ten times faster per minute compared to the inactivated state. The favored aerobic glycolysis of activated immune cells makes glucose their primary energy substrate (110), using strategies to redistribute energy to themselves to keep their metabolism running (9). New insights indicate that these characteristics can also be observed in microglia depending on their polarization state (10,88,111).

Assuming that brain macrophages become overactive during prolonged strenuous exercise (8), their energy needs could reduce energy provision to neurons, thereby promoting the occurrence of fatigue symptoms. In patients with tuberculous meningitis, the infection with Mycobacterium tuberculosis represents a huge allostatic load indicated (112). The infection is accompanied by microglial activation and the allocation of astrocytic lactate to microglia via astrocyte-microglia lactate shuttles, thereby providing an adequate energy supply activated microglia. As a result, the allocation of lactate to neurons decreases significantly, which leads to neuron inactivation (10). Similarly, when lactate shuttling from astrocytes to neurons decreases during strenuous exercise, neurons are not able to maintain their metabolism (11,113). In consequence, exercise performance declines.

Acute bouts of strenuous exercise mobilize highly differentiated T-cells from peripheral tissues into the blood stream (49,114) referring to exercise-induced leukocyte demargination (115). Since a high differentiation level is associated with decreased mitochondrial content and function, these immune cells mainly rely on the glucose-consuming anaerobic metabolism (116). The trafficking rate depends on the aerobic fitness level with untrained people showing higher redistribution of these energy consuming immune cells into the blood

stream (117,118), potentially contributing to the earlier onset of exercise-induced fatigue in this population.

A high energy turnover induces ATP breakdown to ADO. ADO is secreted by ATP-depleted tissues or is extracellularly generated from ATP, which is released from metabolically stressed cells (119). In a Drosophila infection model, ADO induces energy reallocation by enhancing uptake of glucose in immune cells at the expense of other glucose-dependent tissues, including the brain (120). Consequently, ADO is considered being a signalling molecule whose effects could increase fatigue in relation to the energetic demand of activated immune cells (121). It is important to note that ADO regulatory and signaling network in Drosophila is similar to mammalian systems (121). Since high levels of ADO accumulate in the brain after prolonged strenuous exercise (13), it is reasonable that there could be similar mechanisms of action.

## 7. Purinergic regulation of neuroinflammation and neurotransmission in the basal ganglia

New insights into mechanisms of action of purines in the CNS with respect to neuroinflammatory processes and behavioral regulation emphasize their neuromodulatory effects, although most results are from animal studies (122). A rise in extracellular ADO favors neuroinflammatory signalling through upregulation of the high-affinity $A_{2A}$ adenosine receptor (123). As high amounts of extracellular ATP are considered to be evolutionarily conserved danger-associated molecular pattern (DAMP) (124), it initiates inflammation via stimulation of the TLR4-dependant cytosolic inflammasome in microglia (125). While both ADO and ATP are able to enhance the production of IL-1 (126), IL-1 in turn promotes ATP and ADO release from neurons (127). Experimental data in mice suggest a potentiation of nitric oxide release by activated microglia after interacting with the $A_{2A}$ adenosine receptor, thereby increasing ROS and reactive nitrogen species (RNS) production (128-130). In addition, the stimulation of the ATP-purinoceptors P2X7R and P2X4R favors synthesis of IL-6 and TNF, what further promotes neuroinflammation (131).

ADO directly influences behavior by decreasing dopaminergic neurotransmission through conformational changes of D2R binding sites at a shared $A_{2A}/D_2$- and $A_{2A}/D_2/mGlu_5$-receptor complex on rat striatopallidal GABA neurons (15,132,133). As dopamine is an important neurotransmitter in exercise regulation, ADO may negatively influence exercise performance in rats (134). In contrast, the ADO antagonist caffeine delays run time to fatigue in rats by 52%, presumably by increasing dopamine release through an antagonism at the $A_1$ and $A_{2A}$ adenosine receptors in the striatum, the nucleus accumbens and the nucleus caudatus (135) or the preoptic area and the anterior hypothalamus (136). However, no effect of caffeine on exercise performance was seen in humans exercising in high ambient temperature (137).

## 8. Neuroinflammation-induced energy reallocation during exercise – a new paradigm?

Not only exercise-induced muscle damage, endotoxemia and leukocytosis contribute to the systemic inflammatory response in exhausted athletes, but also the release of ROS/RNS and, to a lower extent, cytokine-dependent apoptosis of leukocytes and neutrophils immediately after prolonged strenuous exercise (138,139). Although circulating lymphocytic subpopulations contain a high antioxidant capacity (140), it is conceivable that leukocytes whose capacity has already been exhausted during prolonged strenuous exercise could undergo apoptosis even before exercise termination. Cells that are not immediately phagocytosed after apoptosis become “leaky” (secondary necrosis). They release DAMPs and stimulate a host response by secreting more proinflammatory signals (141).

Exercise-induced rise in serum LPS concentration may induce changes at the BBB and favors microglia proliferation at the CVO, thereby inducing neuroinflammation (80,88). If gut-derived LPS accumulates in the liver by overwhelming the capability of the liver´s reticulo-endothelial system (63), the resulting stimulation of Kupffer cells may force the secretion of cytokines. Binding of LPS and IL-1 to receptors on terminal nerve endings of the hepatic vagus nerve may activate microglia (69,142).

There is some evidence that IL-6 acts as a major factor and is contributing to exercise-induced fatigue (7,36,37). Results from prolonged (marathon) and highly prolonged (spartathlon) endurance exercise show a 128-fold and respectively 8000-fold increase in IL-6 plasma levels, peaking at exercise termination and rapidly normalizing afterwards (53,143). This outcome may support the fatigue-inducing character of IL-6 instead of being a proinflammatory cytokine in the context of exercise. However, as energy availability declines drastically due to the physical strain in such events, muscle-derived IL-6 may also work in its hormone-like fashion by increasing energy substrate mobilization (38-40).

Since increased neuronal metabolism alters microglia functioning, neurons can be regarded as key immune modulators in the brain (144). As neuronal metabolism and extracellular levels of ‘neuron-microglia signalling factors’ rise, they function as "On" signals (Fig. 1: right box, dark blue arrows) by recruiting microglia which then support the neuron´s metabolism (Fig. 1: microglia-astrocyte-neuron lactate shuttles = right box, purple arrow). Already before, astrocytes begin to serve the energy needs of the neurons through cellular lactate transfer (Fig. 1: astrocyte-neuron lactate shuttles = light blue arrow).

The rise in extracellular ADO due to the high glial and neuronal ATP turnover may increase astrocyte proliferation and activation (145). The significant increase in brain ADO during strenuous exercise (13), could, therefore, aim to enhance astrocytic lactate production to supply the cells in need (Fig. 1). Furthermore, cerebral ADO modulates BBB permeability through stimulation of endothelial $A_{2A}R$ and $A_1R$ (146). An enhanced uptake of blood lactate may be the consequence, as

a moderately increased permeability of the BBB is regarded as a functional mechanism during exercise by serving neuronal metabolism (27). Marked changes, however, could may limit the individual's capacity to perform optimally by allowing the accumulation of unwanted substances in the CNS (27).

Because almost all metabolic processes show a dose-response relationship during stress exposure with both beneficial and detrimental outcomes (147), exercise above a certain threshold can cause mal-adaptations as well (148). Regarding prolonged strenuous exercise, the exercise-related dose response induces an inflammatory state (Fig. 1) and may also provoke an acute neuroinflammatory response (8) due to the high allostatic load on brain cell metabolism. However, experimental data are lacking to make clear conclusions about brain metabolism during exercise and its relation to neuroinflammation. But to integrate the existing knowledge about exercise-related dose response into the concept of neuroinflammation, we propose a model of continuum in which the astrocyte-neuron lactate shuttle expands to the microglia-astrocyte-neuron lactate shuttle (149) when energy demand of neurons increase during exercise (Fig. 1, right box). Both, the intensity-dependent systemic inflammatory response and brain cell-derived purines may switch the microglial phenotype from the M2/anti-inflammatory form to the M1/proinflammatory form, thereby making them more "energy-craving". That is followed by a step-by-step inactivation of neurons through astrocyte-microglia lactate shuttles (10) (Fig. 1: right box, red arrow).

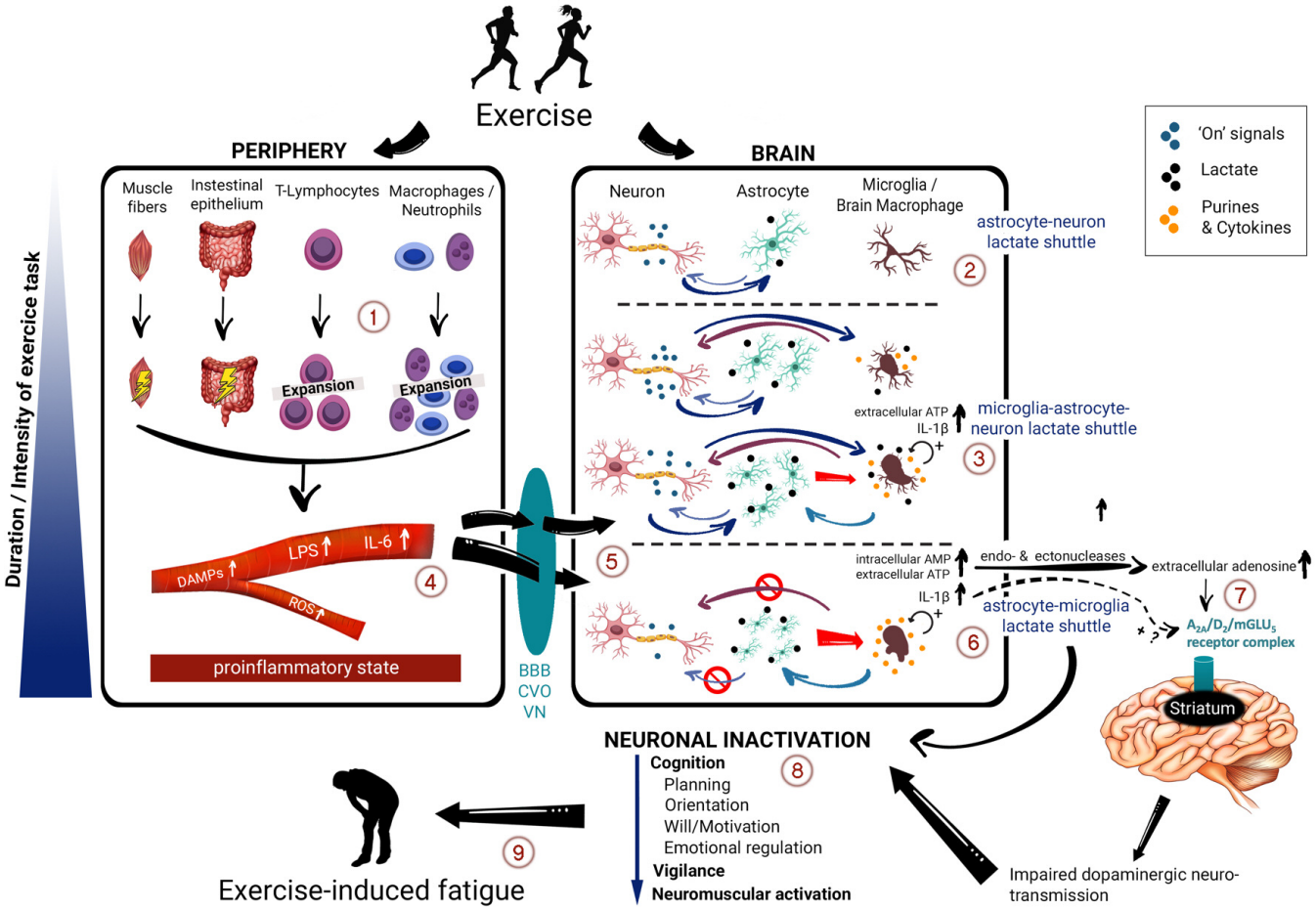


**Figure 1:** Hypothetical integrative model showing how neuroimmunological and neuroenergetic mechanisms induce feelings of fatigue during prolonged strenuous exercise, ultimately provoking exercise termination.
Strenuous exercise favors exercise-induced muscle damage, gut-derived LPS translocation and immune cell expansion (leukocytosis) [1]. At the same time, the exercise-induced and intensity-dependent increase in neuronal metabolism favors the release of neuronal 'On'-signals, which induce lactate transfer from glial cells to neurons, beginning with the astrocyte-neuron lactate shuttle [2] and extending to the microglia-astrocyte-neuron lactate shuttle in order to serve the increasing energy needs of the neurons [3]. Microglial autoactivation through microglia-derived IL-1β and extracellular ATP may promote a switch to the M1/proinflammatory form. As strenuous exercise continues, that leads to a proinflammatory state characterized by high circulating amounts of LPS, DAMPs (e.g. HSPs), IL-6 and ROS-damaged immune cells. These proinflammatory signals act either on the BBB, CVOs and VN which then signal to the CNS or they act directly on the CNS by passing the BBB or CVOs [4]. In doing so, these signals may stimulate microglia/brain macrophages through TLR-4 and IL-1β receptors [5] which then continuously shut down the lactate transfer from astrocytes to neurons through a yet unknown ("selfish"?) mechanism in order to benefit most from astrocytic lactate [6]. Further, the degradation of ATP and AMP through endo- and ectonucleases favor accumulation of extracellular adenosine that impairs dopaminergic neurotransmission by acting on the A2A/D2/mGLU5 receptor complex on striatal neurons [7]. A possible contribution of IL-1β to adenosine signalling may further enhance the down regulation of dopaminergic neurotransmission. The resulting neuronal inactivation [8] leads to a decline in cognition, vigilance and neuromuscular activation, ultimately inducing exercise-induced fatigue [9].
$A_{2A}$: adenosine $A_{2A}$ receptor; $D_2$: dopamine $D_2$ receptor; $mGLU_5$: metabotropic glutamate receptor 5; IL-1β: interleukin 1β LPS: lipopolysaccharide; IL-6: interleukin 6; DAMP: danger-associated molecular patterns; BBB: blood-brain barrier; CVO: circumventricular organs; VN: vagus nerve; AMP: adenosine monophosphate; ATP: adenosine triphosphate; TLR-4: toll-like receptor 4; HSP: heat shock protein; CNS: central nervous system.

This microglial polarization is often accompanied by a shift from oxidative phosphorylation to aerobic glycolysis for energy production due to increasing concentrations of nitric oxide by inducible nitric oxide synthetase which reversibly inhibits mitochondrial respiration (111). With that, ROS and RNS production is increased which, in turn, activates downstream signaling pathways resulting in the up-regulation of a variety of proinflammatory proteins and more ROS/RNS.

Whether there is a similar mechanism of energy reallocation from neurons to activated microglia/brain macrophages during non-infectious stress is unknown. However, haemodynamically stressed microglia express monocarboxylate transporter-1 and -2 (150), which may enable them to utilize astrocytic glycogen-derived lactate. Since there is remarkable cerebral haemodynamic stress during prolonged strenuous exercise (151), expression of monocarboxylate transporters may promote the uptake of astrocytic lactate in microglia or brain macrophages.

Although the amount of LPS crossing the BBB is low (80,81), some athletes show plasma concentration of 1 ng/ml after an ultramarathon (63). If LPS crosses the BBB at that concentration is unknown, but conceivable since the BBB becomes leakier during strenuous exercise. As LPS-TLR4 interactions resemble proinflammatory pathways induced by Lipoarabinomannan, the major cell wall component of mycobacterium tuberculosis (152,153), high amounts of LPS in the brain may be able to induce the expression of astrocyte-microglia lactate shuttles. Further, cerebral DAMPs may promote astrocyte-microglia lactate shuttles in a similar fashion by triggering the microglial TLR4 (Fig. 1).

Heck et al. (55) propose that the exercise-induced increase in circulating levels of extracellular 70-kDa heat shock proteins from lymphocytes promote fatigue via marked influence on motor neurons and deeper structures of the CNS. Although specific receptors for heat shock proteins in brain tissue have not been identified yet, their ability to induce proinflammatory signalling in TLR4/2-expressing cells is well established (154,155).

Because lactate does not accumulate in cerebrospinal fluid after an exhaustive exercise task (156), unlike during tuberculous meningitis (157), we do not know whether it is appropriate to think of the astrocyte-microglia lactate shuttles as a relevant mechanism in exercise-induced fatigue. Further it is unknown whether extracellular ADO reallocates energy substrates to demanding cerebral immune cells and thereby shutting down the less relevant neuronal metabolism as shown in a Drosophila infection model on the peripheral level. Extracellular ADO definitively compromises exercise performance in animals due to its inhibitory effect on dopaminergic neurotransmission (134,135). To connect the potential fatigue-inducing property of ADO, Hanff et al. (158) assume that it plays an important role in the induction of sickness behavior via the A2A/D2/mGLU5-receptor-complex (Fig. 1). In fact, LPS-induced swim deficits is reversed by systemic administration of an A2A receptor antagonist (159). A similar receptor-ligand interaction appears to be relevant in the induction of sleep (160). The stimulation of A2AR and mGLU5R inhibits the activity in vigilance-regulating brain areas by presynaptic inhibition, postsynaptic hyperpolarization and amplifying GABAergic projections (161,162). Increased dopamine release in the ventral tegmental area reduces the inhibitory activity in the nucleus accumbens and is promoting vigilance.

Dopaminergic neurotransmission in the substantia nigra pars compacta inhibits neuroinflammation by activating astrocytic $D_2$-receptors (163). Based on the assumption that IL-1 may contribute to motivational and vigilance regulation via an important interaction with ADO signalling in the CNS, i.e. activation of A2A receptors in the striatum (158) (Fig. 1), the attenuated dopamin-induced anti-inflammatory effect could promote synthesis of IL-1. Both, inflammation- and exercise-induced peripheral hyperammonaemia promote cerebral synthesis of ADO (164,165), which may force exercise-induced fatigue by altering cognition (165). The increasing impairment of the fronto-striatal network down-regulates cognition and motivation, which makes exercise termination rather a relative than an absolute event due to the athlete´s volitional and forced conscious decision (see Fig. 1) (3,166,167). The impact of peripheral cytokine signalling and central microglia/brain macrophage activation on this fronto-striatal network should be taken into account (69).

## CONCLUSION

Exercise-induced fatigue does not emerge from a single peripheral or central mechanism, but rather result of a synergistic effect of various mechanisms involving both peripheral and central aspects. As an evolutionary conserved protective mechanism, neuron inactivation and the concomitant increase in feelings of fatigue are extremely useful to maintain systemic homeostasis at all bodily levels, also during exercise. If the immune system is even selfish in the brain, microglia/brain macrophage-derived extracellular ADO could mediate the metabolic switch and energy reallocation, thereby inducing neuron inactivation, feelings of fatigue and ultimately exercise termination. Due to the impact of IL-1 on feelings of fatigue and behavior modulation, the synthesis of IL-1 from perivascular and meningeal macrophages during strenuous exercise has to be considered when approaching the complexity of exercise-induced fatigue. Changes in cerebral haemodynamics are not investigated in this article but should be subject of further studies about the regulation of exercise performance. In order to get deeper insights into the brain metabolism during prolonged strenuous exercise and its relation to neuroinflammation, the hormesis-like dose response of brain macrophage activation during exercise should be investigated in future studies.

As presented here, the majority of aspects concerning neuroimmune-neuroenergetic interactions in sports performance are not very well established and need to be evaluated in the future. Therefore, it is inevitable to improve interdisciplinary research in this field.

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