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Influence of exercise on serotonergic neuromodulation in the brain

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Summary. Implications of exercise on serotonergic neuromodulation in the brain have been investigated in two studies. Acute paroxetine (selective serotonin (5-HT) reuptake inhibitor) administration to endurance athletes, who performed a cycle ergometer test to exhaustion at moderate intensity, reduced time to exhaustion and post exercise cognitive performance in comparison to trials with placebo or BCAA administration. Furthermore, during a 3-week moderate endurance training of sedentary males basaline values of B_{max} of 5-HT transporters (5-HTT) and 5-HT_{2A} receptors (5-HT_{2A}R) on isolated platelet membranes increased while plasma prolactin (PRL) concentrations decreased as well as mood and physical efficiency improved. In contrast, after an excessive training program over four weeks, well-trained endurance athletes showed no change of B_{max} of 5-HTT, but a decline of 5-HT_{2A}R density and an increase in basal plasma PRL concentration. Mood was impaired and central fatigue increased. Thus, the impact of exercise on 5-HT neurotransmission may depend on training state of athletes and extent of exertion. The theoretical background of the implication of exercise and the effect of long lasting exhaustive exercise in athletes on mental and physical efficiency or central fatigue are evaluated. The significance of the primary disturbance of central neuromodulation and dysfunction of 5-HTT, 5-HT receptor subtypes and the phosphoinositol signal transduction as well as the limited modulation capacity of the 5-HT system in overstrain are also addressed.

Keywords: Amino acids – 5-HT transporter – 5-HT_{2A} receptor – 5-HT reuptake inhibition – Overstrain

Introduction

Exercise-induced increase of the essential amino acid free L-tryptophan (free TRP) in blood occurs due to liberation from albumin, which is caused by

adrenergically induced lipolysis of free fatty acids (FFA). It results in a higher free TRP uptake at the competitive L-carrier at the blood brain barrier (BBB) (Chaouloff, 1997; McMenamy, 1965). The consecutively enhanced serotonin (5-HT) biosynthesis in the brain by tryptophan hydroxylase as unsaturated key enzyme does not per se initiate mood impairment or central fatigue. However, long lasting exhaustive training regiments and dense competitive events may exceed metabolic and neuromuscular capacity of athletes, especially when ergogenic aid during exercise and following periods of regeneration are insufficient. After depletion of glycogen stores in the body and decline of blood glucose and insulin, there is adrenergic-induced mobilization of FFA from adipose, while mitochondrial uptake and oxidative energy production from FFA are reduced (Weicker and Strobel, 1994). Preliminary evidence suggests that this is followed by an overproportional increase of free TRP liberation from albumin and consequently higher central 5-HT biosynthesis, which may disturb 5-HT neurotransmission. In this state, mood is impaired, central fatigue is increased and the mental as well as physical efficiency of athletes are reduced (Blomstrand et al., 1988; Davis and Bailey, 1997; Newsholme et al., 1987).

Exploration of exercise-induced alterations of 5-HT neurotransmission in the brain is experimentally restricted. 5-HT transporters (5-HTT) and 5-HT_{2A} receptors (5-HT_{2A}R) on isolated blood platelets are useful biological marker, since they are easy to obtain by venous puncture and have similar functions and identical biochemical, biomolecular and genetical properties compared to central 5-HT neurons (Da Prada, 1988; Table 1). Basal values of prolactin (PRL), a hypothalamic neuropeptide, may also be used as window to the brain as changes in peripheral blood concentration are affected by 5-HT receptor subtype activation.

To gain further insight into the impact of exercise on 5-HT neurotransmission, we have evaluated the effect of a 5-HT reuptake inhibitor (SSRI) and branched-chain amino acids (BCAA) on physical and cognitive performance. We have also determined plasma concentrations of free TRP,

Table 1. Comparison between platelets and serotonergic neurons (modified from Da Prada, 1988)

	Neurones	Platelets
active transport for 5-HT	+	+
5-HT_{2A} receptors	+	+
[^{3}H]imipramine binding sites	+	+
subcellular storage of 5-HT in vesicles	+	+
MAO type B	+	+
biosynthesis of 5-HT	+	−
5-HT transporter at the plasma membrane	+	+
5-HT transporter at the vesicular membrane	+	+
neuron-specific enolase	+	+
serotonin binding protein	+	−
serotonin secretory vesicles	+	−

BCAA and PRL as well as platelet 5-HTT and 5-HT_{2A}R before and after moderate/excessive endurance training and repeated TRP administration.

Materials and methods

Experiment A

Ten endurance-trained male cyclists (age 25.5 ± 2.1 yr, wt: 76.5 ± 4.4 kg, ht: 181.5 ± 5.6 cm, 4 mmol/l lactate threshold at 307 ± 37 W) were subjected in 3 trials (T I–III) to exercise until exhaustion on an electrically braked cycle ergometer. Time interval between trials was one week. Subjects received a standardized meal at 9 p.m. the night before test days, fasted overnight and obtained a standardized breakfast at 8 a.m. on the test days. In a double-blind fashion using a randomized study design subjects were administered following breakfast 20 mg of the SSIR paroxetine (Tagonis, Janssen, Neuss, Germany) in T II while a placebo was given in T I and III. At 12:45 a.m. subjects of T III were given dissolved in water 14 g BCAA (Lactostrict spezial: 7.22 g L-leucine, 3.88 g L-valine, 2.9 g L-isoleucine, Fresenius, Bad Homburg, Germany). Placebo was administered in T I and II. At 1:00 p.m. cycle ergometry began. Workload (256.0 ± 19.5 W) corresponded to a blood lactate level of 2.0 mmol/l in an graded exercise test until exhaustion. After 60 min of exercise subjects were again administered 7 g BCAA in T III while placebos were given in T I and II.

Exhaustion was defined as the point in time at which subjects were unable to maintain a frequency of 50 rpm on the ergometer. Immediately after cessation of exercise subjects were exposed to a cognitive test (KL-test, Düker, 1976) which evaluates mental performance under the aspect of endurance and fatigue resistance. Test tasks were mathematical calculations for 30 min (e.g. 4 + 5 − 3 = x and 4 − 2 + 7 = y, if x is lower than y results have to be added, otherwise y is subtracted from x. Only end scores were allowed to be written down). Amount of correct and incorrect calculations (T_N) reflects the subjects' drive or motivation. T_M stands for number of mistakes. $F_{\%}$ was received by calculating $100 \times T_M/T_N$.

Experiment B

Modifications in the 5-HT system induced by 3 weeks of moderate endurance training in 6 untrained subjects (age 25.4 ± 1.8 yr, wt: 75.9 ± 5.4 kg, ht: 177.1 ± 3.0 cm; trial MT) or 4 weeks of excessive training in 6 endurance athletes (age 24.3 ± 2.1 yr, wt: 71.5 ± 7.5 kg, ht: 179.8 ± 5.0 cm; trial OT) were evaluated and compared with changes induced in sedentary subjects who received for 3 weeks 1.5 g/day TRP (n = 6; age 27.3 ± 2.7 yr, wt: 75.5 ± 4.9 kg, ht: 180.0 ± 6.9 cm; trial TRP) or placebo (n = 6; age 30.7 ± 7.2 yr, wt: 73.2 ± 4.8 kg, ht: 177.5 ± 8.6 cm; n = 6; trial PL). MT consisted of 3x/wk running at an intensity corresponding to 75% of the 4 mmol/l blood lactate threshold for 40, 50 and 60 min during the first, second and third week, respectively. OT consisted of an immense increase in training demands (weekly training amount: 453 ± 100 min vs. 1,958 ± 357 min). Training intensity did not differ to normal training habits prior to the study. Participants of all trials reported to the laboratory at 8 a.m. after an overnight fast one day before and after the respective program. A catheter was placed into an antecubital vein and after 60 min of rest, EDTA blood samples (10 ml) were collected, cooled for 10 min on ice prior to centrifugation at 3,000 rpm for 10 min at 4°C. Plasma was divided into fractions. Separation of free TRP from albumin-bound tryptophan was carried out immediately by an ultrafiltration method according to Bloxam et al. (1977). Ultrafiltrate and fractions of original plasma were stored at −80°C. Amino acid analysis was carried out as described before (Strüder et al., 1997) using a methode by Schuster (1988). PRL was determined with the Enzyme-Imunoassay-Automate ES 300 and kits from Boehringer (Mannheim,

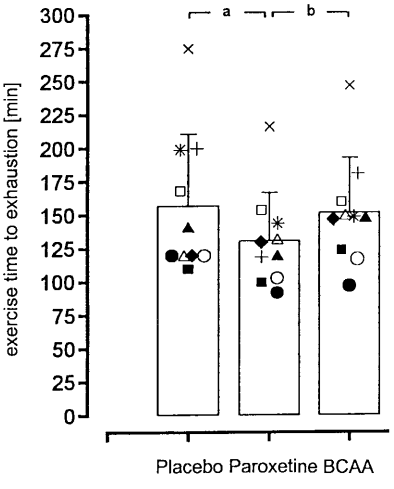
Germany). Platelets were isolated from 40 ml of blood (Mellerup and Langer, 1990). Pellets were frozen at −80°C until analysis. 5-HTT binding was assayed using 100 μl aliquot of membrane suspension, which was incubated with 50 μl [^{3}H]paroxetine (0.01–0.03 pmol/l; 60 min). Non-specific binding was defined as [^{3}H]paroxetine binding in the presence of 10 nM citalopram. 5-HT_{2A}R binding was assayed using [^{3}H]ketanserin. Non-specific binding was defined as [^{3}H]ketanserin binding in the presence of mianserin. Protein concentration was determined according to the BIORAD assay (Munich, Germany). Before and after the trials, subjects filled out the EZ-scale by Nitsch (1976). The EZ-scale consists of a list of 40 adjectives designed to assess momentary self-perceived state.

Data are presented as mean ± standard deviation. Multiple-factoral analysis of variance with repeated measurement and Newman-Keuls post-hoc test were used to assess differences between test units and with time. Significance level for all analyses was set at $p < 0.05$.

Results

Exhaustion during cycle ergometry was reached significantly earlier after paroxetine administration (T I: 157 ± 53 min, T II: 131 ± 36 min, T III: 152 ± 41 min; Fig. 1). No significant differences were found between the other trials. During KL-test, T_N was lower after paroxetine ($p < 0.05$) compared to placebo and amino acid supplementation. T_M did not differ between trials, however, $F_{\%}$ was higher in T II compared with T III ($p < 0.05$).

Three weeks of TRP application did not influence platelet density of 5-HT_{2A} receptors and 5-HT transporters, basal plasma PRL concentration, performance capacity or self-perceived state even though basal free TRP



	T_N	T_M	$F_{\%}$
Placebo	108.9	7.6	7.8
	SD 43.3	SD 4.9	SD 4.8
Paroxetine	95.1	8.9	9.5
	SD 34.4	SD 5.9	SD 4.6
BCAA	126.4	6.0	4.8
	SD 45.8	SD 5.9	SD 3.9

Fig. 1. Left side: exercise time to exhaustion during test units with placebo, paroxetine and branched-chain amino acids (*BCAA*) administration. Each symbol represents the same participant in trial I–III. Significance level (ANOVA, Newman-Keuls) was set at $p < 0.05$ (*b*) and $p < 0.01$ (*a*). Right side: KL-test scores (T_N calculations, T_M mistakes, $F_{\%}$ $100 \times T_M/T_N$) after exercise in trials. Values are mean and standard deviation. T_N was lower and $F_{\%}$ was higher after paroxetine administration. Significance level (ANOVA, Newman-Keuls) was set at $p < 0.05$

concentration and free TRP/BCAA ratio was increased ($p < 0.01$) (Fig. 2). Endurance training did not induce alterations in basal amino acids concentrations. Moderate training over 3 weeks increased platelet binding of [^{3}H]ketanserin to 5-HT_{2A} receptors (16.4 ± 14.9%; $p < 0.05$) and [^{3}H]paroxetine to 5-HT transporter (9.6 ± 5.9%; $p < 0.01$) in sedentaries. An immense increase in training volume induced a decline of 5-HT_{2A} receptor radioligand bindings sites (8.4 ± 5.5%; $p < 0.05$) but did not affect 5-HT transporters. Basal plasma PRL concentrations were lower ($p < 0.01$) in endurance athletes than in untrained subjects. Plasma PRL concentration decreased during moderate endurance training (16.3 ± 9.7%; $p < 0.01$) while it increased during excessive training (35.3 ± 19.9%; $p < 0.01$). Moderate endurance training improved physical and mental efficiency, while self-perceived state of "fatigue" increased in endurance athletes during the training regiment.

Discussion

5-HT transporters and 5-HT_{1A} autoreceptors

Exercise-induced alterations of 5-HT neurotransmission in the brain are affected by changes in function of presynaptic 5-HTT and 5-HT autoreceptors at the nerve endings and postsynaptic 5-HT receptor subpopulations (Fig. 3). 5-HTT are hydrophobic polypeptides with 12 membrane spanning segments and two putative glycosilated sites in the second extracellular loop (Lesch et al., 1993). Extent of 5-HT in the synaptic cleft is adjusted by 5-HTT together with presynaptic 5-HT_{1A} autoreceptors, which reduce the 5-HT releasing impulse frequency by hyperpolarisation of the axon terminal membrane (Fig. 3). This occurs after stimulation of the presynaptic somatodendritic 5-HT_{1A} autoreceptors by 5-HT or its agonists, which inhibit the adenylate cyclase system followed by a reduction of the cAMP formation. Subsequent increase of G_0 protein opens the K^+ channel of the axon terminal membrane and the enhanced K^+ efflux elicits the membrane hyperpolarisation, which reduces the impulse frequency of the secretory 5-HT release from the vesicles (Rudnick and Clark, 1993). At the same time this membrane hyperpolarisation diminishes the velocity of anterograde plasma membrane transport of TRP hydroxylase, the key enzyme of the 5-HT synthesis, from the neuron body to the axon terminal resulting in a reduction of 5-HT formation.

Short and long term effect of SSRI on 5-HT_{1A} autoreceptors

This mechanism is initiated by short term application of SSRI, i.e. paroxetine, which inhibits 5-HT release after activation of somatodendritic 5-HT_{1A} autoreceptors. After long term application of SSRI, however, the 5-HT_{1A} receptor in desynthesized and the liberation of 5-HT into the synaptic cleft increases. Thus, the short term effect of paroxetine is reversed by long term application, an observation which is in line with other antidepressants reaching

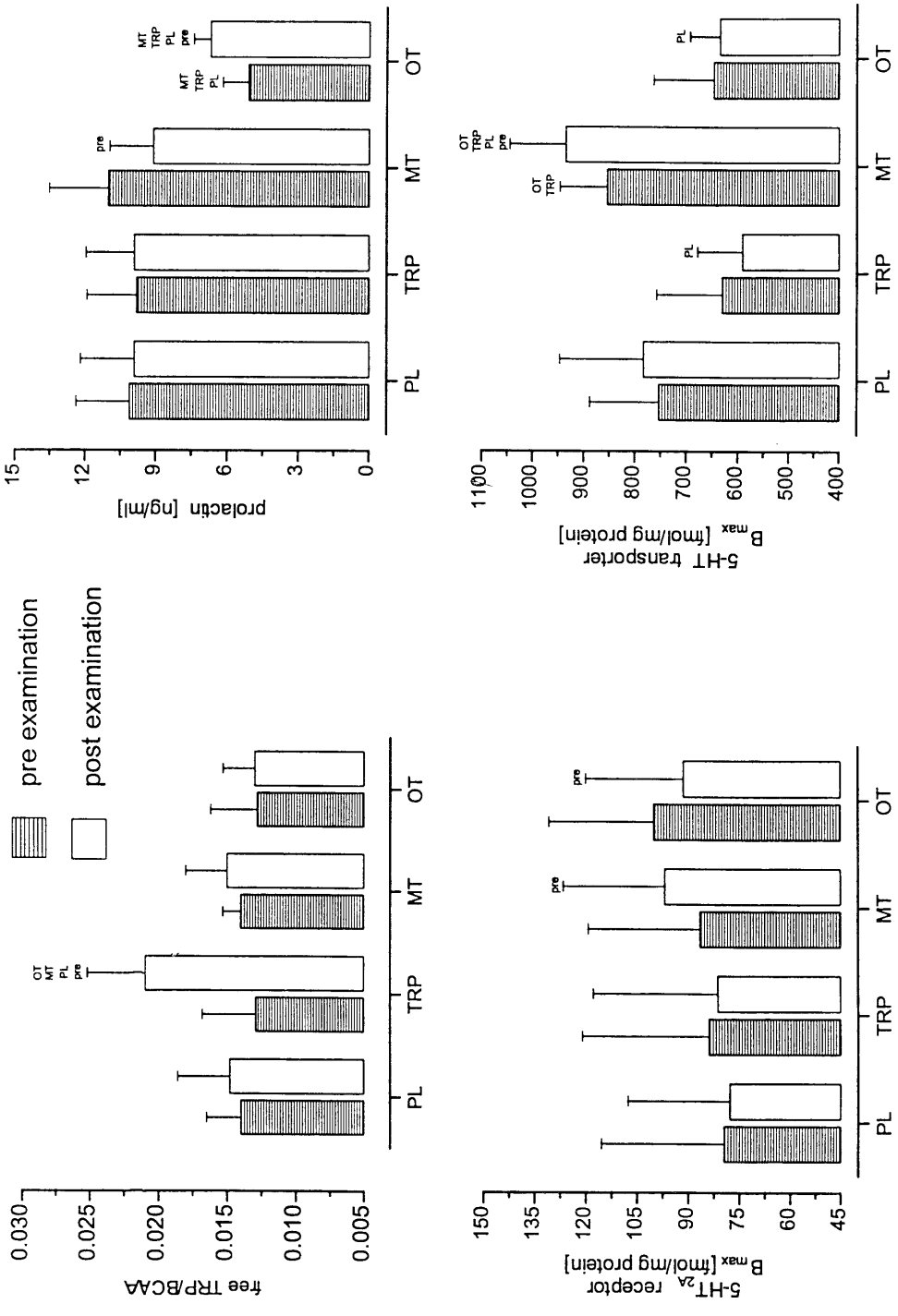


Fig. 2. Basal values of the plasma ratio of free tryptophan to branched-chain amino acids (*free TRP/BCAA*), plasma concentration of prolactin as well as maximum binding capacity (B_{max}) of [^{3}H]ketanserin to 5-HT$_{2A}$ receptors and [^{3}H]paroxetine to 5-HT transporters on prefrozen platelets before (striped bars) and after (white bars) three week of placebo (*PL*) or tryptophan (TRP, 1.5 g/day) application, three weeks of moderate endurance training in untrained subjects (*MT*) or four weeks of excessive increase in training volume in endurance athletes (*OT*). PL, TRP, MT and OT above bars marks significant difference of the respective trial. pre stands for significant difference to preexamination. Significance level was set at $p < 0.05$

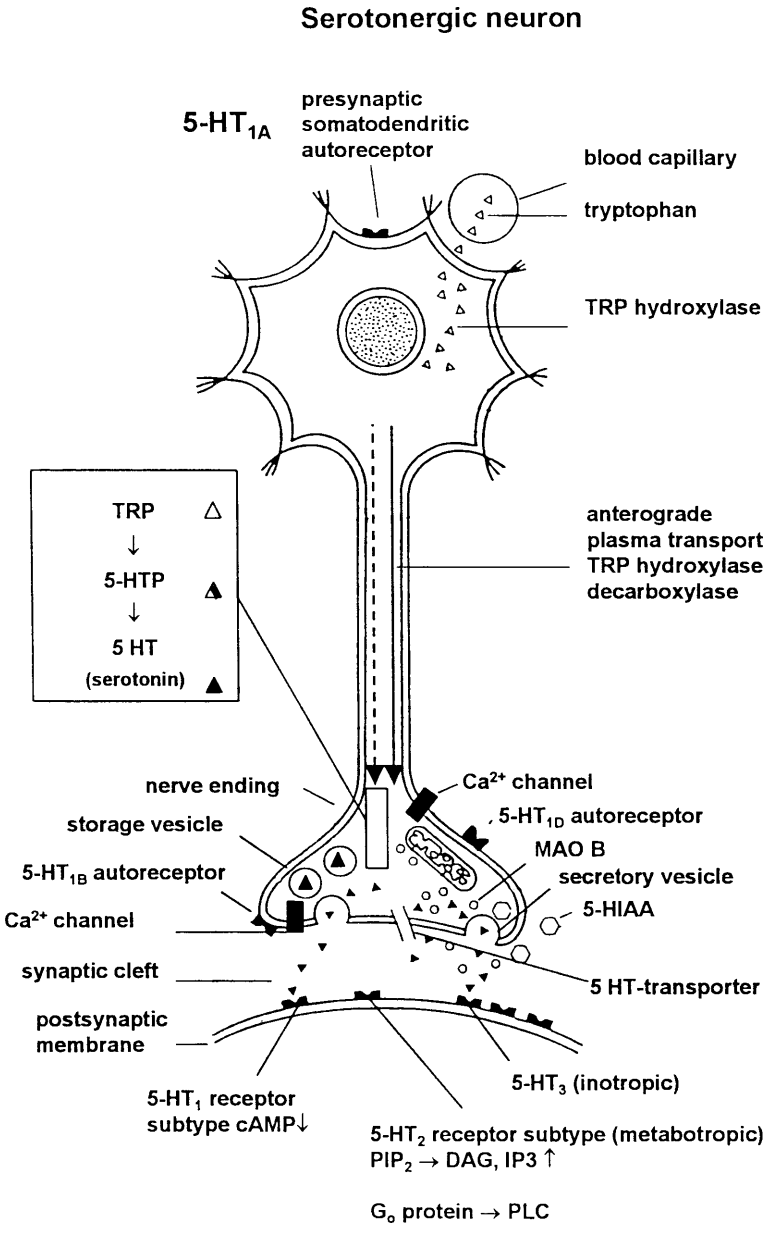


Fig. 3. Serotonergic neuron and synapsis. In the terminal axon of the serotonergic neuron free TRP is converted to 5-HTP by TRP hydroxylase as unsaturated rate limiting enzyme in synthesis of 5-HT. 5-HTP is decarboxylized to 5-HT. 5-HT can be released in the synaptic cleft or stored in vesicles. 5-HT that is not stored in a vesicle is degraded by MAO to 5-HIAA. 5-HT-transporter regulate reuptake of 5-HT from the synaptic cleft. The presynaptic somatodendritic autoreceptor 5-HT_{1A} attenuates the secrectory 5-HT release from membranous vesicles of axon terminals by reduction of impulse frequency of 5-HT after the hyperpolarization of the membrane due to increased K^+ efflux after G_i protein stimulation of K^+ channels and 5-HT synthesis by decline of anterograde plasma transport velocity of TRP hydroxylase in terminal axon. Postsynaptic 5-HT_1 receptors have no autoreceptor function and work in cooperation with 5-HT_2 receptor subtypes responsible for metabotropic postsynaptic second messenger regulation, influencing phosphoinositide signal transduction. 5-HT_3 is a ionotropic receptor without second messenger system. (*Ca* calcium, *MAO B* monoamine oxidase B, *TRP* tryptophan, *5-HIAA* 5-hydroxyindoleacetic acid, *5-HT* 5-hydroxytryptamine (serotonin), *5-HTP* 5-hydroxytryptophan)

first therapeutical benefit several weeks after the onset of medication. This observation described by Graeff (1997) might be the explanation for the results in experiment A, in which trained cyclists showed reduced performance capacity after receiving only a single dose of 20 mg paroxetine before the exhaustive cycle ergometer test. The exercise dependent regulation of presynaptic 5-HT release by activation of somatodendritic 5-HT_{1A} autoreceptors might be a crucial function for the adjustment of the presynaptic neurotransmission to work intensity and duration. Thus, although our data confirm results from Wilson and Maughan (1992), we suggest that reduced physical performance after SSIR administration might be due to a reduction of 5-HT in synaptic cleft rather than an increase as has been postulated by these authors.

5-$HT_{1 \text{ and } 2}$ receptors and exercise dependent modulation of 5-HT neurotransmission

Prolonged exercise and especially extreme exertion might elicit various responses to presynaptic autoreceptor activity which affect 5-HT concentration in synaptic cleft and postsynaptic 5-HT receptor subtypes density. Hypersensitivity of 5-HT_2 receptor subtypes should be discussed in the context of exhaustive work, initiating central fatigue or mental and physical deficiency, which is often combined with depressive behavior during overstrain.

The biochemical characteristics of 5-HT_2R subpopulations are important for exercise-induced adaptations of the central 5-HT system and also depend on the function of the presynaptic 5-HT_{1A} somatodendritic receptors. The signal transductor MARCKS (myristolated, alanin-rich phosphoprotein) has a prominent significance for postsynaptic 5-HT signal transduction (Lenox and Watson, 1994). The stimulated 5-HT_2R subtypes initiate the phosphatidyl-inositol-4-5-bisphosphate (PIP2) metabotropic metabolization to the second messenger inositol trisphosphate (IP3) and diacylglycerol (DAG) caused by G_0 protein activation of phospholipase C (Fig. 4). DAG stimulates membraneous protein kinase C (PKC), which phosphorylates MARCKS as main substrate. This plasmatic phosphoprotein also possesses calmodulin binding sites. The signal transductor mediates the release of 5-HT but also of dopamine (DA) and norepinephrine (NE) in different specific brain areas, also facilitating the neuropeptide secretion from HPA and HPG axis (Klemfuss, 1992; Lenox and Watson, 1994). Enhanced 5-HT_2 receptor activation after exercise-induced increase of 5-HT concentration in the synaptic cleft also potentiates phosphoinositide signaling with subsequent enhanced neurotransmitter release in the projected serotonergic areas of the brain by signal transductor MARCKS.

Effect of exercise on feedback regulation of 5-HT signal transduction at 5-HT_2 receptors

The implemental signal transduction during physiological exertion is attenuated by a feedback regulation at receptor level. This conclusion might explain

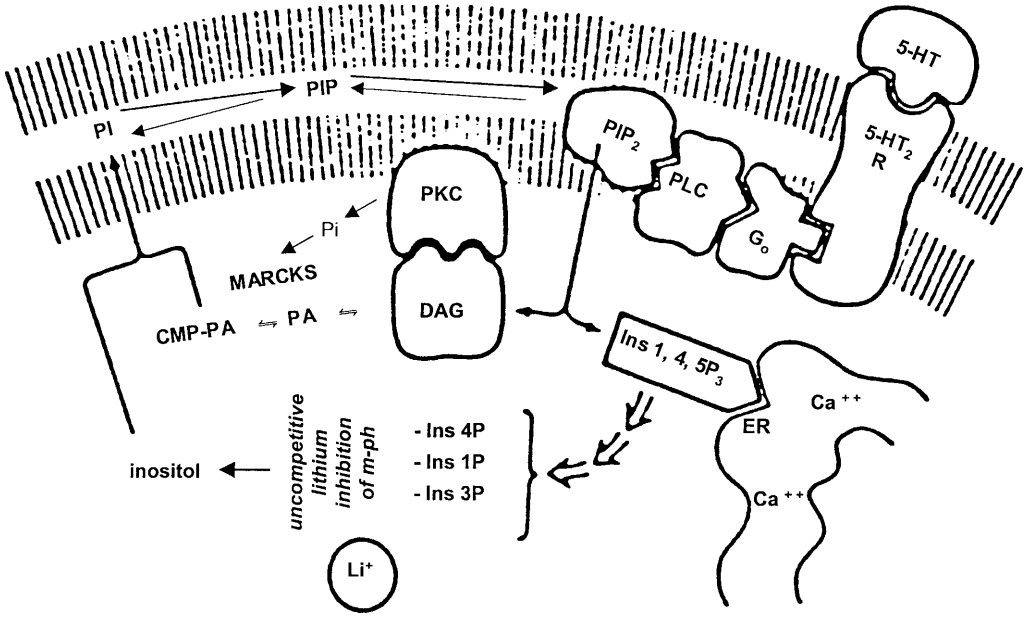


Fig. 4. Serotonin (5-HT) occupancy of the 5-HT_2 receptor binding site results in G_0 protein-mediated coupling and activation of phospholipase C, which induces the hydrolysis of phosphatidylinositol 4,5-bisphosphate (*PIP_2*) and the generation of the two second-messengers diacylglycerol (*DAG*) and *myo*-inositol 1,4,5-trisphosphate. The latter binds to receptors in the endoplasmic reticulum and releases intracellular calcium. DAG is an endogenous activator of proteinkinase C which phoshorylates MARCKS (myristoylated alanine-rich C kinase substrate). MARCKS carries the signal transduction to other brain areas, thereby also interacting with neurotransmitters and peptide hormones. Lithium inhibits uncompetetively the enzyme inositol monophosphatase, which prevents the recycling of inositol and thus the increase of DAG (*R* receptor, *PKC* protein kinase C, *PI* phosphatidyl-inositol; *PLC* phospholipase C)

some alterations found after moderate endurance training of three weeks performed by sedentary subjects, such as the increase of B_{max} of 5-HTT and 5-HT_{2A}R at isolated platelet membranes. Furthermore, after the training program basal values of PRL were diminished and mood improved. Moderate physical activity did not increase central fatigue. From these results it might be concluded that the exercise program resulted in beneficial alteration of physical efficiency and behavior due to a rational TRP uptake at the BBB and an adapted central 5-HT biosynthesis. The exercise-induced presynaptic 5-HT release was adjusted and the physiological concentration in snyaptic cleft seems to have been well equilibrated, avoiding postsynaptic receptor downregulation. This was also demonstrated by the decline of PRL, exhibiting that no stress or central 5-HT overproduction occurred, which usually increases hypothalamic PRL secretion.

After the excessive training regiments of four weeks performed by well-trained endurance athletes, B_{max} of 5-HT_{2A}R at the platelet membranes declined whereas the density of the 5-HTT did not change. However, basal blood PRL concentration increased significantly in comparison to the lower

values before the excessive training regiments. Behavior and mood were impaired and central fatigue increased. These symptoms led us to expect an overstrain after the excessive training regiment. Overstimulation of the signal transduction might have contributed to this and it was not slowed down by a feedback regulation due to the hypersensitized postsynaptic 5-HT_{2A} receptors.

Effect of long term TRP supplementation on free TRP and free TRP/BCAA ratio

The dose of 1.5 g TRP per day applied in experiment B was lower than the dosage usually administered in other studies (e.g. Van Praag, 1984). However, the total amount of TRP supplemented over three weeks was considerably higher than reached by TRP-enriched food. It significantly increased basal values of free TRP as well as the ratio of free TRP/BCAA. But as expected, oral application of this dosage did not change basal values of PRL or B_{max} of 5-HTT and 5-HT_{2A}R, nor did it affect mental or physical efficiency. In contrast, after acute intensive physical exertion an increase of basal TRP values is usually accompanied by a PRL increase and an alteration of 5-HT receptor density (Strüder et al., 1997, 1999).

Considerations on overtraining

The results of the present study may allow some new considerations in the discussion of overstrain. It seems that central general stress of long lasting exhaustion might already disturb the impact on the physiological, well adapted neuromodulation by serotonin, afflicting the interaction of central neurotransmitters or hypothalamic neuropeptides and releasing factors. Central fatigue, mental and physical deficiency and behavioral alteration with depressive mood in overstrained athletes are probably not primarily caused by the metabolic and neuromuscular deficiency after long lasting exhaustive exercise, as was inaugurated by Newsholme et al. (1987). But the complex stress induced by central alterations of neuromodulation will be amplified by the catabolic enhancement of the 5-HT system after exhaustion in order to attenuate the central neuromodular disturbance. This implies an increased free TRP liberation from albumin after the adrenergically lypolictic FFA mobilization and rise of FFA blood concentration with consecutive higher free TRP uptake at the BBB, supported by reduced BCAA concentrations. These are factors which contribute to the exaggeration of central neuromodular dysregulation. Additionally, they increase central 5-HT formation due to a higher TRP hydroxylase activity. However, the exhaustion dependent amplification of 5-HT impulses to various brain areas seems to disturb the equilibrating effect on physiological central 5-HT neurotransmission, thus eliciting dysfunctions of 5-HTT or 5-HTR subtypes, respectively. This dysbalance might be enhanced by reduction of ergogenic aid during exercise and insufficient regeneration units after work. In well conducted intensive

training regiments exercise-induced 5-HT implication on extent of metabolic alteration did not differ significantly from those in overstrained athletes, whereas mental fatigue and behavioral impairment belong to the decisive symptomes of this state. Therefore, it has to be considered that the central exhaustive exercise stress might be the primary trigger of overstrain, eliciting impairment of complex neuromodulation, which will be amplified by the central dysregulation after the exertion-induced enhancement of the central 5-HT impact. Especially the second messenger response of 5-HT_{2A}R subtypes, which support formation of the second messenger DAG and IP3 after receptor dependent metabolization of PIP2, is important for overproportional phosphoinositide signaling by signal transductors, e.g. MARCKS. They might dysregulate behavioral modulation, adjustment of interaction between diverse central neurotransmitter interactions and forced excitation of hypothalamic secretion of neuropeptides and releasing factors with consecutive liberation of central and peripheral hormones.

Significance of Raphe nuclei for central 5-HT distribution in the brain

The Raphe nuclei of the midbrain are the serotonergically richest area and regulate presynaptic 5-HT release by the somatodendritic 5-HT_{1A} autoreceptors. Raphe nuclei are the pacemakers of the 5-HT central propagation, which controls the 5-HT projection by collaterals and receptor activation of many brain areas as indicated in Fig. 5 (Graeff, 1997). From diverse cortical regions Raphe nuclei receive information of behavioral modulation. These impulses are already integrated in the Raphe nuclei before ascending and descending impulses arise. They are working with constant tonic impulse projections, which are rarely interrupted by phasic alterations. This considera-

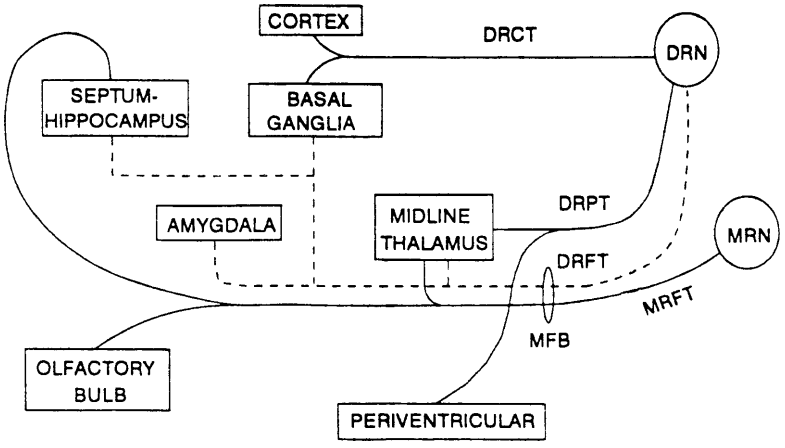


Fig. 5. The main ascending tracts from the dorsal and median raphe nuclei. *DRN* dorsal raphe nucleus; *MRN* median raphe nucleus; *MFB* medial forebrain bundle; *DRCT* dorsal raphe-cortical tract; *DRPT* dorsal raphe periventricular tract; *DRFT* dosal raphe forebrain tract; *MRFT* medial raphe forebrain tract (from Graeff, 1997)

tion about the equilibrating key function of the 5-HT system is essential in order to adjust the neuro and behavior modulation by coordination of different central neurotransmitters, such as NA, DA, glutamate, ACh or Gaba, which are prerequisites for efficient neuronal networks. Hoyer et al. (1993) and Baumgartner et al. (1995) postulated that 5-HT is one of the oldest neurotransmitters in the brain, preceeding even the catecholamines, Gaba, ACh and glutamate. Thus, the 5-HT system must have beneficial properties for central neurotransmitter cooperation, otherwise it would not have survived millions of years of evolution. The question arises as to why exhaustive long lasting physical exertion can abolish the beneficial 5-HT effect, and elicit an overstrain, which is then emphasized by a catabolic dysfunction of the 5-HT system. It seems that the adjustment of the central neuromodulation by 5-HT compensates central stress-induced dysregulation. However, if the equilibrating capacity of the 5-HT system is overreached it amplifies the dysfunction of the 5-HTT, the pre- and postsynaptic receptor properties and the second messenger dependent phosphoninositol signaling to areas in the brain. This might induce the primary neuromodular disturbance of the complex central stress increasing the impact of the metabolic alterations on mental and physical efficiency and central fatigue. This state is reached in overstrain when behavioral and mood afflictment, central fatigue or depression dominate and the symptomatology in athletes does not respond to ergogenic aid, successful regeneration units after work and abstinence of intensive exercise.

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