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Stochastic Resonance Activity Influences Serum Tryptophan Metabolism in Healthy Human Subjects

Berthold Kepplinger¹⁻³, Halina Baran¹, Brenda Sednitzky-Semler¹, Nagy-Roland Badawi² and Helene Erhart²

¹Neurochemical Laboratory, Karl Landsteiner Research Institute for Pain Treatment and Neurorehabilitation, Landesklinikum Mauer, Mauer-Amstetten. ²Department of Neurology, Neuropsychiatric Hospital, Landesklinikum Mauer, Mauer-Amstetten. ³Department of Neurology, General Hospital, Landesklinikum Amstetten, Amstetten, Austria. Corresponding author email: halina.baran@mauer.lknoe.at

Abstract

Background: Stochastic resonance therapy (SRT) is used for rehabilitation of patients with various neuropsychiatric diseases. An alteration in tryptophan metabolism along the kynurenine pathway has been identified in the central and peripheral nervous systems in patients with neuroinflammatory and neurodegenerative diseases and during the aging process. This study investigated the effect of SRT as an exercise activity on serum tryptophan metabolites in healthy subjects.

Methods: Serum L-tryptophan, L-kynurenine, kynurenic acid, and anthranilic acid levels were measured one minute before SRT and at one, 5, 15, 30, and 60 minutes after SRT. We found that SRT affected tryptophan metabolism. Serum levels of L-tryptophan, L-kynurenine, and kynurenic acid were significantly reduced for up to 60 minutes after SRT. Anthranilic acid levels were characterized by a moderate, non significant transient decrease for up to 15 minutes, followed by normalization at 60 minutes. Tryptophan metabolite ratios were moderately altered, suggesting activation of metabolism after SRT. Lowering of tryptophan would generally involve activation of tryptophan catabolism and neurotransmitter, protein, and bone biosynthesis. Lowering of kynurenic acid by SRT might be relevant for improving symptoms in patients with neuropsychiatric disorders, such as Parkinson's disease, Alzheimer's disease, schizophrenia, and depression, as well as certain pain conditions.

Keywords: stochastic resonance therapy, exercise, serum, tryptophan, L-kynurenine, kynurenic acid, Parkinson's disease, dementia

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Introduction

A phenomenon called stochastic resonance, in which vibration increases the response of a nonlinear system to a weak signal, may influence molecular biological machinery and physiological responses. The first report on the mechanism of stochastic resonance was published by Benzi et al,¹ and its significance was used as a theoretical explanation for the periodic recurrences of Earth's ice ages.^{2,3} Interestingly, in biology, stochastic resonance has been demonstrated experimentally in various sensorineural systems, including the crayfish,⁴ shark,⁵ cricket,⁶ and also in humans.^{7,8} Collins et al⁷ showed that the tactile sensation of the human fingertip can be enhanced by mechanical vibration, and the findings reported by Collins et al⁸ suggest that mechanoreceptors can be influenced by stochastic resonance. Tanaka et al⁹ have shown that low-amplitude, broad-frequency vibration increases the expression of osteocalcin mRNA, and suggested that stochastic resonance might enhance mechanosensation in bone tissue. In an *in vivo* animal study, Tanaka et al¹⁰ showed that low-amplitude, broad-frequency vibration combined with simulated exercise enhanced new bone formation, and suggested a potential role of exercise in elderly people as well as after injury to build up bone mass and help prevent osteoporosis. Generally, walking and running might influence the elementary functions of the central nervous system. In an animal experiment, a strong positive correlation was found between running distance and release of brain-derived neurotrophic factor,¹¹ running distance and increased release of nerve growth factor,¹² and running exercise and increasing cell proliferation and neurogenesis in the hippocampal area.¹³ Kepplinger et al¹⁴ showed that treadmill running significantly lowered serum kynurenic acid levels in the rat, while Alaei et al¹⁵ demonstrated that treadmill running enhanced mid-term memory. In this regard it is important to note that kynurenic acid may interfere with working memory,¹⁶ and enhancement of endogenous kynurenic acid levels may induce spatial memory deficits.¹⁷

Central and peripheral tissues are actively involved in tryptophan metabolism, including in synthesis of serotonin, and along the kynurenine pathway, where it can form several neuroactive compounds.^{18,19} One of them, kynurenic acid, is a well known endogenous antagonist of glutamate ionotropic excitatory amino

acid receptors,^{20,21} and a nicotine cholinergic subtype alpha-7 receptor^{22,23} is altered significantly in patients with various neuropsychiatric and immunological disorders and in the aging process.²⁴⁻²⁸ Notably, enhancement of kynurenic acid in the central nervous system has been suggested to contribute to impairment of memory and cognition.^{29,30} Furthermore, we have suggested that rehabilitation strategies leading to kynurenic acid reduction might have a therapeutic role,³¹ at least in conditions involving elevation of kynurenic acid.

The aim of this study was to determine if SRT can affect tryptophan metabolism in the human body. L-tryptophan, L-kynurenine, kynurenic acid, and anthranilic acid levels were measured in the serum of healthy subjects one minute before and one, 15, 30, and 60 minutes after SRT. Some of the data from this study have already been published in abstract form.³²

Materials and Methods

Chemicals

L-tryptophan, L-kynurenine, kynurenic acid, anthranilic acid, 3-OH-kynurenine, and 3-OH-anthranilic acid was purchased from Sigma (St. Louis, MO). All other chemicals used were of the highest commercially available purity.

Subjects

Ten non-smoking volunteers, comprising two men and eight women, aged 33.2 ± 4.1 years, participated in this study. SRT was applied in all cases between 11 am and noon. All subjects had breakfast as usual before 7.30 am. In order to minimize stress, all subjects underwent insertion of a mini cannula (butterfly needle) before SRT. Blood was taken one minute before SRT and at one, 5, 15, 30 and 60 minutes after SRT. The serum obtained was subjected to centrifugation for five minutes at 3000 rpm, and was stored at -40 °C until analysis. Blood samples were also taken from a further three subjects who did not receive SRT, in order to demonstrate a lack of effect on tryptophan metabolites due to blood collection. Samples of serum were coded and the study was carried out according to lower Austrian ethical regulations.

Methods

The SRT-Medical Zeptoring™ system (GmbH and Co Lifescience, KG Berlin, Germany), a training and

medical therapy device with stochastic vibration up to 12 levels was used. Volunteers were exposed to five two-minute exercise periods at the level of 10 on the SRT-Medical Zeptoring system, with a 30-second interval between each 2-minute exercise period.

Measurement of tryptophan and tryptophan metabolites

Briefly, 200 μL samples of serum were mixed with 14 μL of 50% trichloroacetic acid and 0.2 M HCl (v/v), and centrifuged for 20 minutes at 14,000 rpm. The supernatant obtained was divided and immediately used for measurement of tryptophan and tryptophan metabolites, and for purification of kynurenic acid followed by determination.

Tryptophan, L-kynurenine, 3-OH-kynurenine, anthranilic acid, and 3-OH-anthranilic acid were measured by isocratic high-performance liquid chromatography (HPLC) with fluorescence and ultraviolet detection as described by Baran et al, with some modifications.³¹ Briefly, the HPLC system consisted of a Merck Hitachi LaChrom Pump L-7100, autosampler L-7200, fluorescence detector L7485, ultraviolet detector L-7400, and a Merck Hitachi D-7500 integrator. The HPLC method utilized a mobile phase of 42 mM ammonium acetate, 7 mM sodium hydrogen phosphate, 7 mM sodium acetate, 11 mM ammonium hydroxide, 59 mM acetic acid, 1.380 mM 1-octanesulfonic acid, and 74 μM sodium disulfide (pH 4.8) pumped through a Chromolith™ Performance RP-18e, 100-4, 6 mm column (Merck KGaA, Darmstadt, Germany) at a flow rate of 0.7 mL/minutes. The injection volume was 50 μL . The fluorescence detector was set at an excitation wavelength of 299 nm and an emission wavelength of 420 nm. The retention time of 3-OH-anthranilic acid, anthranilic acid, and tryptophan was approximately 7.4, 15.6, and 17.7 minutes, respectively, with a sensitivity of 80, 800 and 150 fmol per injection, respectively (signal:noise ratio 5). Using the same HPLC conditions and an ultraviolet detector set at a 366 nm wavelength, 3-OH-kynurenine and L-kynurenine were eluted, with a retention time of 4.3 and 7.7 minutes and a sensitivity of 700 and 500 fmol per injection, respectively (signal:noise ratio 5).

Measurement of kynurenic acid was performed according to the method described by Swartz et al,³³ with modifications as described by Baran et al.³⁰

Briefly, the serum samples were mixed with 0.2 M HCl (v/v) and centrifuged for 20 minutes at 14,000 rpm. The supernatant obtained was applied to a Dowex 50 W cation exchange column prewashed with 0.1 M HCl. The column was then washed with 1 mL 0.1 M HCl and 1 mL distilled water, and kynurenic acid was eluted with 2 mL distilled water³⁴ and quantitated using an HPLC system coupled with fluorescence detection. The recovery of kynurenic acid extraction was approximately 40% and was taken into consideration in the data processing.

Data analysis

All data are presented as the mean \pm standard error of the mean. For statistical analyses, one-way analysis of variance and a Student's *t*-test were applied. Each sample was determined in duplicate or triplicate. **P* < 0.05, ***P* < 0.01, and ****P* < 0.001 indicate a significant difference compared with baseline (15 minutes before administration of SRT).

Results

Serum tryptophan metabolites in controls

Control data for the serum tryptophan metabolites were comparable with those from other human studies.⁵⁰ Determination of tryptophan metabolites in the serum of human control subjects (*n* = 10) revealed the following concentrations: L-tryptophan 74,682.0 \pm 4581.0 fmol/ μL , L-kynurenine 3331.90 \pm 240.93 fmol/ μL , kynurenic acid 75.49 \pm 4.95 fmol/ μL , and anthranilic acid 30.74 \pm 3.41 fmol/ μL . 3-OH-kynurenine and 3-OH-anthranilic acid were not detectable in serum in this study. In subjects who were not exposed to SRT, no differences in tryptophan metabolite levels were seen during the different periods after blood collection. After SRT, all control subjects reported feeling well during and at two hours following exercise.

Influence of SRT on tryptophan metabolites

Application of SRT significantly affected tryptophan metabolism in serum. We found moderately lowered L-tryptophan levels at one minute after SRT; this reduction progressed significantly and was present at one hour after SRT (13%; *P* < 0.01, Fig. 1). Significant differences in serum L-tryptophan

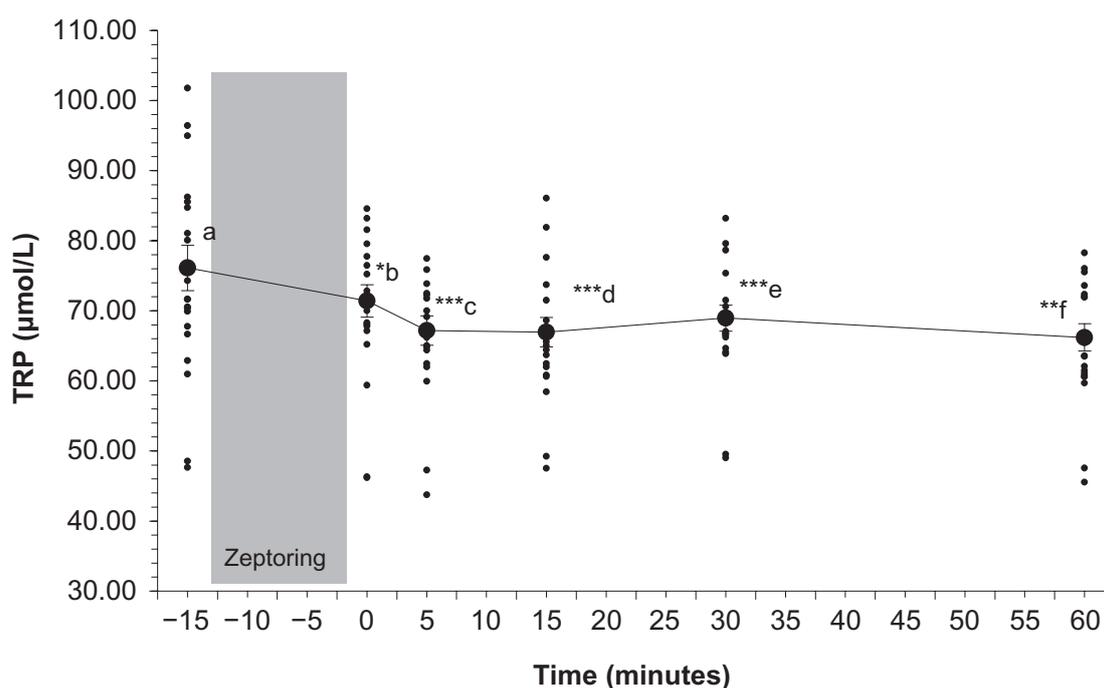


Figure 1. Serum L-tryptophan levels at various time points after stochastic resonance therapy.

Notes: Data represent the mean \pm standard error of the mean of 20 independent measurements. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with time before stochastic resonance therapy. a,b; b,c; b,d; d,e; and e,f indicate statistical significance at $P < 0.05$. a,d and c,e indicate statistical significance at $P < 0.01$. a,c; a,d; a,e; and b,f indicate statistical significance at $P < 0.001$. Analysis of variance: $F = 2.4646$; $P = 0.0369$.

Abbreviation: TRP, L-tryptophan.

levels after SRT for the different time points were demonstrated ($F = 2.4646$, $P = 0.0367$, one-way analysis of variance, Fig. 1).

L-kynurenine levels were moderately lower 5 minutes after SRT, and this effect lasted until one hour after SRT (11%, $P < 0.01$, Fig. 2). No changes in serum L-kynurenine levels could be shown after SRT for the different time points ($F = 0.7739$, $P = 0.5706$, one-way analysis of variance, Fig. 2).

Anthranilic acid levels were moderately decreased at 5 and 15 minutes after SRT, and were normalized at one hour (Fig. 3). No differences in serum anthranilic acid levels were detected at the different time points after SRT ($F = 0.6033$, $P = 0.6975$, one-way analysis of variance, Fig. 3).

Kynurenic acid levels decreased at 5 minutes after SRT, and this reduction was still seen at one hour after SRT (20%, $P < 0.001$, Fig. 4). Differences in serum kynurenic acid levels after SRT for the different time points were demonstrated ($F = 2.1910$, $P = 0.0601$, one-way analysis of variance, Fig. 4).

The ratio of L-kynurenine to tryptophan did not change significantly at any of the time points after SRT for up to one hour ($F = 0.2906$, $P = 0.9173$,

one-way analysis of variance, Fig. 5). The ratio of anthranilic acid to L-kynurenine was moderately increased at 30 minutes and showed a tendency to increase at 60 minutes (about 23%, $P < 0.05$) after SRT (Fig. 6). No change in the anthranilic acid:L-kynurenine ratio was found at the different time points after SRT ($F = 0.5689$, $P = 0.7237$, one-way analysis of variance, Fig. 6). The ratio of kynurenic acid to L-kynurenine showed a sinusoidal but not significant pattern of change up to 60 minutes after SRT (Fig. 7). No change in the ratio of kynurenic acid to L-kynurenine was found at any of the time points after SRT ($F = 0.5857$, $P = 0.7176$, one-way analysis of variance, Fig. 7). The ratio of kynurenic acid to anthranilic acid showed a moderate increase at 15 minutes and a decrease at 30 and 60 minutes (about 39% versus 15 minutes, $P < 0.05$, Fig. 8), but no change in the ratio of kynurenic acid to anthranilic acid was seen at any time point after SRT ($F = 1.0341$, $P = 0.4012$, one-way analysis of variance, Fig. 8).

Discussion

SRT is used in the treatment and rehabilitation of patients with various neurological and

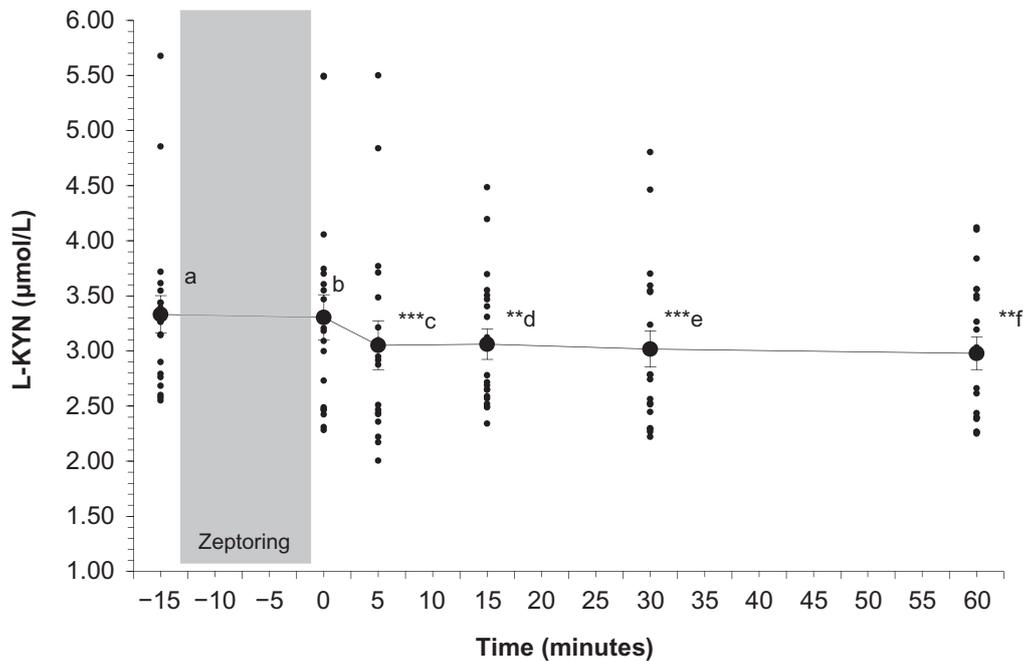


Figure 2. Serum L-kynurenine levels at various time points after stochastic resonance therapy.

Notes: Data represent the mean \pm standard error of the mean of 20 independent measurements. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with time before stochastic resonance therapy. b,d; b,e; and b,f indicate statistical significance at $P < 0.05$. a,d; a,f; and b,c indicate statistical significance at $P < 0.01$. a,c and a,e indicate statistical significance at $P < 0.001$. By analysis of variance, $F = 0.7739$; $P = 0.5706$.

Abbreviation: L-KYN, L-kynurenine.

psychiatric disorders, eg, Parkinson's disease,³⁵⁻³⁹ multiple sclerosis,⁴⁰ Alzheimer's disease,^{41,42} stroke,⁴³ depression and schizophrenia,^{44,45} and also for the treatment of low back pain and as prophylaxis against osteoporosis.^{46,47} The effectiveness of SRT as an

additive treatment for these diseases is significant, but the mechanism(s) of action involves many biochemical events and further elaboration is necessary. It is known that body vibration modifies a wide spectrum of bioprocesses, eg, activation of brain neurotrophic

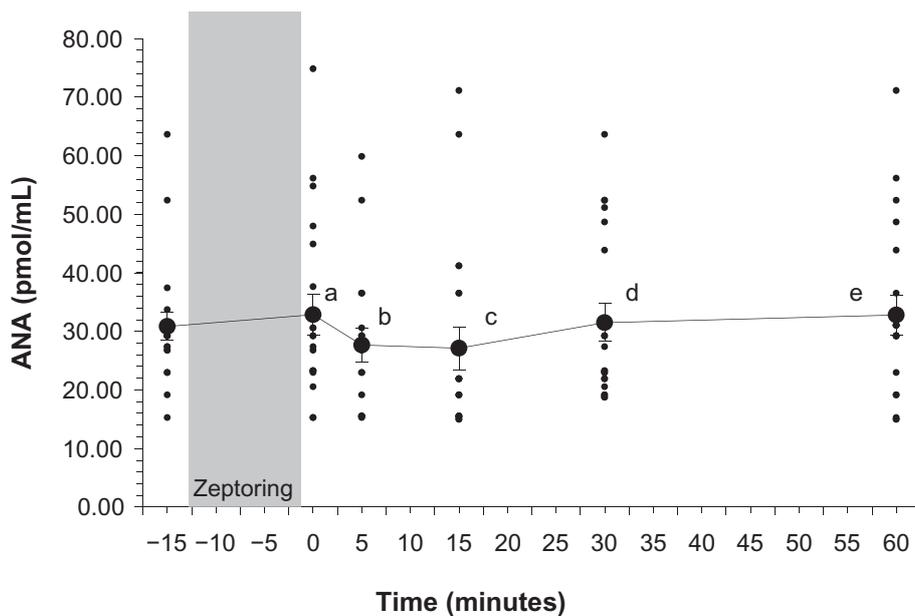


Figure 3. Serum anthranilic acid levels at various time points after stochastic resonance therapy.

Notes: Data shown are the mean \pm standard error of the mean of 20 independent experiments. a, b indicates statistical significance at $P < 0.05$. c,d indicates statistical significance at $P < 0.01$. a,c and c,e indicate statistical significance at $P < 0.001$. By analysis of variance, $F = 0.6033$; $P = 0.6975$.

Abbreviation: ANA, anthranilic acid.

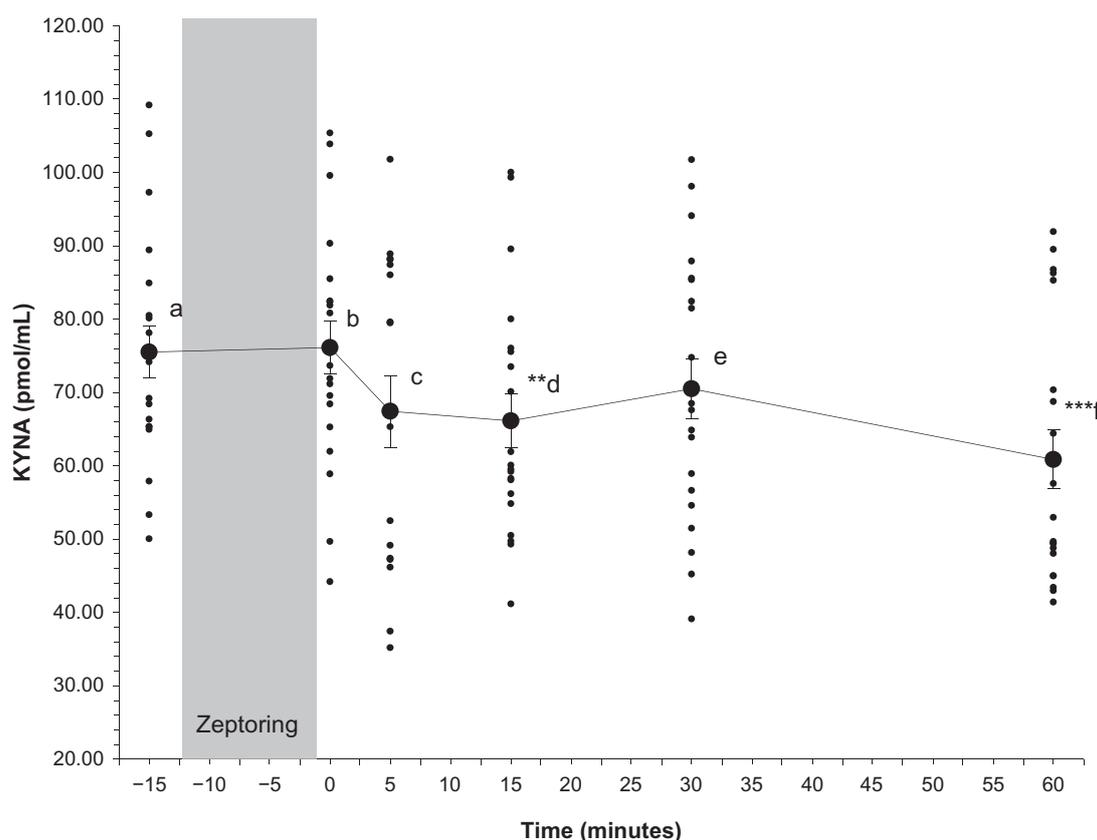


Figure 4. Serum kynurenic acid levels at various time points after stochastic resonance therapy.

Notes: Data represent the mean \pm standard error of the mean of 20 independent measurements. * $P < 0.05$; ** $P < 0.01$ compared with time before stochastic resonance therapy. c,f and e,f indicate statistical significance at $P < 0.05$. a,d; b,c; and b,d indicate statistical significance at $P < 0.01$. a,f and b,f indicate statistical significance at $P < 0.001$. By one-way analysis of variance, $F = 2.1912$; $P = 0.0601$.

Abbreviation: KYNA, kynurenic acid.

factors, induction of neurotransmitter and hormone synthesis and release, stabilization of skeletal and muscle activity, and strengthening and recovery of balance and posture.^{9–13}

The present study demonstrates for the first time that SRT influences tryptophan metabolism in healthy human subjects via a moderate but significant lowering of serum L-tryptophan, L-kynurenine, and kynurenic acid levels. Subjects reported increased stability as well as ease in taking steps in the hours following SRT. The effect on tryptophan metabolites was time-dependent, and the reduction was still measurable at 60 minutes after SRT, indicating a long-lasting effect. The changes in L-tryptophan metabolism would suggest increased incorporation of amino acids into ongoing protein synthesis and bone formation, since availability of L-tryptophan during bone growth is indispensable.⁴⁸ Enhancement of new bone formation due to exercise has been reported in an animal experiment.⁴⁹ Lowered serum L-tryptophan levels have

also been reported in rats exposed to exercise.⁵⁰ Given that L-tryptophan crosses the blood-brain barrier in significant amounts, changes in serum levels might also involve nicotinamide adenine dinucleotide and/or serotonin synthesis, not only in the periphery, but also in the central nervous system.⁵¹ The well-being reported by subjects after SRT would suggest an anti-depressant action.^{39,40,56}

The moderate reduction of L-kynurenine induced by SRT was accompanied by lower levels of L-kynurenine metabolites, anthranilic acid, and kynurenic acid. Whereas the reduction of kynurenic acid was progressive through to one hour after SRT, anthranilic acid levels were normalized. Interestingly, treadmill running has been shown to decrease serum kynurenic acid levels in rats.¹⁴

The ratio of L-kynurenine to L-tryptophan and moreover the ratios of anthranilic acid to L-kynurenine and kynurenic acid to L-kynurenine were moderately altered after SRT, suggesting activation of tryptophan

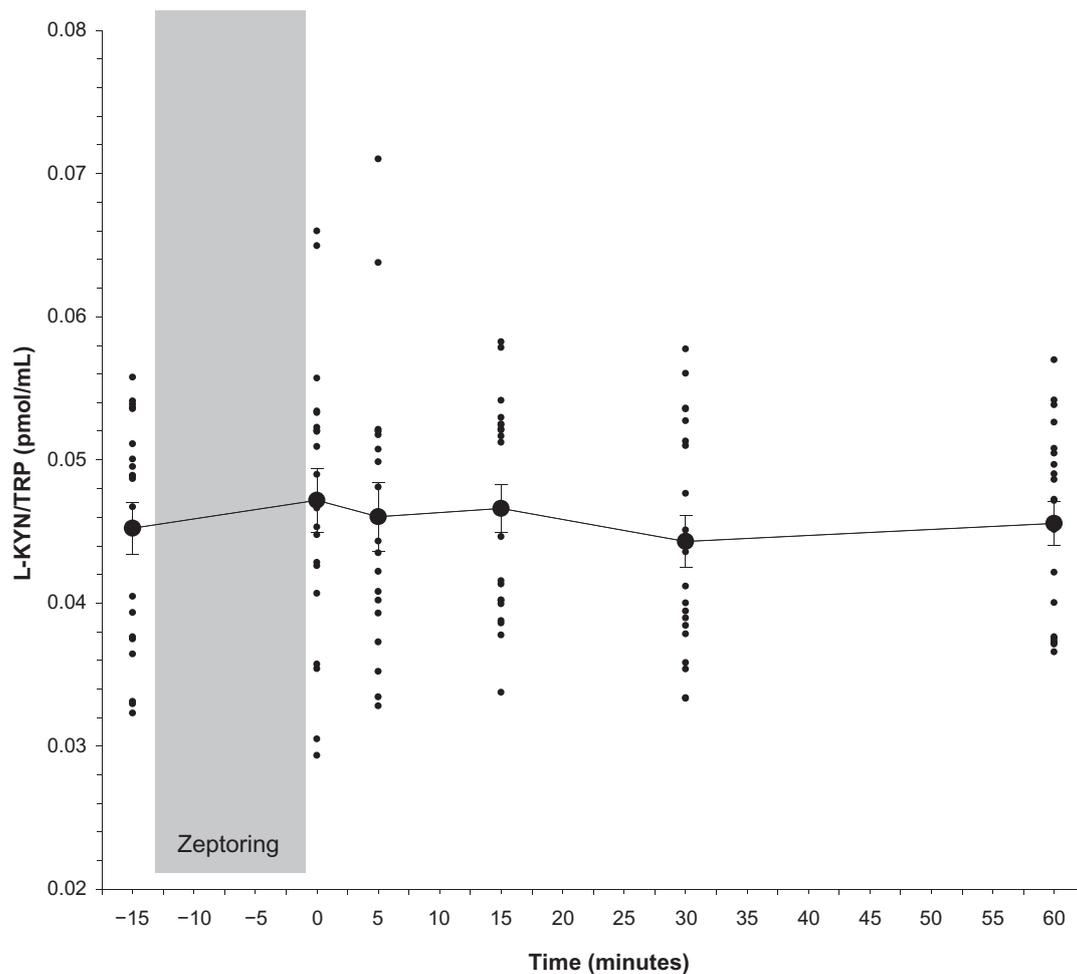


Figure 5. Serum L-kynurenine to L-tryptophan ratio at various time points after stochastic resonance therapy.

Notes: The data represent the mean \pm standard error of the mean of 20 independent measurements. By one-way analysis of variance, $F = 0.2906$; $P = 0.9173$.

Abbreviation: L-KYN/TRP, ratio of L-kynurenine to L-tryptophan.

metabolism after exercise. It is questionable whether moderately activated kynurenine metabolism influences the activity of the neuronal network and therefore has a detectable therapeutic impact. Interestingly, the first indication of the therapeutic effect of exercise was provided in 1880 by Jean-Martin Charcot who described using a shaking chair in patients with Parkinson's disease, which led to improvement of symptoms, in particular tremor and instability.⁵² A marked deficit of dopaminergic neurotransmission and its significance for Parkinson's symptoms was described by Hornykiewicz.⁵³ Interestingly, running activity in an animal model of Parkinson's disease led to improvement of motor symptoms and less degeneration of the dopaminergic system,⁵⁴⁻⁵⁷ suggesting a protective effect of movement on dopaminergic neurons. Furthermore, in an animal study, it

was shown that dopamine synthesis and metabolism in the striatum increased significantly in rats exposed to exercise, and the investigators suggested that physical exercise might contribute to adjustment of extracellular dopamine to within an adequate range.⁵⁷ Further, the therapeutic potential of vibration in patients with Parkinson's disease has been confirmed by many investigators.^{35-37,58} There are also human data showing that exercise transiently increases plasma dopamine levels in healthy stressed subjects.⁵⁹⁻⁶¹ Our present findings make it reasonable to question if SRT-induced lowering of tryptophan levels and the accompanying reduction of plasma kynurenic acid levels might also involve enhancement of plasma dopamine levels,⁵⁹⁻⁶¹ which could be important for restoration of normal biochemical events and have a therapeutic effect, not only in the periphery, but

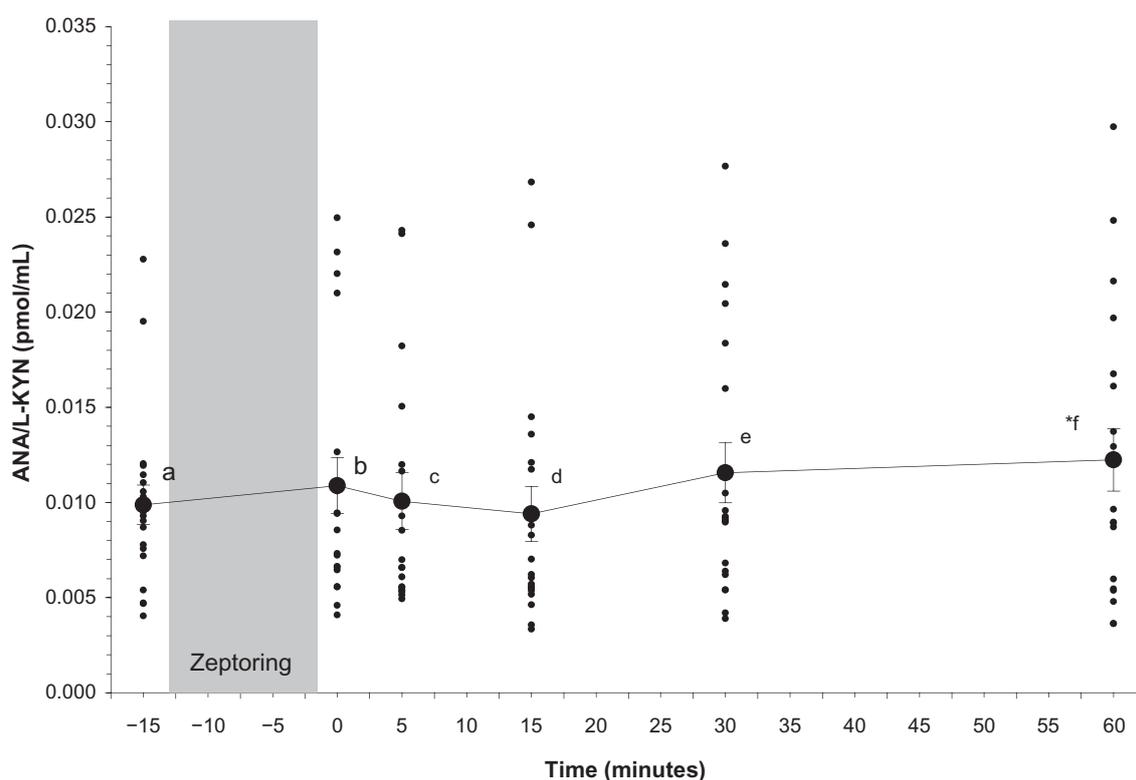


Figure 6. Serum anthranilic acid/L-kynurenine ratio at various time points after stochastic resonance therapy. **Notes:** The data represent the mean \pm standard error of the mean of 20 independent measurements. * $P < 0.05$ compared with time before stochastic resonance therapy. a,f; b,d; and c,d: indicates statistical significance at $P < 0.05$. d,e indicates statistical significance at $P < 0.01$. d,f indicates statistical significance at $P < 0.001$. By one-way analysis of variance, $F = 0.5689$; $P = 0.7237$. **Abbreviation:** ANA/L-KYN, anthranilic acid/L-kynurenine.

likely also in the central nervous system. Endogenous kynurenic acid has been shown to control extracellular levels of dopamine in the rat striatum in an in vivo study.⁶² Furthermore, the significance of a tryptophan diet and the interaction between increased kynurenic acid and lower dopamine levels in the striatum has been demonstrated recently.⁶³

There are also human data demonstrating discrepancies with respect to neurochemical changes after exercise, and that whole body vibration leads to a moderate increase in cortical dopamine as well as a lowering in the striatum and an increase of tryptophan in serum after exercise.⁶⁴ These discrepancies are probably due to the use of different kinds of exercise (running versus sinusoidal vibration versus stochastic vibration), different parameters (frequency, amplitude, time), and vibrational characteristics (whole body versus local), and are a reason to study further the value of exercise in therapeutic management.

The marked deficit of dopaminergic neurotransmission in Parkinson's disease⁵³ is partially addressed by levodopa therapy.⁶⁵ Interestingly, a comparison

between levodopa treatment and physical exercise in patients with spinal cord injury revealed a similar positive effect for both types of treatment,⁶⁶ indicating enhanced dopamine function during exercise. Consistent with this research, use of exercise in patients with Parkinson's disease significantly increased the therapeutic efficacy of levodopa.⁶⁷ Although the improvement in Parkinsonian symptoms after SRT is transient, the positive effect would nevertheless confirm an advantage of SRT and suggests that it has therapeutic value in the rehabilitation process. Importantly, the combination of levodopa therapy and SRT might enable a decrease in the levodopa dose, thereby reducing the side effect of dyskinesia.

Increased dopamine levels in rat and human plasma due to physical exercise have also been described by Yoshizumi et al,⁶⁸ who suggested that the dopamine increase is not only due to increased release from the sympathoadrenal system, but also to accelerated conversion of sulfoconjugated catecholamines in plasma. The activity of phenol sulfotransferase, an enzyme which conjugates dopamine,

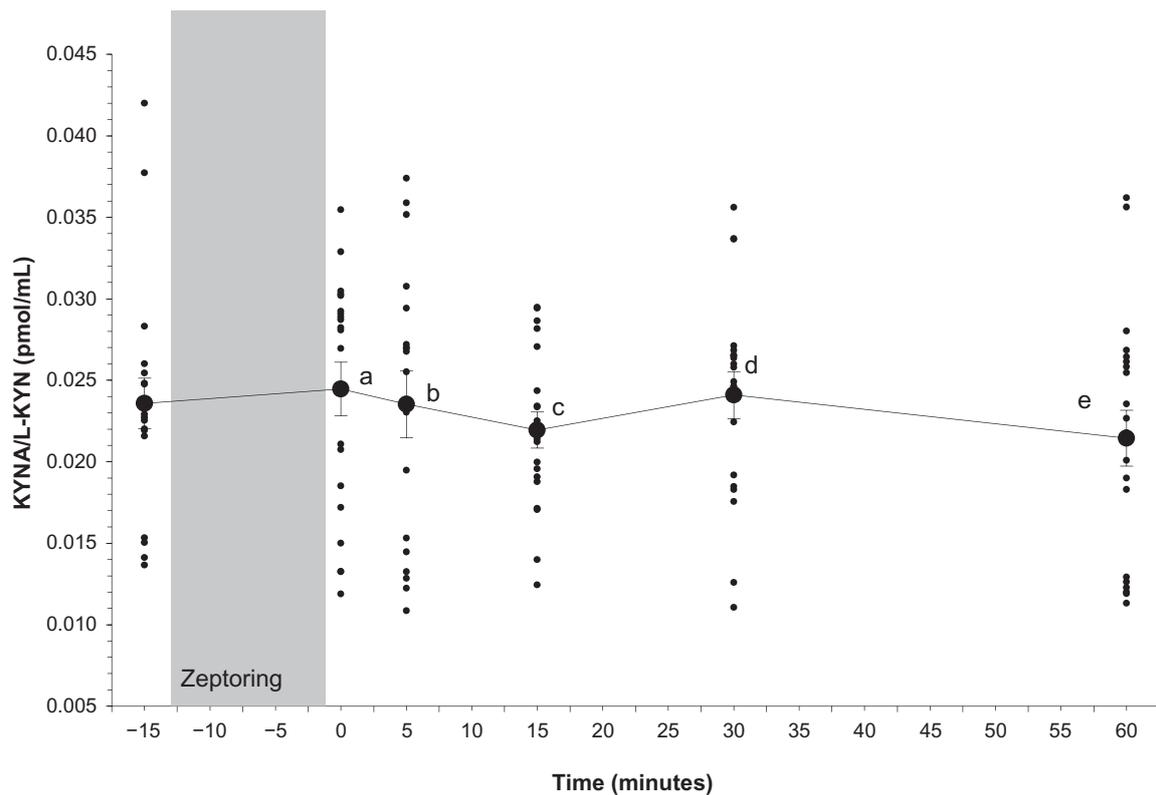


Figure 7. Serum kynurenic acid/L-kynurenine ratio at various time points after stochastic resonance therapy. **Notes:** Data represent the mean \pm standard error of the mean of 20 independent measurements. b,e and d,e indicate statistical significance at $P < 0.05$. a,e indicates statistical significance at $P < 0.01$. By one-way analysis of variance, $F = 0.5859$; $P = 0.7108$. **Abbreviation:** KYNA/L-KYN, kynurenic acid/L-kynurenine ratio.

varies widely among different species and within various organs, but shows highest activity in the rat liver.⁶⁹ In the normal aged human brain, the highest activity of phenol sulfotransferase was reported in the cortical regions and limbic structures, while the lowest was found in the basal ganglia regions.⁷⁰ Interestingly, in Parkinson's disease, a marked increase in phenol sulfotransferase activity has been seen in the caudate nucleus, whereas in other brain regions, particularly in the hypothalamus and cortical brain regions, it was reduced.⁷⁰ Given that conjugated dopamine is decreased after exercise while free dopamine is increased,⁶⁸ it is unclear whether the therapeutic effect of exercise and SRT in Parkinson's patients is also in part due to deconjugation of sulfoconjugated dopamine in the caudate nucleus. The kynurenine aminotransferases responsible for kynurenic acid synthesis are widely distributed throughout the mammalian body, particularly in the liver.¹⁹⁻²¹ Increased kynurenine aminotransferase activity in the striatum has been found in patients with Alzheimer's disease and in those with Parkinson's disease.³⁰ Interestingly,

kynurenic acid has an inhibitory effect on several human recombinant sulfotransferases.⁷¹ The effect is very moderate, with the IC_{50} for kynurenic acid being in the micromolar range in experimental conditions, and the physiological mechanisms for this are not as yet clear.

The decrease in kynurenic acid levels after SRT might involve activation of glia-depressing factor, recently proposed by Baran et al.⁷² Glia-depressing factor has the ability to block kynurenine aminotransferase and probably simultaneously blocks glial activity, thereby exerting a direct or indirect neurotrophic effect. In multiple sclerosis, glia-depressing factor is reduced⁷² while kynurenic acid is increased,⁷³ and use of SRT in patients with multiple sclerosis improved their clinical status significantly.⁴⁰ Amelioration of some pain conditions has also been reported after use of SRT.^{46,47}

Summary

SRT offers a new opportunity to influence tryptophan metabolism along the kynurenine pathway. Our data

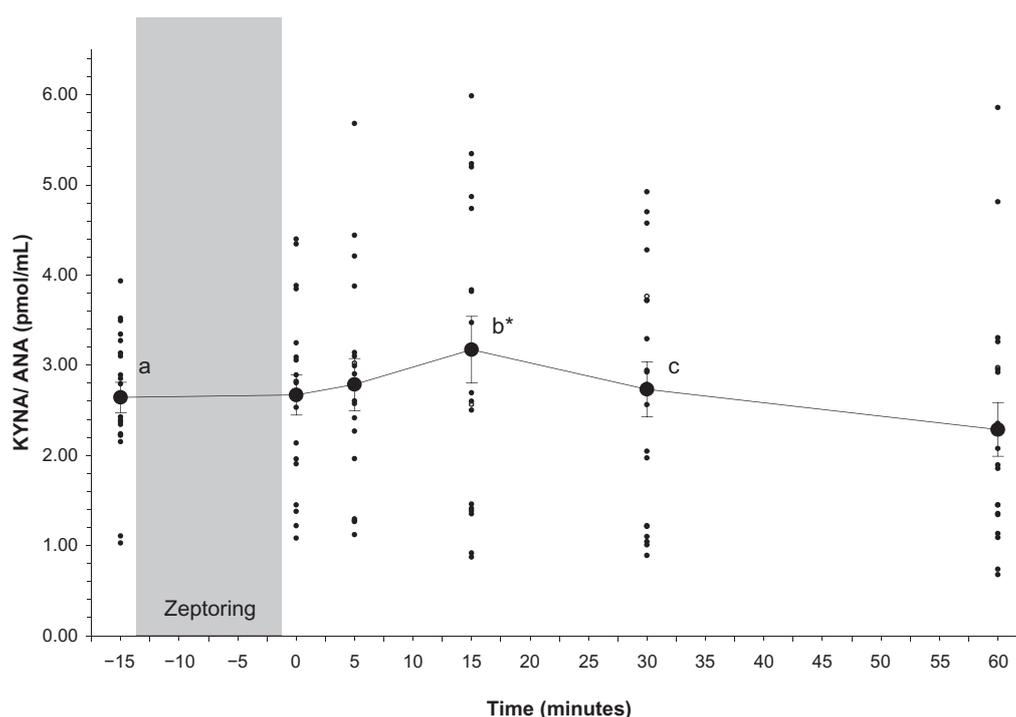


Figure 8. Serum kynurenic acid/anthranilic acid ratio at various time points after stochastic resonance therapy.

Notes: Data represent the mean \pm standard error of the mean of 20 independent measurements. * $P < 0.05$ compared with time before stochastic resonance therapy. a, b; b, c; and c, d indicate statistical significance at $P < 0.05$. b, d indicates statistical significance at $P < 0.01$. By one-way analysis of variance, $F = 1.0341$; $P = 0.4012$.

Abbreviation: KYNA/ANA, kynurenic acid/anthranilic acid ratio.

add to the body of evidence showing the importance of SRT, and indicate that exercise is a useful method for balancing biochemical and physiological processes in the body. Furthermore, SRT can be very useful in the repair of biochemical processes in pathological conditions, including motor impairment, dementia, and chronic low back pain, as well as improving well-being. In the near future, it would be necessary to identify the duration of efficiency of SRT in respect to changes in tryptophan metabolism and, furthermore, to confirm the proposed mechanism(s) of interaction between kynurenic acid and the dopaminergic system in patients with disease and in healthy control subjects.

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Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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