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Letter to the Editor

Inflammation, immunology, stress and depression: a role for kynurenine metabolism in physical exercise and skeletal muscle

Dear editor,

Recent research has highlighted the importance of inflammatory properties in the underlying neurobiology of depression (1). However, in complement of the research mentioned above, we would like to highlight a few points, which in turn may have treatment implications for patients with depressive symptoms and in view of inflammatory processes, immunological factors and stress.

In particular, recent research findings relating to the tryptophan and kynurenine pathway, which stands in close relationship to inflammatory processes and associated mood changes, need to be considered. Research has shown that physical exercise can be considered as a potential further strategy for intervention in patients with depressive symptoms with somewhat moderate effect sizes, as well as regards anxiolytic properties with smaller effects (2).

However, the complete mechanism of action of this approach is not entirely understood. Tryptophan and thus kynurenine metabolism can be impacted via exercise-induced skeletal muscle peroxisome proliferator-activated receptor gamma coactivator 1-alpha-1 (PGC-1α1) (3). This mechanism, which builds on activation of a specific pathway involving PGC-1α1 and peroxisome proliferator-activated receptors alpha/delta (PPARα/δ) increases skeletal muscle expression of kynurenine aminotransferases, has protective properties with regards to stress-induced depressive symptoms, in particular as a reduction in kynurenine brain accumulation levels can protect the brain from stress-induced changes that are related to depressive symptoms (3). More precisely, an increased peripheral conversion of kynurenine into its metabolite kynurenic acid (which cannot overcome the blood–brain barrier) has been discussed as a main mechanism of action with regards to this process. Recent research carried out in rodents showed that skeletal muscle-specific PGC-1α1 transgenic mice were resistant to displaying depressive-like behaviours induced via kynurenine administration or exposure to chronic mild stress (3). As a consequence, changes in tryptophan metabolism and the closely related kynurenine pathway that impact skeletal muscle function via the PGC-1α1-PPAR could be explored as a new translational strategy for intervention, in particular with regards to the inflammatory properties that are thought to be related to depressive symptoms. Moreover, as outlined by Kiecolt-Glaser et al. (1), the gut microbiome as a factor potentially impacting systemic inflammation (i.e. as regards intestinal permeability) needs to be mentioned, in particular given the fact that the gut microbiome has been discussed to affect the availability of tryptophan and kynurenine (1,4). Such a mechanism could serve as an important regulating factor, in particular with regards to crosstalk within the brain–gut axis serving as a bidirectional communication system between the brain and the gastrointestinal tractus (1,4).

Besides the points highlighted, a further important aspect that needs to be outlined in the context of immunological processes that can be linked to depressive symptoms in humans is antiphospholipid syndrome. In patients with this particular syndrome, antibodies against phospholipids that are comparable with those detected in patients with systemic lupus (also known as lupus anticoagulant) can bind to proteins and cell membrane-based phospholipids and can be related to depressive symptoms (5–7). These particular antiphospholipid antibodies hold an important position in conditions such as depression, psychosis and dementia, and have recently been discussed in the context of suicidal ideation (5–7).

In summary, in the light of the outlined factors, we like to propose that research into inflammatory and immunological mechanisms as well as stress-related factors underpinning depressive symptoms needs to be fostered, in particular as regards the above-mentioned factors and mechanisms as well as their relationship to features of depressive symptoms in different populations.

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