Gender Effects on Association of Serotonin Transporter Gene Polymorphism with Symptoms of Central Fatigue

N. V. Maluchenko, J. V. Schegolkova, M. A. Kulikova, M. A. Timofeeva, V. A. Shlepcova, O. V. Sysoeva*, A. G. Tonevitsky*

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 147, No. 4, pp. 445-448, April, 2009
Original article submitted October 3, 2008

In order to test the "serotonin" hypothesis of the genesis of central fatigue, we studied association between genotype and fatigue (3-hour mental workload consisting of information processing and logical task solution) using analysis of variance for different indices (well-being, activity, mood, mental fatigue index). It was concluded that young men with serotonin deficit (LL genotype) and girls with serotonin excess (S genotype) were less tolerant to long-lasting mental workload. Thus, we confirmed that the degree of central fatigue depends on the function of the serotonin system and revealed gender differences in adaptive capacities of carriers of different variants of serotonin transporter.

Key Words: *polymorphism; serotonin transporter; central fatigue; gender differences*

Fatigue is a characteristic of human functional status which is a result of long-lasting work and leads to temporary performance impairment [10]. Fatigue is divided into muscular (physical) and central (neuropsychic) types [6]. Physical fatigue results from intense physical exercise and is characterized by impaired muscular function: decreased coordination and rhythmicity of muscular activity and reduced strength and speed of movement. Biochemical mechanisms underlying the development of muscular fatigue are clearly understood [9]. Neuropsychic (central) fatigue is caused by long-lasting mental work. Monotonous work, bad working conditions, emotional factors, and some diseases can promote the development of central fatigue. The problem of central fatigue has been attracting attention of scientists for a long time. According to one hypothesis of central fatigue development, the loads are followed by the release of free tryptophan, a biochemical precursor of serotonin, intensification of tryptophan penetration through the blood-brain barrier, and accumulation of serotonin in the brain [4,5,7,11,14]. Increased serotonin (5-HT) concentration is responsible for weariness effect. Resistance to mental workload was tested on individuals with genetic variations of serotonin transporter (5HTT). 5HTT supports serotonin reuptake from the synaptic cleft [8]. After serotonin release into the synapse, the transporter transfers it into the presynaptic neuron and it rejoins the neurotransmitter pool. In humans, the 5HTT gene is located in chromosome 17q11.2, it consists of 14 exons and covers 37.8 Kb. Transcriptional activity of 5HTT is modulated by variable repeat sequence polymorphism (20-23 b.p.) in the promoter region, which leads to the appearance of two forms: L-allele presented by repeats consisting of 16 elements and S-allele consisting of 14 repeats. 5HTT polymorphism leads to differences in mRNA concentration (S-allele corre-

Biological Faculty, M. V. Lomonosov Moscow State University; *Russian National Institute of Physical Education and Sport, Moscow, Russia. ***Address for correspondence:*** mal_nat@mail.ru. N. V. Maluchenko

sponds to lower transcription level), changes in protein density on the membrane, and the degree of 5-HT binding [12].

Here we studied "serotonin" hypothesis of central fatigue genesis on example of 5HTT polymorphism.

MATERIALS AND METHODS

The study included 143 individuals (students of M. V. Lomonosov Moscow State University: 71 young men and 72 young women, mean age 20±3 years; Table 1). Participants signed informed consent to the use of their DNA and results of psychological tests in the investigation. Genetic and psychological research was approved by local ethical committee. Students were put through psychological tests and solved computer logical tasks for 3 hours. Before and after the workload, feeling of weariness was evaluated using WAM (well-being—activity—mood) and AMF (acute mental fatigue) questionnaires [1, 10]. Venous blood samples were used for genetic investigation. 5HTT polymorphism was detected using PCR based on identification of differences in the length of PCR product of each allele. Protocols for DNA purification, primers, and PCR-amplification program were described previously [2]. The association between the genotype and fatigue (individual scales for well-being, activity, mood, men-

TABLE 1. Number of Participants

Sex	Allele	
	S (SS+SL)	LL
Young men	52	19
Young women	44	28

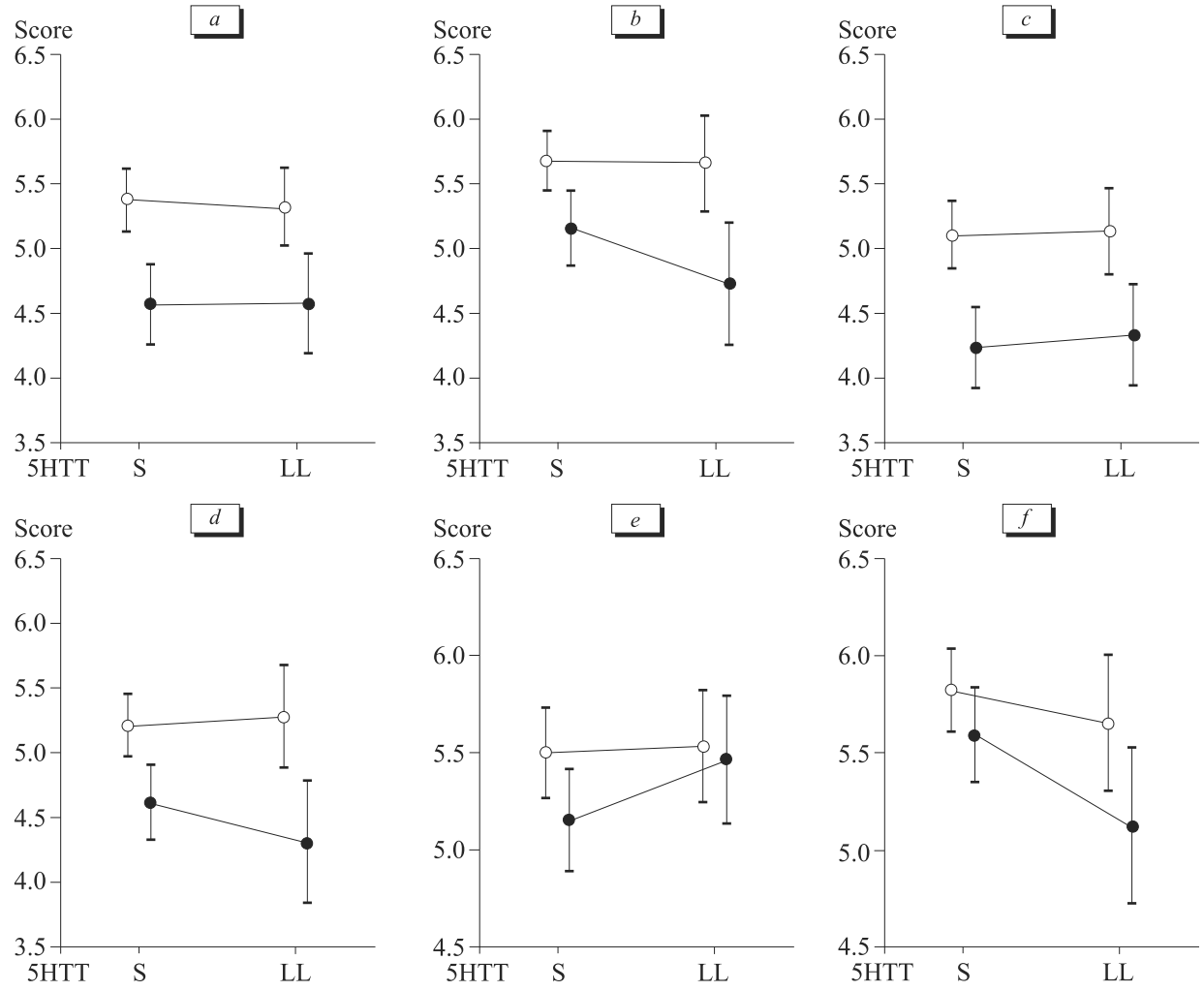

Fig. 1. Results of analysis of variance for interaction of 5HTT genotype and "well-being" (*a*, *b*), "activity" (*c*, *d*) and "mood" (*e*, *f*) indices. *a*, *c*, *e*) young women, *b*, *d*, *f*) young men. Here and on Fig. 2: light dots: before workload, dark dots: after the workload. Confidence interval: 0.95.

tal fatigue index) was investigated using analysis of variance, where the genotype was selected as categorical predictor with three codes (SS, SL, LL). To reveal the factor underlying the observed differences we used the method of multiple paired comparisons (post-hoc test).

RESULTS

Results of assessment of the state of subjects after 3-hour monotonous work consisting of information processing and logical task solution are presented in Table 1 and Fig. 1. Changes in state in three indices indicate that young men carrying two LL alleles are more sensitive to workload than those carrying S-allele (a group consisting of SS- and SL-carriers). In girls this effect concerning well-being and activity was not observed (Fig. 1, *a*, *b*); their mood was weakly affected by 5-HTT polymorphism. In contrast to young men, an inverted effect was observed in girls: the mood was worsened by monotonous mental workload in S-allele, while stable good mood in LL-allele carriers remained unchanged (Fig. 1, *c*). Analysis of another questionnaire focused on mental fatigue assessment demonstrated a more pronounced effect of 5HTT polymorphism. Young men with two LL-alleles felt more tired than S-allele carriers (Fig. 2, *a*). The extent of performance impairment and cognitive discomfort was more expressed in young men with LL genotype (Fig. 2, *b*). An inverse effect was observed in girls: LL-carriers were more resistant to mental workload.

Thus, 5HTT polymorphism differently affected the development of central fatigue in men and women. 5-HT neurons express estrogen receptor mRNA and estrogen controls transcriptional activity of 5HTT [3,13]. Although the data on estrogen effect on 5HTT expression are controversial, scientists agree that estrogen activates 5-HT system functioning. Thus, based on the results of our experiments and taking into account the data on the effect of sex steroids on the 5-HT system functioning we can conclude that young men with 5-HT deficit (LL geno-

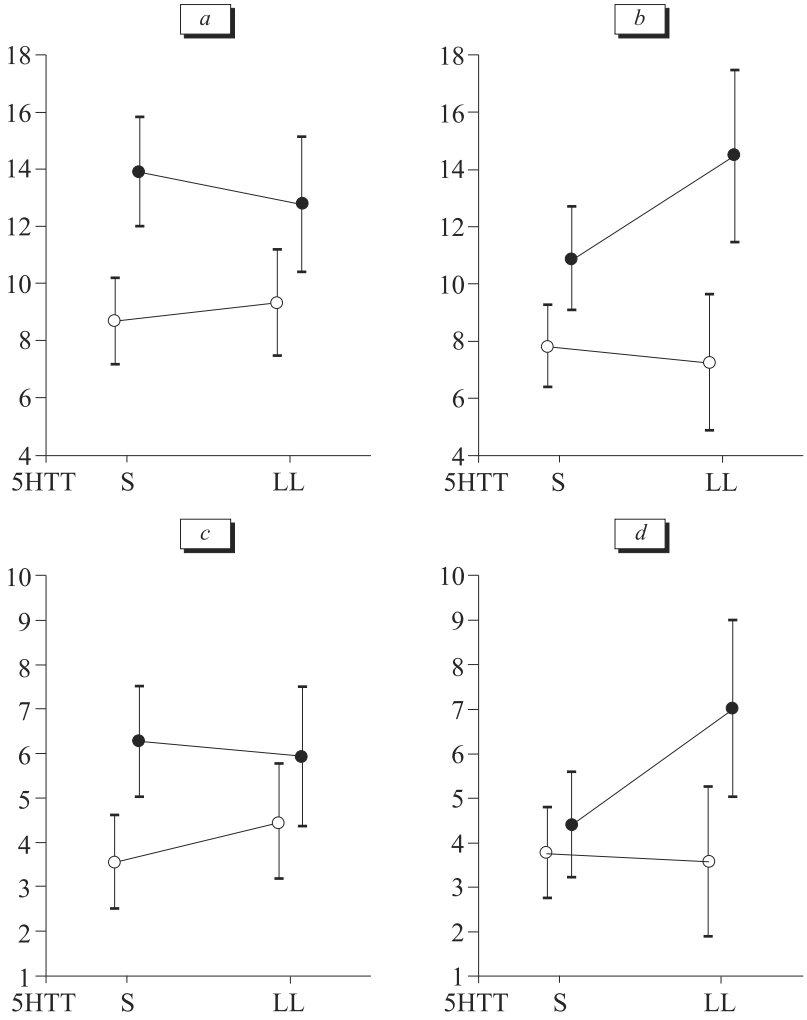

Fig. 2. Results of analysis of variance for interaction of 5HTT genotype and acute mental fatigue (*a*, *b*) and performance impairment and cognitive discomfort (*c*, *d*) indices. *a*, *c*) young women, *b*, *d*) young men.

type) and young women with 5-HT excess (S genotype) are less resistant to long-lasting mental workload. Thus, we have demonstrated the dependence of the degree of central fatigue on the 5-HT system function and specified gender differences in the adaptive capacity of carriers of different 5HTT variants.

The work was supported by government contracts (No. 02.522.12.2001 and No. 02.512.11. 2230) of Federal Agency for Science and Innovation of Ministry of Education and Science of the Russian Federation.

REFERENCES

1. A. B. Leonova, *Psychodiagnostics of human physiological state* [Russia], Moscow (1994).
2. N. V. Maluchenko, O. V. Sysoeva, A. M. Vediakov, *et al.*, *Zh. Vyssh. Nerv. Deiat.*, **57,** 276-281 (2007).
3. Z. Amin, T. Canli, and C. N. Epperson, *Behav. Cogn. Neurosci. Rev.*, **4**, No. 1, 43-58 (2005).
4. E. Blomstrand, *Amino Acids*, **20,** No. 1, 25-34 (2001).
5. E. Blomstrand, *J. Nutr.*, **136**, No. 2, 544s-547s (2006).
6. A. Chaudhuri and P. O. Behan, *J. Neurol. Sci.*, **179**, No. S1-2, 34-42 (2000).
7. J. M. Davis, N. L. Alderson, and R. S. Welsh, *Am. J. Clin. Nutr.*, **72,** Suppl. 2, 573S-578S (2000).
8. L. Dennis, D. L. Murphy, A. Lerner, *et al.*, *Mol. Intervent.*, **4**, 109-123 (2004).
9. S. L. Halson and A. E. Jeukendrup, *Sports Med.*, **34**, No. 14, 967-981 (2004).
10. R. Meeusen, P. Watson, H. Hagesawa, *et al.*, *Appl. Physiol. Nutr. Metab.*, **32**, No. 5, 857-864 (2007).
11. E. A. Newsholme and E. Blomstrand, *Adv. Exp. Med. Biol.*, **384**, 315-320 (1995).
12. L. Pezawas, A. Meyer-Lindenberg, E. M. Drabant, *et al.*, *Nat. Neurosci.*, **8**, No. 6, 828-834 (2005).
13. C. A. Shively and C. L. Bethea, *ILAR J.*, **45**, No. 2, 189-199 (2004).
14. H. K. Strüder and H. Weiker, *Int. J. Sports Med.*, **22**, No. 7, 467-497 (2001).