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Exercise-Neuro-Immunology – From Bench to Bedside

Sport-Neuro-Immunologie – von der Grundlagenforschung in die Praxis

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Summary

› **Increased levels of physical activity** are associated with a risk reduction for several neurodegenerative disorders (e. g. Multiple Sclerosis, Parkinson's disease). Moreover, physical exercise is known to improve the physical capacity and to reduce commonly-observed symptoms, such as motoric, cognitive and affective impairments. In addition to the ameliorating effects on specific symptoms, first evidence also suggests that physical exercise interventions may counteract and/or alleviate the progress of these diseases.

› **Considering the side effects** of drug therapy, exercise interventions represent a promising non-pharmacological supportive treatment option and are therefore increasingly being investigated in clinical research on neurological diseases. More knowledge about the underlying biological mechanisms is warranted in order to improve tailored exercise programs.

› **However, the reduced accessibility** of the central nervous system in humans and problems in the transferability of rodent models complicates research in this field. Nevertheless, several peripheral markers indicating distinct biological pathways involved in the pathogenesis and progression of neurodegeneration have been revealed to date. Interestingly, these biomarkers have recently been described to be sensitive to exercise stimuli.

› **In this review,** we provide an overview of the interaction between potential mechanisms linked to physical exercise and the alleviation of neurodegenerative processes. More precisely, we focus on different aspects of exercise-induced impacts on neuronal growth factors, inflammation, blood-brain barrier permeability and the kynurenine pathway.

Zusammenfassung

› **Erhöhte Level körperlicher Aktivität** sind mit einer Risiko-reduktion für zahlreiche neurodegenerative Erkrankungen assoziiert (z. B. Multiple Sklerose, Parkinson-Krankheit). Darüber hinaus ist bekannt, dass Bewegungs- und Sportprogramme die physische Kapazität von Betroffenen verbessern und häufigen Symptomen, wie motorischen, kognitiven und affektiven Einschränkungen, entgegenwirken. Zusätzlich zu einer symptomlindernden Wirkung, weist erste Evidenz auch darauf hin, dass Bewegungsinterventionen einem Fortschreiten dieser Erkrankungen entgegenwirken können.

› **In Anbetracht der Nebenwirkungen** medikamentöser Therapien stellen Trainingsinterventionen eine vielversprechende, nicht-pharmakologische supportive Behandlungsstrategie dar, welche bei klinischer Erforschung von neurologischen Erkrankungen immer häufiger untersucht wird. Um gezielte Bewegungsempfehlungen zu optimieren, muss mehr Wissen über die zugrundeliegenden biologischen Mechanismen generiert werden.

› **Die schlechte Zugänglichkeit** des humanen zentralen Nervensystems und die eingeschränkte Übertragbarkeit aus Tiermodellen stellt die Forschung hier vor eine besondere Herausforderung. Nichtsdestotrotz wurde aktuell eine Reihe peripherer Marker von unterschiedlichen molekularen Signalketten aufgedeckt, welche ihrerseits in die Pathogenese und die Progression von Neurodegeneration involviert sind. Interessanterweise sind diese Marker sensibel für körperliche Belastungsstimuli.

› **In diesem Übersichtsartikel** liefern wir einen Überblick zum Zusammenspiel von potentiellen Mechanismen im Kontext von Bewegung/Sport und der Linderung neurodegenerativer Prozesse. Im Detail fokussieren wir uns auf die unterschiedlichen Aspekte belastungsinduzierter Einflüsse auf neuronale Wachstumsfaktoren, Inflammation, Blut-Hirn-Schranken Permeabilität und den Kynureninpfad.

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Introduction

Results from epidemiological studies indicate that increased levels of physical activity are associated with a decreased risk for several neurodegenerative and neurological disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (7, 19). First evidence also suggests, that both general physical activity and targeted exercise programs counteract a progress of neurodegenerative and neurological disorders (28, 38).

Besides its positive effects on physical function (endurance, strength and balance), exercise programs have proven to reduce cognitive and affective impairments in clinical and non-clinical populations (8, 58). In order to define general (e. g. for prevention) and specific exercise recommendations (i.e. to reduce specific symptoms) more precisely, detailed knowledge about the underlying mechanisms is warranted.

›

To date, these mechanisms are largely unknown due to several reasons. The human central nervous system (CNS) allows only restricted access in clinical trials. Although neurophysiological and imaging techniques can give hints on biological processes, they are not able to elucidate the molecular and cellular mechanisms within the CNS. In contrast, preclinical (mostly rodent) models overcome these methodological limitations and additionally provide a higher standardization (more homogenous samples, better control of confounding factors, etc.). However, it is suggested that less than 10% of results from rodent studies can be transferred to humans (33). In fact, the CNS and especially the prefrontal cortex, which is involved in cognitive and emotional processes, differs strongly between species. To provide some numbers, the prefrontal cortex accounts for less than 3,5% of the telencephalon in rodents, whereas it covers around 29% in humans (62). Therefore, only few, evolutionary highly conserved brain structures are comparable. The best investigated anatomical structure in this context is the hippocampus. As part of the temporal lobe of the telencephalon it is involved in varying cognitive processes among which memory consolidation represents the most prominent one. In regard to neurodegenerative disorders, it is worth mentioning that rodents usually do not develop these diseases due to their limited life span. Experimental inductions of these diseases may cause similar impairments as in humans, nevertheless, the underlying mechanism may differ.

Within this work, we provide an overview of biological mechanisms that are suspected to be influenced by physical activity and exercise and that are further associated with the development and progress of neurodegenerative/neurological disorders (Figure 1). Of note, these neuroprotective mechanisms are rather of general nature and do not account for only one type of disease or symptom.

Exercise and Growth Factors

The most investigated and sensible neuronal growth factors in response to exercise are the Brain-derived neurotrophic factor (BDNF), the Vascular endothelial growth factor (VEGF) and the Insulin-like growth factor (IGF)-1. In fact, chronic exercise training can lead to preserved brain volume in humans (13), potentially being a result from increases in neuronal growth factors.

Overall, most evidence exists on exercise impacting BDNF. Besides stimulating neuro-, synapto- and gliogenesis, BDNF is largely involved in processes of neuroprotection (43). In view of brain regions, BDNF is closely linked to the hippocampus, which represents a frequently affected area in different neurodegenerative diseases. Interestingly, evidence suggests a dose-response interaction between acute bouts of exercise and peripheral BDNF concentrations. Especially acute aerobic exercise lasting for at least 30 minutes provokes an intensity-dependent increase in peripheral BDNF concentrations, whereby higher intensities – e.g. 10% above ventilatory threshold (VT) compared to 20% below the VT (12) – are associated with higher BDNF levels in healthy populations. In contrast, low to moderate intensities seem to be sufficient for distinct elevations of BDNF concentration in patients with neurological (54% of maximal heart rate (48) or psychiatric (e.g. 70% of maximal oxygen uptake (57)) disorders (71). In view of chronic exercise interventions, minor increases in resting peripheral BDNF concentrations were reported (59). However, evidence suggests elevations of resting BDNF concentrations provoked by aerobic but not resistance exercise (11). Beside classical exercise protocols of continuous intensities over the whole exercise period,

high intensity interval training seems to represent a superior stimulus to increase BDNF concentrations in respect to both, acute and chronic interventions (26). The potential sources of exercise-induced BDNF release is still insufficiently understood. Nevertheless, the brain itself is suggested to be responsible for a majority of peripheral BDNF elevations (46). In this context, the myokine irisin could be a key regulator of BDNF expression in response to acute exercise stimuli (14). Concerning chronic exercise, the link between irisin and BDNF appears to be questionable since BDNF concentrations have been described to increase whereas irisin levels decrease following longer-term exercise interventions (45).

VEGF is mainly responsible for angiogenesis and contributes to enhanced blood flow by restoring injured tissue. Additionally, it provokes neurogenesis and synaptic plasticity (50). Its expression is stimulated by physiologically occurring hypoxic and hypoglycaemic conditions, as they appear during acute exercise. More precisely, an elevated concentration of lactate during acute exercise leads to a stabilisation of the hypoxia-induced transcription factor 1-alpha (HIF1-α), which is followed by an activation of VEGF expression (23). Of note, animal studies reveal comparable concentrations in periphery and CNS with increased levels of VEGF after high-intensity interval exercise (39, 60).

IGF-1 is primarily expressed by the liver but can be produced by several other cell types. A variety of important functions in the development and recovery of CNS are promoted by IGF-1, such as neuroprotection and the inhibition of astrocytic response to inflammation (30). Acute aerobic and resistance exercise lead to temporary increased peripheral IGF-1 concentrations. Elevated levels were mainly observed following acute high-intensity aerobic exercise (63) and acute moderate to high-intensity resistance exercise (64). Furthermore, also chronic training interventions increase peripheral serum concentrations of IGF-1. However, no distinct dose-response relationship was revealed up to date (25). Evidence from animal studies has already shown both, an increase of IGF-1 in peripheral blood and hippocampus (6).

In conclusion, acute bouts of exercise indicate similar responses of BDNF, VEGF and IGF-1. More detailed, a dose-response relationship is suggested for all neuronal growth factors mentioned above. Beyond that, animal models reveal acute exercise-induced elevations within the CNS. Potential correlations between increased levels of central neurotrophic growth factors in humans and cognitive functioning remain unclear. However, an animal study indicated a relationship between elevated concentrations in the hippocampus and improved learning and memory (6).

Exercise and Inflammation

Chronic low-grade systemic inflammation represents a well-approved risk factor for several chronic diseases, such as internistic (e.g. cancer) or neurodegenerative diseases (e.g. AD, PD, MS) (16, 66). Low-grade systemic inflammation implies an increased number of circulating pro-inflammatory mediators, as especially indicted by interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and C-reactive protein (CRP) (16).

Highly regarded, physical inactivity and sedentary behaviour favour the development and persistence of chronic low-grade systemic inflammation (20, 29). An inactive lifestyle promotes the accumulation of adipose tissue, leading to an increased production of pro-inflammatory cytokines (42). Moreover, in adipose tissue numbers of type 1 macrophages and
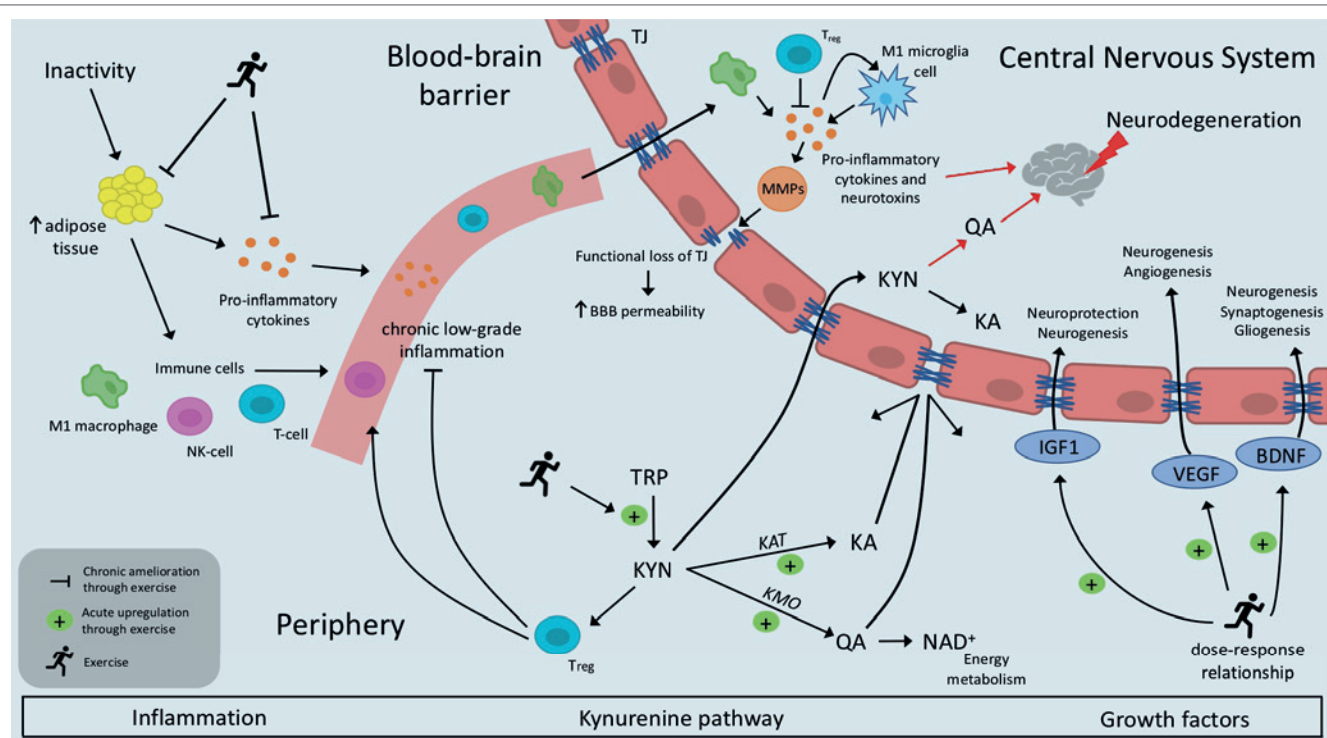
Figure 1

Overview of neurodegenerative mechanisms and suspected exercise-induced counteractions. NK cell=natural killer cell; Treg=regulatory T cell; BBB=blood-brain barrier; TJ=tight junction; MMP=matrix metalloproteinase; KYN=kynurenine; KA=kynurenic acid; QA=quinolinic acid; TRP=tryptophane; KAT=kynurenine aminotransferase; KMO=kynurenine 3-monooxygenase; NAD⁺=oxidized form of nicotinamide adenine dinucleotide; IGF1=insulin-like growth factor 1; VEGF=vascular endothelial growth factor; BDNF=brain-derived neurotrophic factor.

other pro-inflammatory immune cell subsets are elevated, while anti-inflammatory regulatory T-cells (Tregs) are decreased (29). Inflammation that was originally located in adipose tissue becomes systematic as pro-inflammatory mediators enter the blood stream, thereby transferring the inflammatory signals to other organs and tissues including the CNS, liver, muscle and intestine. This transfer of locally derived inflammation in adipose tissue to systemic milieu, also described as "metaflammation", indicates a progressive metabolically induced inflammation and is a substantial factor for chronic low-grade inflammatory conditions (29). In addition, ageing is directly linked to low-grade systemic inflammation. This "inflammaging" can partially explained by alterations in body composition during the process of ageing. However, studies have shown, that ageing also activates pro-inflammatory signalling on the epigenetic level, a negative development which can be reduced by physical exercise (40).

A vast body of evidence suggests that exercise has various anti-inflammatory properties (16, 66). In this context, direct and indirect anti-inflammatory effects can be distinguished. Regarding the indirect effect, a reduction of adipose tissue in response to chronic exercise stimuli counteracts the previously described inflammatory effects (66).

Concerning direct effects, several mechanisms have been suggested. Firstly, acute bouts of exercise induce the release of IL-6 from contracting muscle (44), which is followed by the expression of anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist. The latter response inhibits further immune reactions (16). Secondly, chronic exercise was described to reduce the expression of Toll-like receptors (TLRs) on monocytes and macrophages (16), resulting in a decreased production of pro-inflammatory cytokines and thereby leading to immune suppression. Finally, evidence suggests that chronic

endurance exercise, as indicated by an increased cardiovascular fitness, is associated with greater numbers of circulating anti-inflammatory Tregs (67).

Exercise and Immune Cells in the CNS

For a long time, the brain has been considered an immune-privileged organ, protected from peripheral inflammation with microglial cells being the only cells that contribute to immune-surveillance in the CNS. Microglia make up 10% of the cells in the CNS and represent the brain-resident macrophages that play an important role in tissue homeostasis and proper brain functioning, but also inflammation (35). However, research in the last two decades disproved the assumption of the brain as an immune-privileged organ by demonstrating that the CNS is just partly immune-privileged (15), since

1. there are immune cells (i.e. macrophages, dendritic cells and T cells) that reside CNS borders such as choroid plexus and meninges and hold supervising function (27)
2. under acute or chronic neuroinflammatory states, peripheral immune cells (i.e. activated macrophages and T cells) invade into the CNS through different sites and contribute to local inflammatory processes (32).

Polarization of otherwise resting microglia to the proinflammatory (M1) phenotype is pivotal for the inflammatory response observed in chronic neurodegeneration such as MS, PD and AD. The secretion of proinflammatory molecules and neurotoxins by activated microglia and infiltrated leukocytes leads to an amplification of microglial activity and further activates astrocytes, which represent the major constituent of glial cells in the brain (9). The emerging chronic proinflammatory microenvironment provokes dysregulation of brain ❯

homeostasis, BBB disruption and neurotoxicity, ultimately leading to neurological symptoms and chronic neurodegeneration.

A recent systematic review of 51 studies revealed that there is a relationship between systemic inflammation and microglial activation (22). Systemic inflammation is a common hallmark of people suffering from neurodegenerative disorders (10, 61). Since physical activity or exercise possesses potent systemic anti-inflammatory and immunoregulatory effects (see section Exercise and Inflammation), there is a clear indication of exercise to counteract microglial activity and neuroinflammation in neurodegenerative disorders. It has been shown that there might be a causal link between both an increase in circulating Tregs and Treg functionality and cardiovascular fitness in humans (67). Peripheral Tregs are able to invade the CNS during neuroinflammation to keep the immune response in check and are a hot topic in the treatment of neurodegenerative disorders (54). Interestingly, a recent mouse model provides substantial evidence of cerebral Tregs to augment neurological recovery, thereby possibly contributing to neuronal protection against neuroinflammatory diseases (24). The exercise intensity seems to play an important role as a mouse model revealed that only high-intensity swimming provokes a significant increase of Tregs in the CNS while the invasion of proinflammatory TH1 and TH17 cells is significantly reduced (68). This improved immune-homeostatic state was accompanied by attenuated clinical scores and reduced demyelination of spinal cords. However, the study design does not reveal whether it is the effect of high-intensity training before or during the induction of experimental autoimmune encephalomyelitis or even the combination of both that entails the beneficial effect.

Another study showed that voluntary exercise for six weeks attenuated the accumulation of amyloid plaques in aged rats and significantly decreased the numbers of activated astrocytes and microglia within the hippocampus and cortex, underlining exercise-induced reduction of neuroinflammation (21).

It is important to keep in mind that such delicate experimental designs can solely be performed in animals due to methodological limitations and, of course, ethical considerations. Despite careful interpretation, those results might give rise to encourage researchers to find some sophisticated ways to do basic research regarding exercise-induced amelioration of neuroinflammation in humans.

Exercise and the Blood-Brain Barrier

The invasion of peripheral immune cells into the CNS during a temporary neuroinflammatory state seems to be a crucial physiological mechanism for CNS protection, repair and maintenance (52). However, in the course of an autoimmune neuroinflammatory disease such as multiple sclerosis (MS) or other neurodegenerative disorders, the chronic proinflammatory microenvironment within the CNS promotes a continuous invasion of activated peripheral immune cells or neurotoxic substances, thereby exacerbating the local inflammatory response (10, 61). An important prerequisite for leukocyte diapedesis into brain parenchyma is an increased permeability of the blood-brain barrier (BBB). The BBB represents the capillary endothelium that separates peripheral blood from the brain parenchyma and serves as a physiological gatekeeper to protect the CNS from the entrance of blood-borne substances or cells with neurotoxic characteristics.

There is now emerging evidence of an impaired BBB integrity in the pathogenesis and disease progression of neurogenerative disorders like MS or PD (10, 17). Mechanistically, intercellular proteins tightly connect adjacent endothelial brain cells – which is why they are called tight junctions – to control paracellular transport of circulating substances. Partial dysregulation or disruption of tight junctions might be mediated by inflammatory and neuroimmune mechanisms and could promote regional hypoxia and translocation of vasculotoxic and neurotoxic molecules into the CNS, leading to neuroinflammation and, ultimately, to neurodegeneration. Souza and colleagues (53) have shown that both, endurance and strength training stabilize tight junctions at the BBB of mice suffering from experimentally induced encephalomyelitis. In contrast, only endurance training significantly reduced the permeability of the BBB and led to a more distinct reduction in clinical signs.

One major underlying mechanism of a functional loss of tight junctions may be the secretion and activation of so-called matrix metalloproteinases (MMPs) by activated brain-resident glial cells and invading proinflammatory immune cells (47). These proteolytic enzymes are able to degrade the cerebrovascular basement membrane and tight junction proteins in brain endothelial cells, which in turn increases BBB permeability. Further, a rat model revealed that MMPs degrade myelin basic protein that is responsible for adhesion of the cytosolic surfaces of multilayered compact myelin, thereby promoting demyelination and possibly driving disease progression in people with MS (36). These immunopathogenic properties make the MMPs a promising target of drugs and adjuvant therapeutic approaches to counteract neurodegeneration (4).

In the last decades, research in the field of exercise science revealed potent immuno- and neuromodulatory effects of regular exercise (see section Exercise and Growth Factors and Exercise and Inflammation). Interestingly, three weeks of high intensity interval training significantly reduced the MMP-2 concentration in persons with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) (70). Furthermore, a recent systematic review of intervention studies concludes that exercise training positively modulates BBB permeability markers in people with MS, i.e. MMPs and S100b (41). The latter is a brain-derived peptide produced mainly by astrocytes and is used in clinical research. It represents a biomarker of BBB integrity with high serum levels indicating an increased permeability. It is also discussed in the context of neurodegenerative diseases (49, 55). It was additionally shown that improved global cognitive function following a moderate intensity aerobic training regimen thrice weekly over six months was related to the reduction in circulating S100b levels (3). A currently published review proposes a theoretical framework on the crosstalk between physical exercise and BBB permeability and highlights the benefits of exercise as a prevention strategy as well as a non-pharmacological, complement treatment of neuroinflammatory and neurodegenerative disorders (34).

The increasing evidence of an exercise-induced amelioration of BBB integrity justifies regular physical exercise as a promising approach to improve clinical outcomes and to delay disease progression in people suffering from neurodegenerative disorders such as MS and PD.

Exercise and the Kynurenine Pathway

Recently, growing research interest focusses on the degradation of the essential amino acid Tryptophan (TRP) along the Kynurenine (KYN) Pathway. In contrast to the most popular

TRP metabolites serotonin and melatonin, the vast majority of available TRP (over 95%) is degraded through the KYN pathway, which is accompanied by distinct neuro-immunological effects (5). A great number of neurological diseases (e.g. MS, PD, AD) is associated with dysregulations along the KYN pathway (65). Currently, several central and rate-limiting KYN pathway enzymes, such as Indoleamine 2,3 dioxygenase (IDO) or Kynurenine 3 monooxygenase (KMO), represent promising therapeutic drug targets (65).

To date, little but promising evidence suggests a modulatory impact of acute exercise bouts and chronic training on KYN pathway regulation (37). Acute endurance exercise can induce an activation of the KYN pathway as indicated by decreased levels of TRP and increased levels of KYN following exercise cessation in healthy adults (56) and persons with MS (2). Since KYN itself possess immunosuppressive properties (e.g. differentiation of Tregs, reduced cytotoxicity of T- and NK-cells) (5), repetitive short-term upregulations of peripheral KYN levels could lead to longer-term anti-inflammatory effects of exercise, as previously described (see section Exercise and Inflammation).

Furthermore, exercise-induced modulations of the KYN pathway were mostly investigated focusing on the TRP metabolite Kynurenine acid (KA). Animal and human studies indicate that both acute exercise and chronic training increases the flux of the KYN pathway yielding KA (1,31). As underlying mechanism, an PGC1-α transcription co-activator mediated upregulation of the rate-liming enzymes Kynurenine aminotransferases (KATs) in skeletal muscle has been suggested (1). KATs are responsible for the conversion of KYN to KA. While KYN can penetrate the BBB, KA cannot. Consequently, an increased peripheral conversion of KYN to KA mediated by an exercise-induced upregulation of KATs prevents an accumulation of KYN within the CNS. Hence, an enhanced peripheral KYN clearance towards KA by exercise describes a neuroprotective mechanism which could be of major relevance for the development and/or progress of neurodegenerative diseases.

Finally, also peripheral levels of the TRP metabolite Quinolinic acid (QA) can be affected by acute exercise. Some studies in humans indicate that peripheral QA concentrations are elevated following acute endurance exercise (31, 51). QA is known to be a highly neurotoxic agent within the CNS, mainly due to its effects as N-methyl-D-aspartate receptor (NMDA) agonist (18). However, QA, just like KA, is neither able to penetrate the BBB. Thus, an acute exercise-induced enhanced peripheral KYN clearance towards QA might represent a similar neuroprotective mechanism as described for KA. Moreover, QA is a direct precursor of the substrate NAD^+, which is highly relevant for oxidative energy metabolism (69). Future research is warranted to focus on a potential link between exercise-induced KYN pathway modulations and NAD^+ demand during and following exercise.

Conclusions

In conclusion, physical activity and exercise seem to be a promising additional treatment for neurodegenerative and neurological disorders, not only to alleviate disease-related symptoms but also to potentially affect the course of disease. Exercise has already shown to improve physical capacity and to reduce motoric, cognitive and affective symptoms leading to an enhanced quality of life. The described alterations in substantial biological mechanisms provoked by exercise might be underlying for the amelioration of symptoms in neurological diseases. In order to improve exercise recommendations more sophisticated approaches with combinations of clinical trials and basic research are needed, thereby filling the gap from bench to bedside.

Conflict of Interest
The authors have no conflict of interest.

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