Persons with secondary progressive and relapsing remitting multiple sclerosis reveal different responses of Tryptophan metabolism to acute endurance exercise and training

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**Abstract**

Disturbances in Tryptophan metabolism play a crucial role in multiple sclerosis (MS). Exercise is suspected to counteract the progress of MS and its side effects. Current research suggests alterations of Tryptophan metabolism in healthy individuals in response to exercise. We investigated the influence of acute aerobic exercise and training on Tryptophan metabolism in 57 inpatients with relapsing remitting ((RRMS) n=33) and secondary progressive ((SPMS) n=24) MS. Serotonin increased after training, whereas the kynurenine pathway was only activated in persons with RRMS. Further research is warranted to investigate whether these changes are associated with clinical measures (e.g. depressions and immune function).

Key words: exercise, MS, kynurenine, tryptophan, 5HT

1. **Introduction**

Alterations in Tryptophan (Trp)[[1]](#footnote-1) metabolism are suspected to be involved in the pathogenesis and progression of neurological disorders such as multiple sclerosis (MS)[[2]](#footnote-2) (Platten et al., 2014; Lovelace et al., 2016). Trp can either be metabolized to serotonin (5HT)[[3]](#footnote-3) or be degraded through the kynurenine (Kyn)[[4]](#footnote-4) pathway. The degradation of Trp to Kyn is catalyzed by the isoenzymes Tryptophan 2,3-dioxygenase (TDO)[[5]](#footnote-5) or by Indoleamine 2,3-dioxygenase 1 and 2 (IDO1, IDO2)[[6]](#footnote-6). While TDO is mainly expressed in the liver, IDO activity can be induced by inflammatory stimuli in various tissues. Consequently, increased breakdown of Trp to Kyn during inflammatory conditions reflects an increase in the activity of IDO, which can be indirectly determined by an elevated Kyn/Trp ratio (Schröcksnadel et al., 2006). Chronically elevated Kyn/Trp ratios have been reported in persons with MS (Lim et al., 2017), although alterations in Trp metabolism seem to be dependent on the subtype of disease (Aeinehband et al., 2016). Kyn itself is further metabolized to Kyn acid or to quinolinic acid by Kyn aminotransferases (KAT)[[7]](#footnote-7). In contrast to Kyn acid, which plays a crucial role in neuroprotection/neurodegeneration, quinolinic acid is known to have neurotoxic effects using different pathways (e.g. by N-methyl D-Aspartate receptor exitotoxcity) (Lim et al., 2017; Guillemin, 2012). Increased quinolinic acid/Kyn acid ratios are reported in depressive disorders and are associated with neurodegenerative processes (Lim et al., 2017). Kyn itself has immunosuppressive properties, such as inducing immune-suppressive regulatory T-cells and reducing the activity of pro-inflammatory Th1- and Th17-cells (Platten et al., 2014; Lanz et al., 2017).

Physical exercise is suspected to counteract progression and side effects of MS (Adamson et al., 2015; Cormie et al., 2017). It is hypothesized that the positive effects of regular exercise on disease development and progression can be partially attributed to its long-term anti-inflammatory properties. It has been proposed that that these properties are mainly attributed to a reduction of fat mass, a chronic increase in anti-inflammatory regulatory T-cells and a subsequently chronic downregulation of inflammatory cytokines (Weinhold et al., 2016; Hojman, 2017). In contrast, acute bouts of exercise have been shown to induce short-term inflammatory conditions, which are characterized by the expression of pro-inflammatory cytokines (Hojman, 2017) and increased levels of circulating cell-free DNA (with subsequent endogenous DNAse activation) (Velders et al., 2014) This finding is congruent with related research reporting increased IDO activity in healthy subjects and athletes after acute bouts of aerobic exercise (Strasser et al., 2016). In terms of chronic effects of exercise on Trp metabolism in humans, only two trials have been conducted, both using a sample of persons with depression (Hennings et al., 2013; Millischer et al., 2017) and both reporting no changes. However, when investigating the role of medical- and non-medical treatments on Trp metabolites in the context of neurodegenerative diseases, one should keep in mind that some of them are not able to cross the blood brain barrier. One possible implication has recently been demonstrated by Agudelo et al. (Agudelo et al., 2014) who showed that exercise increases muscle expression of KATs. Thereby, exercise leads to a peripheral breakdown of Kyn to Kyn acid which is not able to cross the blood brain barrier. Consequently, reduced central levels of Kyn metabolites, decreased central inflammatory stress, increased levels of neurotrophic/neuroprotective factors and decreased depressive symptoms were observed.

In order to build upon the existing research, this study aimed to examine (i) effects of acute exercise and short-term rehabilitative exercise intervention-induced changes in serum Trp, Kyn, Kyn/Trp ratio and 5HT levels in persons with MS. In addition, we explored (ii) how potential exercise-induced changes in these biomarkers varied across MS subtypes (secondary progressive MS (SPMS8) vs. relapsing remitting (RRMS9)) and exercise modalities.

1. **Material and Methods**

As previously described in detail (Zimmer et al*.*, 2017), endurance capacity (V02 peak) was assessed in 57 persons with SPMS (n=24) and RRMS (n=33) before participants were allocated either to a high intensity training group (HIT10) or a standard training group (CT11) using stratified block randomization (strata: cardiopulmonary fitness and cognitive fatigue). A detailed description of the training program is published elsewhere (Zimmer et al., 2017). We used different endurance exercise protocols, since a vast body of literature suggests positive effects of aerobic exercise on the primary outcome (cognitive performance) of this trial. HIT was chosen because it has been proven to be time efficient. This was important for our study since study participants stayed in the rehabilitation clinic for only three weeks (Zimmer et al*.*, 2017). Participants did not receive selective serotonin reuptake inhibitors. No immune-therapy was applied 24 hours before all measurement time points. Blood samples were collected before (t0) and after (t1) the initial cardio-pulmonary exercise test (acute effects: t0 vs. t1) as well as after the three-week exercise intervention (t2, 24-48 hours after last training session) (training effects: t0 vs. t2). Resting blood samples were taken from the antecubital vein after 15 minutes' rest in a seated position and post-acute exercise samples were taken immediately after the initial cardio-pulmonary exercise test with participants seated on the bike. Samples were centrifuged at 3000 g for 10 minutes at 4°C and the supernatant was stored at –40°C until analysis. Trp and Kyn were determined by enzyme linked immunosorbent assay according to the manufactures instructions (Neuroimmun GmbH, Germany). 5HT was assessed by high-performance liquid chromatography. The study was registered prior to recruitment (NCT02571335), approved by the local ethic committee and in accordance with the declaration of Helsinki.

1. **Results**

Participants` characteristics, baseline comparison between RRMS and SPMS, as well as ANCOVA results for acute and chronic effects are listed in table 1. Bonferroni corrected post-hoc simple effects analysis (SEA12) is shown in figure 1. Persons with SPMS showed significantly decreased serum Trp levels compared to those with RRMS (p=.005) and a tendency for increased cardio-pulmonary fitness (p=.050).

Mixed ANCOVA revealed significant time effects for Trp, Kyn and Kyn/Trp ratio, with increased Kyn (p=.001, F=12.081, df=1, partial η2=.189), Kyn/Trp ratio (p=.001, F=11.861, df=1, partial η2=.186) and decreased Trp levels (p<.001, F=17.490, df=1, partial η2=.252) after acute exhaustive exercise. SEA revealed a significant reduction in Trp only in persons with RRMS (p=.014, SPMS: p=.932). In view of Kyn, SEA revealed no significant alterations.

A significant group x time interaction indicated different responses to acute exercise in Kyn/Trp ratio (p=.015, F=6.397, df=1, partial η2=.110). Subsequent SEA revealed a significant increase in Kyn/Trp ratio only in persons with RRMS (p=.001, SPMS: p=.756).

Regarding effects of the training interventions, ANCOVA showed no differences between exercise interventions (HIT vs. CT) on Trp metabolites over time. Significant time effects were found for serum 5HT (increase) (p=.005, F=8.818, df=1, partial η2=.150), Trp levels (decrease) (p=.002, F=10.575, df=1, partial η2=.178) and Kyn/Trp ratio (increase) (p=.010, F=7.116, df=1, partial η2=.129). Similar to acute effects, SEA revealed a significant reduction in Trp only in persons with RRMS (p=.020, SPMS: p=.665). In view of 5HT, SEA revealed no significant alterations. A significant interaction between time and MS subtype was observed for Kyn/Trp ratio (p=.025, F=5.377, df=1, partial η2=.101). Post-hoc analysis revealed a significant increase of Kyn/Trp ratio only in RRMS (p=.002, SPMS: p=.751).

As previously reported both training interventions (HIT and CT) increased VO2 peak although the increase was more pronounced in HIT (Zimmer et al., 2017).

Spearman correlations were calculated to determine associations between fitness and biomarkers. Excepting a negative association between V02 peak and Kyn levels, no correlations were detected in the overall sample. V02 peak negatively correlated with both Kyn levels and Kyn/Trp ratio only in RRMS.

1. **Discussion**

The results of this study underline those of Aeinehband et al. that reported decreased resting Trp levels in cerebrospinal fluid of persons with SPMS (Aeinehband et al., 2016).

A higher cardio-respiratory fitness was associated with lower Kyn levels in the overall sample and additionally with decreased IDO activity in persons with RRMS. Because IDO activity is known to be up-regulated by inflammatory stimuli, these results match with the idea that regular physical exercise has anti-inflammatory properties (Weinhold et al., 2016; Hojman, 2017). Indeed, we have previously shown, that the applied training intervention was able to decrease serum levels of the pro-inflammatory MMP-2 (Zimmer et al., 2017). Additionally, regular exercise may increase KAT expression in skeletal muscle leading to an increased Kyn breakdown in individuals with a higher cardio-pulmonary fitness (Agudelo et al., 2014). However, we also observed elevated resting Kyn/Trp ratio and decreased Trp levels after HIT and CT in RRMS. These results do not fit with the hypothesis that exercises induces an anti-inflammatory environment on the long-term. Although speculative, these findings may be explained by the relative intense interventions and missing follow-up measurements. In trained athletes, a training camp, which can be compared to the stationary rehabilitation also leads to increased immune activation (Weinhold et al., 2016). Another hypothesis is that Trp decreased due to a transfer to muscle tissue to cover the elevated need of amino acids for protein synthesis after training. In contrast to RRMS, the training interventions did not change Trp and Kyn/Trp ratio in persons with SPMS. These results support those of Millischer et al. who did not find any chronic changes of Trp metabolism in persons with major depressions (Millischer et al., 2017). Different responses of Trp metabolism could be argued by the already strongly decreased Trp levels in persons with SPMS or by their almost significantly increased cardio-pulmonary fitness.

As previously described for healthy subjects, acute exhaustive exercise activates the Kyn pathway in RRMS (Strasser et al., 2016). Evidence suggests that this activation is mainly driven by strongly elevated levels of inflammatory mediators such as IL-6 and IFN-gamma during and immediately after acute exercise, thereby activating IDO (Schröcksnadel et al., 2006; Walsh et al., 2011). Again, persons with SPMS did not show the expected response of Trp metabolism. Further research has to elucidate if this lack of response is due to the decreased Trp baseline levels or if this may be influenced by their increased physical fitness at baseline.

Regarding 5HT, persons with RRMS and SPMS indicated similar responses to acute exercise and training. Although data suggest an empirical increase in 5HT after acute exercise, it did not reach statistical significance. In contrast, significantly elevated 5HT levels were found in both subtypes of disease after the three-week interventions. In healthy subjects, acute exercise resulted in increased serum 5HT levels (Zimmer et al., 2016). It has been speculated that this increase is attributable to a shear stress-induced release of 5HT of platelets (Lu et al., 2013). Although peripheral 5HT is not able to cross the blood brain barrier, it has been shown that peripheral and central 5HT levels are closely related (Audhya et al., 2012). Further research is recommended to examine the exercise-induced increases in 5HT, particularly in relation to anti-depressive effects. As 5HT levels negatively correlated with Kyn in RRMS, it is plausible that more Trp is metabolized to 5HT than is degraded within the Kyn pathway.

In summary, the clinical relevance of the present findings for persons with MS needs to be elucidated in further investigation. On the one hand, animal models may provide new information of direct effects of exercise-induced changes in Trp metabolism on the central nervous system. One may suggest that a systemic and central decrease in Kyn and its metabolites is beneficial in this context due to its reduction of potential neurotoxic agents (Quinolinic acid, Kyn acid). On the other hand, exercise-induced alterations in Trp metabolism and especially increased Kyn levels could lead to adaptions of the immune system (e.g. increase in regulatory T-cells) which are highly relevant to counteract chronic inflammation and an immune over-activation (as they appear in MS).

Following research in this field should also include other MS subtypes, other promising exercise paradigms (e.g. resistance exercise) and a wider range of Trp metabolites and enzymes such as Kyn-, quinolinic acid and KAT. Additional follow-up measurement time points after acute exercise and exercise interventions will provide important information on the kinetics of Trp and its metabolites. Finally, a major challenge for following research investigating the impact of exercise on Trp metabolism in humans will be to distinguish between tissue specific and systemic alterations.

In conclusion, this study is the first to demonstrate the different responses of Trp metabolism to acute and chronic exercise stimuli in persons with RRMS and SPMS. Future research is warranted to investigate if the described alterations influence targets of Trp metabolites, such as immune function, depressions and cognitive performance in persons with MS.

**Conflict of interest**

None

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Table 1: Study participants` baseline (t0) characteristics and response of Trp metabolites to acute (t0 vs. t1) and chronic exercise (t0 vs.t2)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **A) Baseline characteristics and acute effects of exercise on Trp metabolites separated by MS subtype** | | | | | | | | |
|  | **t0** | | | | **t1** | | | |
| SPMS  n=24 | | RRMS  n=33 | | SPMS  n=24 | | RRMS  n=33 | |
| **Sex (female/male)** | 15/9 | | 23/10 | |  | |  | |
| **Age (years)** | 48.42 (11.35) | | 50.79 (10.93) | |  | |  | |
| **BMI (kg/m2)** | 23.28 (0.04) | | 23.08 (0.04) | |  | |  | |
| **EDSS** | 4.042 (1.19) | | 4.60 (1.13) | |  | |  | |
| **VO2 peak (ml/min/kg)** | 21.31 (6.34) | | 18.18 (5.42) | |  | |  | |
| **5HT (μg/l)** | 121.73 (18.5) | | 117.3 (14.3) | | 166.26 (23.7) | | 145.11 (19.8) | |
| **Trp (μmol/l)A, B** | 90.43 (5.1) | | 112.6 (5.1) | | 96.37 (5.4) | | 100.9 (3.8) | |
| **Kyn (μmol/l)B** | 2.12 (0.1) | | 2.3 (0.1) | | 2.23 (0.1) | | 2.35 (0.1) | |
| **Kyn/Trp ratioB, C** | .02477 (.007) | | .02176 (.007) | | .02425 (.006) | | .02399 (.006) | |
| **B) Chronic effects of exercise on Trp metabolites, separated by MS subtype and training intervention** | | | | | | | | |
|  | **t0** | | | | **t2** | | | |
| SPMS | | RRMS | | SPMS | | RRMS | |
| **Intervention** | HIT  n=11 | CT  n=13 | HIT  n=16 | CT  n=17 | HIT  n=11 | CT  n=13 | HIT  n=16 | CT  n=17 |
| **5HT (μg/l)B** | 107.17 (18.9) | 135.08  (31.4) | 104.06  (23.3) | 130.58  (17) | 122.76  (20.8) | 164.22  (39.7) | 131.71  (22.8) | 131.11  (23.7) |
| **Trp (μmol/l)B** | 86.47 (9.6) | 94.06  (4.6) | 110.3  (7.01) | 114.7  (7.6) | 94.36  (10.8) | 91.36  (4.2) | 101.4  (5.6) | 103.7  (6.1) |
| **Kyn (μmol/l)** | 2.004 (0.14) | 2.23  (0.13) | 2.31 (0.109) | 2.30  (0.17) | 2.07  (0.14) | 2.28  (0.12) | 2.36  (0.14) | 2.33  (0.17) |
| **Kyn/Trp ratioB, C** | 0.024 (0.002) | 0.025  (0.002) | 0.02  (0.001) | 0.021  (0.002) | 0.02 (0.002) | 0.02  (0.002) | 0.023  (0.001) | 0.024  (0.002) |

BMI: Body Mass Index, EDSS: Expanded Disability Status Scale, VO2 peak: endurance capacity, 5HT: Serotonin, Trp: Tryptophan, Kyn: Kynurenine.

A) Baseline differences in participants’ characteristics and outcome measures between persons with secondary progressive and relapsing remitting multiple sclerosis (SPMS, RRMS) were determined by independent t-tests or Fischer's exact tests. Patients’ characteristics are presented as means (standard deviation) and longitudinal data are presented as means (standard error of the mean). Significant baseline differences are marked by A. Responses of Trp metabolites to acute exercise were determined by 2 (SPMS vs. RRMS) x 2 (t0 vs. t1) ANCOVA, adjusted for baseline levels. Significant time effects are marked by B. Significant group x time interactions are marked by C.

B) Chronic effects of the different exercise programs, as well as the influence of MS subtype on blood markers were determined using 2 (t0 vs. t1) x 2 (HIT vs. CT) x 2 (RRMS vs. SPMS) ANCOVA, adjusted for baseline measures. Significant time effects are marked by B. Significant group x time interactions are marked by C. All statistical analysis (SPSS25, IBM) were conducted two tailed and alpha was set at .05.

Figure Legends

Figure 1: Post-hoc analysis of acute and chronic effects of exercise on Trp metabolites

5HT: Serotonin, Trp: Tryptophan, Kyn: Kynurenine. Graphs represent the baseline adjusted acute and chronic response of Trp metabolites to exercise, depending on subtype of disease and training intervention. Post-hoc simple effects analysis (SEA) was only conducted if ANCOVA (table 1) revealed significant main effects or interaction. Significant results of SEA are marked by \*. Data are presented as means (standard error of the mean). A)-D) Acute effects of exercise on Trp metabolites depending on subtype of disease (relapsing remitting multiple sclerosis (RRMS) vs. secondary progressive MS (SPMS)). E)-H) Chronic effects of exercise depending on subtype of disease and training modality (HIT vs. CT).

1. Trp: Tryptophan [↑](#footnote-ref-1)
2. MS: Multiple Sclerosis [↑](#footnote-ref-2)
3. 5HT: Serotonin [↑](#footnote-ref-3)
4. Kyn: Kynurenine [↑](#footnote-ref-4)
5. TDO: Tryptophan 2,3-dioxygenase [↑](#footnote-ref-5)
6. IDO: Indoleamine 2,3-dioxygenase [↑](#footnote-ref-6)
7. KAT: Kynurenine-aminotransferase

   8 SPMS: secondary progressive multiple sclerosis

   9 RRMS: relapsing remitting multiple sclerosis

   10 HIT: High Intensity Training

   11 CT: Control Training

   12 SEA: Simple Effects Analysis [↑](#footnote-ref-7)