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Serum level of serotonin during rest and during exercise in paraplegic patients

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The purpose of this study was to evaluate the serum level of serotonin (5-HT) during rest and response to exercise in subjects with spinal cord injury (SCI) with different levels of physical activity. Twenty-five male subjects with traumatic paraplegia, the neurological levels being between T1 and T12, volunteered for the study. They were divided into two groups matched for age, weight and time since injury, according to the level of physical activity: 14 inactive and 11 subjects regularly involved in sports activity and considered active. They all performed a maximal spiroergometric test with an arm crank ergometer. Two samples of blood were collected for 5-HT determination, during rest (PRE) and immediately after exercise test (POST). Serum 5-HT concentration was measured by high performance liquid chromatography using electrochemical detection (HPLC-ED). The results showed that peak oxygen uptake ($\dot{V}O_{2peak}$) was higher in the active group (27.08 ± 2.60 *vs* 18.89 ± 5.58 mL.kg^{-1}.min^{-1}, $P < 0.001$). There were no significant differences between the inactive and active groups for the 5-HT PRE (respectively 176.96 and 193.73 ng.mL^{-1}, $P > 0.05$) or POST values (275.44 *vs* 311.05 ng.mL^{-1}, $P > 0.05$). Both groups showed an increment in 5-HT after maximal exercise, but only in the active group it reached statistical significance (Wilcoxon test, $P < 0.02$). Our results show that chronic paraplegic individuals have normal resting serum serotonin levels and normal response to exercise. The relationship between training status, mood elevation and 5-HT in SCI could not be established in the present study, and further investigation is needed to clarify this issue.

Keywords: serotonin; paraplegia; exercise; monoamines; spinal cord injury

Introduction

Serotonin (5-HT) is a neurotransmitter synthesized from the essential amino acid tryptophan. The serotoninergic pathways emanate from cell bodies situated mainly in the midbrain raphe nuclei, with diffuse projections in the forebrain (hippocampus, hypothalamus, striatum, cortex), medulla and spinal cord.[1] It is also present in the peripheral system and plays its physiological role by activating different 5-HT receptors.[2]

In the past two decades several studies have addressed the role of serotonin in different physiological mechanisms, such as control of thermoregulation, cardiovascular regulation, sympathoadrenal outflow,[2] and in the pathogenesis of various symptoms and diseases such as pain,[3] fatigue, anxiety and depression.[5]

Physical exercise increases brain 5-HT synthesis and metabolism,[6] and possibly the mood-elevating effects of exercise are related to these changes in monoaminergic metabolism.[1,6,7]

So far, the serum level of 5-HT in spinal cord injured subjects has not been investigated. Considering that depression is frequently associated with spinal cord injury[8] and 5-HT plays a role in different types of depression,[5] the purpose of this study was to investigate the serum level of serotonin in paraplegic individuals, during rest and after maximal exercise test.

Methodology

Subjects

Twenty-five subjects with complete spinal cord injury (ASIA grade A)[9] with upper motor neuron lesion between T1 and T12 for at least 11 months volunteered for the research. All gave their written informed consent to a protocol approved by the ethics committee for human experimentation, and were screened for any contraindication for a maximal spiroergometric test.

The subjects were divided in two groups according to the level of physical activity: active (regularly

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involved in sports activities, ie wheelchair basketball, tennis or swimming practice at least twice a week) – 11 subjects and inactive (not involved in sports activities) – 14 subjects. All were male, and the groups were matched for age, weight and time since injury (Table 1).

Spiroergometric test
All exercise tests were performed with an arm crank ergometer (Cybex MET300, Lumex Inc., New York). The incremental test began with 25 watts and increased 12.5 watts every 2 min until exhaustion. An open circuit system was used to monitor the ventilatory and metabolic responses. Expired ventilation, oxygen and carbon dioxide concentrations were measured every 20 s by a Vista Metabolic System and the data were analyzed by a software designed for this purpose (Turbofit, Ventura, CA). Heart rate was recorded every 5 s by a heart rate monitor (Polar Vantage XL, Finland).

Serotonin
Two samples of blood (5 mL) were collected in dry tubes from the antecubital vein, during rest (PRE) and immediately after (POST) exercise test. Serum was separated by centrifugation, stored at $-80°C$ and prepared according to a methodology described elsewhere.[10] Serotonin level was determined using liquid chromatography with electrochemical detection (HPLC-ECD).

Stastistical analysis
The parametric variables ($\dot{V}O_{2peak}$, HR-bpm, maximal power output $-$ PO_{max} and weight) were contrasted using a *t*-test for independent variables. The non-parametric data (age, time since injury, HR-% and 5-HT) were assessed using Mann-Whitney test for unpaired values (active *vs* inactive) and Wilcoxon test for paired values (PRE *vs* POST). The level of significance was set at 0.05.

Table 1 Demographic and anthropometric data

	n	*Age yrs.*	*Time injury mo.*	*Weight kg*
Active	11	28.00 ± 2.53	174.73 ± 7.72	66.53 ± 10.48
Inactive	14	33.36 ± 11.49	174.29 ± 8.00	63.09 ± 12.55

$P > 0.05$

Results

The data from the physiological response to exercise are shown in Table 2. $\dot{V}O_{2peak}$ and PO_{max} were higher in the active group, while HR (in bpm and % of predicted), basal and post-exercise serum 5-HT did not show statistical difference among the groups. Only the active group had a significant increase in 5-HT after exercise when compared to the PRE values (Figure 1).

Discussion

The present study shows that, under resting conditions, the serum level of serotonin in paraplegics is within the normal range of values.[10–14] Several chronic neurological conditions such as multiple sclerosis, Alzheimer's disease and trigeminal neuralgia are associated with changes in platelet- and serum serotonin.[12,15] No differences were found between the active and inactive groups, while Soares *et al*[16] reported higher serum 5-HT levels during rest in trained than in untrained able-bodied individuals. Differences in training status of the subjects between the studies might have accounted for the discrepant results, since the active group of their study was constituted of national and international track and field able-bodied athletes, while in the current study recreational athletes were included.

Our data show that active and inactive paraplegics were able to increase serum 5-HT after a single session of maximal exercise, although only in the active group it reached statistical significance. This might have been caused by their difference in level of activity, but other factors must be considered. The active group exercised more vigorously in absolute terms, exercise since higher $\dot{V}O_{2peak}$ and maximal workload were observed in the active subjects and possibly led to a more pronounced response to exercise. The relatively small size of the sample might have contributed to the lack of significance between PRE and POST values in the inactive group. So far, the response of serum 5-HT after arm crank exercise has not been investigated and for that reason it is not possible to compare the present findings with other studies in spinal cord injured or able-bodied subjects with the same type of exercise.

Nevertheless the increment after exercise detected in the present study is in accordance to findings in animals and healthy human subjects after leg exercise.[11,13,14]

Table 2 Physiological and serotonin response to maximal exercise in paraplegic individuals, according to the level of physical activity

	$\dot{V}O_{2peak}$ $mL.kg^{-1}.min^{-1}$	HR_{max} bpm	HR_{max} %pred	PO_{max} watts	5-HT PRE $ng.mL^{-1}$	5-HT POST $ng.mL^{-1}$
Active	27.08 ± 2.60	182.08 ± 18.65	94.27	98 ± 23	193.73	311.05
Inactive	18.89 ± 5.58*	172.71 ± 26.37	92.38	57 ± 17*	176.96	275.44

*lower than active ($P < 0.001$)

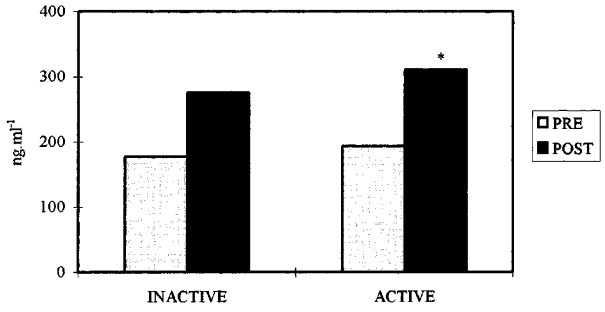

Figure 1 Serum serotonin in paraplegic individuals, during rest (PRE) and after (POST) maximal exercise test.

Acute exercise raises the blood-brain transport of tryptophan (the precursor of serotonin), thereby increasing the rate of 5-HT synthesis and metabolism[4,7] and it could also lead to an increment in serum levels.[11,13,14] Changes in platelets due to exercise could also lead to an augmentation in serum 5-HT, since they are the main carrier of 5-HT in the periphery,[11] but Jensen *et al*[13] recently rejected this hypothesis.

Severely ill patients show serum 5-HT higher than normal during rest and a blunted response to exercise and these alterations are associated with uncontrollable or uncoping stress mechanisms.[14,15] Although spinal cord injury is a severe medical condition with several potential complications, it does not seem to interfere with normal serum 5-HT response to exercise, at least in subjects with spinal injury for longer than 11 months.

Our findings are consistent with previous findings that previous studies have shown a reduction in depression and anxiety in physically trained spinal cord injured individuals,[17–19] but further investigations are necessary. Although one of the possible mechanisms for the mood elevation after training is related to an increase in serotonin synthesis and metabolism,[1,20] our results do not confirm the role of 5-HT in mood elevation after training in spinal cord injury. Thus, further investigation is needed in order to clarify our knowledge on the effects of exercise upon mood state in SCI individuals.

Conclusions

In short, chronic paraplegic individuals have normal resting serum serotonin levels and a normal response to exercise.

References

1 Chaouloff F. Physical exercise and brain monoamines: a review. *Acta Physiol Scand* 1989; **137:** 1–13.
2 Sugimoto Y, Yamada J, Horisaka K. Activation of peripheral serotonin$_2$ receptors induces hypothermia in mice. *Life Sciences* 1991; **48:** 419–423.
3 Auerbach S, Fornal IC, Jacobs BL. Response of serotonin-containing neurons in nucleus raphe magnus to morphine, noxious stimuli and periacqueductal gray stimulation in freely moving cats. *Exp Neurol* 1985; **88:** 609–628.
4 Davis JM, Bailey SP. Possible mechanisms of central nervous system fatigue during exercise. *Med Sci Sports Exerc* 1997; **1:** 45–57.
5 Léonard BE. New approaches to the treatment of depression. *J Clin Psychiatry* 1996; **57:** S26–33.
6 Chaouloff F. Influence of physical exercise on 5-HT$_{1a}$ receptor- and anxiety-related behaviours. *Neuroscience Letters* 1994; **176:** 226–230.
7 Chaouloff F. Effects of acute physical exercise on central serotonergic systems. *Med Sci Sports Exerc* 1997; **1:** 58–62.
8 Judd FK, Burrows GD, Brown DJ. Depression following acute spinal cord injury. *Paraplegia* 1986; **24:** 358–363.
9 Ditunno Jr JF, Young W, Donovan WH, Creasey G. The international standards booklet for neurological and functional classification of spinal cord injury – American Spinal Injury Association. *Paraplegia* 1994; **32:** 70–80.
10 Naffah-Mazzacoratti MG *et al.* Serum serotonin levels of normal and autistic children. *Braz J Med Biol Res* 1993; **26:** 309–317.
11 Soares J. Níveis séricos de serotonina frente ao exercício agudo máximo en indivíduos não treinados e treinados em corridas de meio-fundo e velocidade. *Tese (Doutor)* Universidade Federal de São Paulo, São Paulo, 1995, 73p.
12 Kumar AM *et al.* Peripheral serotonin in Alzheimer's disease. *Neuropsychobiology* 1995; **32:** 9–12.
13 Jensen PN, Møller HJ, Smith DF, Rosenberg R. Acute effect of exercise on human blood platelet serotonin uptake and monoamine oxidase activity. *Biol Psychiatry* 1995; **38:** 125–127.
14 Lechin F *et al.* Plasma neurotransmitters, blood pressure and heart rate during supine-resting, orthostasis, and moderate exercise conditions in major depressed patients. *Biol Psychiatry* 1995; **38:** 166–173.
15 Lechin F *et al.* Plasma neurotransmitters and cortisol in chronic illness: role of stress. *J Med* 1994; **25:** 181–192.
16 Soares J, Naffah-Mazzacoratti MG, Cavalheiro EA. Increased serotonin levels in physically trained men. *Braz J Med Biol Res* 1994; **27:** 1635–1638.
17 Horvat M, French R, Henschen K. A comparison of the psychological characteristics of male and female able-bodied and wheelchair athletes. *Paraplegia* 1986; **24:** 115–122.
18 Sherril C, Silliman L, Grench B, Hinson M. Self-actualisation of elite wheelchair athletes. *Paraplegia* 1990; **28:** 252–260.
19 Twist DJ *et al.* Neuroendocrine changes during functional electrical stimulation. *Am J Phys Med Rehab* 1992; **71:** 156–163.
20 Dey S. Physical exercise as a novel antidepressant agent: possible role of serotonin receptor subtypes. *Physiol Behav* 1994; **55:** 323–329.