



The effectiveness of selank in the treatment of adjustment disorder

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Abstract

Background. Adjustment disorder (AD) is one of the most common mental disorders. Considering the social and economic situation in Ukraine at present, in almost 50% of the population, there are non-psychotic mental health disorders, and this number tends to increase. Individual risk factors that are particularly important for the AD development include the experience of significant stress in childhood, problems with mental health in the past, difficult life circumstances, etc. At the same time, pathogenetically approaches to AD therapy are not fully understood. Pathogenetically oriented therapy of AD should be based on neurotransmitter causes and systemic therapeutic approach. The neurometabolic, anxiolytic, and psycho-stimulating action of the regulatory peptide allows it to be used in the therapy of psychogenic adaptation disorders.

Methods. Clinical manifestations of the AD were studied in different age groups - 21-34 years (n=153), 35-50 years (n=257), 51-65 years (n=167) using the Patient Health Questionnaire (PHQ) and Questionnaire of Stress Resistance (QSR). For the study on the effectiveness of the selank (a synthetic analogue of the immunomodulatory peptide tuftsin) were included 30 patients with the AD. Main (experimental group) received selank for two weeks; the control group didn't receive any treatment (wait list). Patients were monitored for additional two weeks after the treatment with an assessment at the end of follow-up.

Results. According to the study results, selank significantly reduced PHQ score in patients with AD compared to control group. PHQ scores in the selank group after 2 weeks of follow-up were significantly lower for somatic symptoms (mean score 1.2 vs. 3.6; $p < 0.05$), nutritional problems (0.1 vs. 3.4; $p < 0.05$), and alcohol misuses (0.3 vs. 1.5; $p < 0.05$)

Conclusion. The use of the synthetic analogue of the immunomodulatory peptide tuftsin has a therapeutic effect on the somatic and mental symptoms of the adjustment disorder.

Keywords: adjustment disorder, diagnostics, therapy, regulatory peptides

1 Introduction

1.1 AD prevalence and diagnostic criteria

Adjustment disorder (AD) is one of the most common mental disorders. Considering the social and economic situation in Ukraine at present, almost 50% of the population has

symptoms of mental health disorders, and this number tends to increase [1]. Personally significant stressful life events, even short-term, affect both the mental and physical health of the individual. Individual risk factors are particularly important for the development of the AD, including the experience of significant stress in childhood, problems with mental health in the past, and challenging life circumstances.

The most significant combination of factors is the presence of provoking agents (individually substantial types of stressful life events) combined with an individual response (stress vulnerability) and constant personal difficulties in combination with other aversive social and psychosocial factors of vulnerability (low self-esteem, self-blame, pessimism) [2],[3]. It should be noted that the fuzzy separation between different manifestations of the AD and normal adaptive responses is difficult to diagnose [3],[4] Therefore, the diagnosis and treatment of adjustment disorder is extremely relevant.

The ICD-10 indicates that a predisposition or individual vulnerability plays the more significant role in the onset of the AD than in other disorders of the same cluster (F43). This association implies a kind of "stress-vulnerability syndrome" that usually declines social or professional functioning, even if it doesn't correspond to the diagnostic group.

In the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5) [5], the chapter "Trauma and Stress Disorder Disorders" combines anxiety disorders preceded by an anxiety or traumatic event and clearly identifies the criteria for a traumatic event. Special attention is paid to sexual violence. Adaptive disorders are redefined as an array of stress response syndromes that occur after contact with an alarm event.

According to DSM-5 criteria, for AD diagnosis emotional or behavioral symptoms should develop within three months after identifiable stress had taken place (A). Symptoms or behavior are clinically significant, as evidenced by one or both of the following (B):

1. A pronounced disorder that does not correspond to the severity or intensity of the stressor, even with an external context and cultural factors that may affect the severity of the symptoms and presentation.
2. Significant deterioration in social, professional or other fields of functioning.

A stress-related disorder does not meet the criteria of another mental disorder and is not simply an aggravation of a pre-existing mental disorder (C). Symptoms do not represent a normal bereavement (D). After the termination of the stressor (or its consequences), the symptoms persist for no more than 6 additional months (D) [5], [6].

Symptoms may include: a feeling of sadness, hopelessness or lack of enjoyment with the things you used; frequent

crying; feeling of anxiety, nervousness, stress; problems with sleep; lack of appetite, concentration of attention; a sense of congestion; difficulties in daily activities; a sense of lack of social support; avoidance of important things (such as work or paying bills); suicidal thoughts or behavior. The persistent or chronic AD can last more than 6 months, especially if the stressor continues, for example, in case of unemployment. Many publications note that AD is most often (up to 37%) observed in primary health care facilities and outpatient psychiatric practice [7],[8]. The AD has high co-morbidity with depression, anxiety, mixed anxiety-depressive states, behavioral disorders, substance abuse.

1.2 Pathophysiological mechanisms of adjustment disorder

AD occurs when the need for adaptation exceeds the ability of a person to maintain a psychological or physiological balance. Adaptation at the physiological level is associated with the activity of monoamine neurotransmitters, hormones (e.g., glucocorticoids) and other neuromodulators that affect several areas of the brain and various organ systems [9]. Excessively high or low levels of glucocorticoids lead to neuronal atrophy, especially in the hippocampus, amygdala and prefrontal cortex (PFC), negatively affecting the grey matter volume in this regions. The disturbance in the PFC activation causes a deficit in the prefrontal cortical function and anomalies in the metabolism of mesocortical dopamine (DA), which leads to hyperactivation of the amygdala, hippocampus, and locus coeruleus. Such changes can provoke hypothalamic-pituitary-adrenal axis hyperactivation, disrupt the metabolism of serotonin, enkephalins, glutamate, etc., and promote the development of mental and behavioral disorders [10]. At the same time, a decrease in the effect of PFC on subcortical reactions potentiates the development of new stress reactions, affects the specific behavior of the individual, including sleep, impulsivity or isolation, autonomic responses, movements and sensitivity to pain. Any of these symptoms may be due to an uncontrolled or excessive reaction to stress. For example, loss of control over suicidal impulses may be associated with a decrease in the availability of serotonin and an increase in serotonin-2A receptor activity [11]. Serum levels of protein carbonyl groups and nitrosylated proteins, which are biological markers of oxidative stress, have been studied [12]. Biomarkers have been identified, suggesting the direct role of oxidative stress in reg-

ulatory disorders.

At the same time, pathogenetically approaches to AD therapy are not fully understood [9], [13]. The studies on AD treatment have revealed an excessive use of different classes of antidepressants without taking into account the concept of time-limited AD [9],[13]. A retrospective analysis aimed at evaluating the effectiveness of antidepressants in patients with AD did not show any difference in the clinical response to any particular antidepressant. The primary statistical difference consisted in the frequency of responses when patients diagnosed with AD were twice as likely to respond to standard antidepressant treatment (approximately 70% of cases) than patients diagnosed with depression. It was found that all antidepressants are equally effective and more efficient than other agents in the treatment of AD, while drugs combinations can increase the risk of possible side effects [14]. The presence of suicidal risk in patients with a this diagnosis requires the choice of the safest treatment.

Modern pathogenetically oriented therapy of AD should be targeted on neurotransmitter causes and use systemic therapeutic approach, taking into account, first of all, the safety of the drugs. In this aspect, in our opinion, the use of new classes of regulatory medications looks promising. Regulatory peptides have a wide spectrum of biological activity, which is of great importance in coordination of body functions, because of neuroendocrine, immunological, cellular and molecular interactions [15]. Regulatory peptides are related to the endogenous body compounds that bind the basic biochemical systems of the body and mediate the reactivity of the organism to various external factors. Exposure to negative environmental factors can increase the effects of regulatory peptides [16]. The advantage of peptide preparations is the extremely low probability of toxicity when administered even in large doses, since the products of their metabolism are natural amino acids that perform mainly homeostatic functions, which significantly reduces the likelihood of side effects. Selank (synthesized analogue of the endogenous regulator of immunity – taftcin) is one of the promising regulatory peptides in the AD treatment. Since it has an original mechanism of neurospecific action on the central nervous system, it affects the exchange of monoamines in the emotogenic structures of the brain (hypothalamus, limbic system) and the activity of brain enzymes tyrosine and tryptophan hydroxylase [17]. Anxiolytic and antidepressant action of “Selank” is associated with regulation at the genome level of the synthesis and metabolism of norepinephrine, serotonin,

and enkephalins in the emotional zones of the brain. “Selank” stabilizes the processes of excitation and inhibition in the brain and increases the stability of neurons of the cerebral cortex to functional loads of high intensity [18]. Thus, the complex action of the regulatory peptide, including neurometabolic, anxiolytic, psycho-stimulating effects, reducing asthenic symptoms and normalizing mental activity [19], allows it to be used in the therapy of AD.

2 Materials and methods of the research

In the study were included individuals aged 21 to 65 years, which were admitted to hospital for routine examination. The survey was conducted using the Health Questionnaire (PHQ) and Express Diagnostics of the Stress Level (BCS) (K. Schreiner, 1993) [20], [21]. Participants in the survey were divided into age categories 21-34 (n=153), 35-50 (n=257), and 51-65 years old (n=167). In the trial on the effectiveness of a regulatory peptide drug participated 30 patients, which met inclusion and didn't met exclusion criteria. The main (MG, n=15) and control group (CG, n=15) included patients with the diagnosed AD. The most prevalent complaints were a feeling of anxiety, nervousness, or stress related to work or family problems; problems with sleep; a sense of congestion; difficulties in daily activities. Each patient was informed of the study's purpose and objectives, medication's characteristics, possible side effects and signed informed consent. The patients from the control group (CG) didn't receive any medication. The groups were comparable in the all of the studied parameters. Psychotherapy, diet therapy, other medicament and non-drug therapies were not used.

Clinical examination included assessment of objective physical and mental status and measurement of physiological parameters. To clarify the nature and severity of psychoemotional status alteration, a PHQ health questionnaire was used [21]. Express diagnostics of the stress level was carried out according to the DSS questionnaire (K. Schreiner, 1993).

Performance parameters were evaluated at an interim and final visit compared to the initial state. Evaluation of the safety of therapy was conducted on the basis of registration of adverse events, analysis of complaints and subjective symptoms, their severity. Statistical processing of the results

was carried out using MS Excel and Statistic 6 software.

3 Results and discussion

The results of the screening revealed the following features in different age groups. The low level of regulation in stressful situations was detected in 31.4% of participants from the age group 21-34 years, 44.0% of participants aged 35-50 years and in 50.9% from the age group 51-65 years, which demonstrates decrease in stress resistance with age (Table 1).

As shown in Table 1, a high level of stress resistance also tended to decrease in the older age group.

The analysis of the clinical examination, including data regarding psychoemotional state and the PHQ, made it possible to assess the presence of somatic symptoms, nutrition characteristics, and attitudes towards alcohol use in the studied age groups. The results of the screening according to the PHQ health status questionnaire are presented in Table 2.

Despite the absence of complaints at the time of the survey, according to the questionnaire, during the last three weeks, 31.4% of participants in the 21-34 age group, 23.3% of participants aged 35-50 years and 50.9% of the age group the group of 51-65 years noted the presence of somatic (predominantly algic) pain with a frequency corresponding to high severity. In the studied sample, 34.6% of participants from the 21-34 age group, 34.2% of participants aged 35-50 years and 27.5% in the age group 51-65 years consumed alcohol more than twice a week. Among frequent reasons of alcohol consumption was to relieve tension and anxiety. Abnormal eating habits were absent in 34.6% of participants in the 21-34 age group, 22.2% of participants aged 35-50 years and 27.5% in the 51-65 age group. The rest noted that they had episodes of diet misuses.

The results of the screening study demonstrated the prevalence of a decrease in stress resistance and subjective deterioration in all age groups with an increase to 50.9% in the age group 51-65 years. The data obtained are comparable with international studies [3], [7], [8], [22], [23]. These studies emphasize the importance of assessing the condition of patients with the AD and choosing the safest therapy.

A study was made of the efficacy of the synthesized analogue of the endogenous peptide taftcin (Thr-Lys-Pro-Arg-Pro-Gly-Pro) in the treatment of symptoms of adaptation dis-

orders. The results of the study are presented in Table 3.

As shown in Table 3, the groups were comparable in the original parameters. In the MG group, at the end of the treatment, in the MG group symptoms improved statistically significant ($p < 0.05$) compared to baseline. AD symptoms improved more significantly in the MG group, compared to CG group ($p < 0.05$). In the CG, in turn, during the observation, not only the preservation of the initial symptomatology was noted, but there was a tendency to overeating and weight gain.

The average score of alcohol consumption in CG was 1.3 ± 0.4 . After 2 weeks of follow-up (28th day of the study), the number of alcohol users did not change, but the frequency of alcohol consumption increased, and the average score on this subscale increased to 1.5 ± 0.4 (Table 3). Two weeks after cessation of therapy with the regulatory peptide (analogue of the endogenous peptide taftcin), its positive effects with respect to the correction of the AD symptoms in MG remained significant (Table 3).

According to the analysis, the regulatory peptide had a significant positive effect on the emotion regulation and AD symptoms; moreover, medication had pronounced post-therapeutic effect. The study confirmed that "Selank" (synthesized analogue of the endogenous peptide taftcin) can be used for the treatment of AD. It significantly improves somatic symptoms, helps to reduce alcohol consumption and correct eating habits in patients with this diagnosis.

4 Conclusion

1. The pharmacological and therapeutic effects of the regulatory peptides, such as synthesized analogue of the endogenous peptide taftcin, is determined by the presence of a normalizing effect on the activity of the primary neurotransmitter systems of the brain.
2. The use of analogue regulatory peptides has a positive effect on the somatic and mental symptoms in patients with AD.
3. One of the therapeutic effects of the "Selank" is the preservation of psychoemotional health, which pre-determines its role not only for treatment but also for prevention of stress-related disorders.

5 Additional information

5.1 Competing interests

The authors have no conflicts of interest to declare.

Table 1: The indicators of stress-resistance in different age groups according to the data of rapid diagnostics of the state of stress (DSS).

Parameters/groups	21-34 years, N = 153	35-50 years, N = 257	51-65 years, N = 167
Mild regulation in stressful situations	48 (31.4%)	113 (44.0%)	85 (50.9%)
Moderate regulation in stressful situations	53 (34.6%)	85 (33.1%)	46 (27.5%)
Severe of regulation in stressful situations	52 (34.0%)	59 (22.9%)	36 (21.6%)

Table 2: Health indicators in different age groups according to the health questionnaire PHQ.

Parameters/groups	21-34 years, N = 153	35-50 years, N = 257	51-65 years, N = 167
Mild somatic symptoms	52 (34.0%)	89 (34.6%)	36 (21.6%)
Moderate somatic symptoms	53 (34.6%)	108 (42.1%)	46 (27.5%)
Severe somatic symptoms	48 (31.4%)	60 (23.3%)	85 (50.9%)
Mild alcohol use	52 (34.0%)	57 (22.2%)	36 (21.6%)
Moderate alcohol use	48 (31.4%)	88 (34.2%)	46 (27.5%)
Severe alcohol use	53 (34.6%)	112 (43.6%)	85 (50.9%)
Mild eating disorders	53 (34.6%)	57 (22.2%)	46 (27.5%)
Moderate eating disorders (overeating)	52 (34.0%)	112 (43.6%)	85 (50.9%)
Severe eating disorders (overeating)	48 (31.4%)	88 (34.2%)	36 (21.6%)

Table 3: The effectiveness of therapy with the synthesized analogue of the endogenous peptide taftcin in the study groups; assessment was performed with the PHQ scale.

Symptoms	Score	Baseline		14 days (end of treatment)		28 days (follow-up)	
		MG	CG	MG	CG	MG	CG
Somatic symptoms	Mean score	5.1±1.0	3.6±0.8	1.9±0.6*	-	1.2±0.5*/**	3.6±0.8
	Symptoms prevalence	100%	100%	80%	-	73%	100%
Nutritional disorders	Mean score	2.3±0.8	2.7±0.7	0.1±0.1	-	0.1±0.1*/**	3.4±0.6*
	Symptoms prevalence	73%	93%	13%	-	13%	100%
Alcohol consumption	Mean score	1.3±0.4	1.3±0.4	0.3±0.1	-	0.3±0.1*/**	1.5±0.4
	Symptoms prevalence	80%	73%	13%	-	13%	80%

Notes: * - statistically significant (p<0.05) compared to the initial state, ** - statistically significant (p<0.05) compared to CG.

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