Bilovol A.M., Tkachenko S.G.

THE LEVEL OF NEUROACTIVE AMINO ACIDS IN BLOOD PLASMA OF PSORIATIC PATIENTS

Kharkov National Medical University, Ukraine

Abstract*. Some amino acids neurotransmitters, such as glutamate, aspartate, glycine and γ-aminobutyric acid may be involved in the pathogenesis of psoriasis and hypertension. But their relationship with dermatosis severity and comorbidities are unclear. The aim of this study was to quantify level of activating and inhibitory amino acids in blood plasma of the patients suffering from isolated psoriasis and psoriasis combined with hypertension depending on severity of disease. The study was conducted on two groups of patients, first group consisted of 74 patients with isolated psoriasis, second group consisted of 48 patients with psoriasis combined with hypertension, control group comprised 30 practically healthy patients. Blood plasma level of glycine, glutamate, aspartate and γ-aminobutyric acid were defined by liquid chromatographic analysis.*

Severe course of psoriasis, especially combined with hypertension is characterized by excitatory and inhibitory mechanisms imbalance with signs of protective inhibition insufficiency; deficiency of GABAergic protective mechanisms along with increased release of excitatory amino acids determines the severity of psoriasis in this contingent of patients. Changes of the level of excitatory and inhibitory amino acids in blood plasma of psoriatic patients indicate their obvious participation in formation of cerebral circulation disturbance and autonomic regulation of peripheral vessels disorder.

Key words: *aspartate, GABA, glutamate, , glycine, neuroactive amino acids, psoriasis.*

This article is a fragment of the study “Diagnostic and prognostic aspects of cardio-metabolic disturbances in patients with systemic dermatoses” of the department of dermatology, venereology, medical cosmetology and the department of propaedeutic of internal medicine № 1 of Kharkiv national medical university, state registration № 0107U001393.

Introduction

Recently it has been prevailing view that psoriasis is a systemic disorder of multifactorial etiology with genetic and exogenous factors involvement, that results

in escalation of functional disorders, metabolic violation and launching of the mechanisms of pathological process formation [1-3].

The question of psoriatic patients' rehabilitation is very actual and socially significant. Treatment of this disorder has been difficult and controversial problem. Even initial and a fortiori prominent psoriatic manifestations often have complicated course, resistant to treatment, with predisposition to aggravation and relapses [4; 5]. In this regard, there is necessity to create a differentiated program of restorative treatment, aimed to boost functional reserves, development of compensatory mechanisms of the organism, prevention of aggravations and complications.

Despite fundamental studies of psoriasis, its many aspects remain poorly understood, especially regarding its combination with somatic diseases. These aspects include issues of cooperative interaction and the role of integrative systems of the body – neurological, endocrine and immunological [6-8].

Resolving of these allows in-depth approach to pathogenesis study from the perspective of multisystem evaluation of the homeostatic function based on the monitoring of metabolism indicators and on the condition of their regulating systems considering principal risk factors [9].

Amino acids glutamate and aspartate are widespread excitatory CNS neurotransmitters and play important role in homeostasis providing. GABAergic and Glutamatergic neurons are widespread in almost all brain structures that signifies undoubted importance of such type neurotransmission [10,11].

The goal of this study was to study the level of activating and inhibitory amino acids in blood plasma of the patients suffering from isolated psoriasis and psoriasis combined with hypertension depending on severity of disease.

The object and methods of the study.

The study was conducted on two groups of patients, age range from 40 to 65 having confirmed diagnosis of psoriasis, that were examined and treated in an outpatient dermatologic city clinic № 5 in Kharkiv (Ukraine). The first group consisted of 74 patients with isolated psoriasis, 40 of which had mild course of disease, 24 – moderate, and 10 – severe course. The second group consisted of 48

patients with psoriasis combined with hypertension, 22 of which had mild course of disease, 16 - moderate and 10 - severe course. Precise anamnesis and laboratory examination were conducted, that consists of generalclinical and biochemical analysis of the peripheral blood. Control group comprised 30 practically healthy patients.

Blood plasma level of glycine, glutamate, and aspartate were defined by liquid chromatographic analysis with amino acidic analyzer AAA-339 (Czech Republic). For calibration tests and quantitative evaluation of chromatographs there were used standard technical solutions of amino acids (the firm “Lachema”), that accompanied the reagent kit of amino acid analyzer. The level of γ-Aminobutyric acid (GABA) was defined after its segregation by chromatographic analysis by Carmona et.al method [12]. To measure the level of GABA there was conducted the reaction with ninhydrin. Fluorescence was measured under the excitation wave length of 380 nm and fluorescence of 450 nm. For processing and analysis of statistical information a computer kit Statistica 6.0 was used for mathematical analysis of the obtained numeral material.

Results of the study and its discussion.

During the conducted study there were determined changes of the level of excitatory amino acids in blood plasma (Table 1). There was statistically reliable increase of the level of glutamate and aspartate in patients with isolated psoriasis of moderate and severe course in comparison to the control group.

The raise of the level of glutamate was 42% and 76 % respectively, of aspartate – 22% and 57%. In case of isolated psoriasis of mild severity these indicators practically did not differ from the control group. In case of psoriasis combined with hypertension there was significant raise of the level of glutamate and aspartate, 53% and 31% in the group of mild severity, 90% and 109% in the group of moderate severity, and 130% and 191% in the group of severe course. It should be noted that the level of excitatory amino acids was statistically higher in patients with moderate and severe course of psoriasis combined with hypertension, in comparison to patients with isolated psoriasis.

Table 1.

The level of glutamate and aspartate in blood plasma of patients with psoriasis depending on its severity (M m).

Indicator	Control group		Severity of	disease
		mild	moderate	severe
		isolated	psoriasis	
glutamate	21,2 +_ 1,9	24,3 +_ 2,5	30,2 +_ 3,0*	37,3 +_ 3,6*
aspartate	5,23 +_0,50	5,92 +_0,53	6,36 +_0,60*	8,23 +_0,77*
	psoriasis	combined with	hypertension	
glutamate	21,2+_1,9	x32,4+_3,0*	x40,2+_3,7*	x48,7+_4,6*
aspartate	5,23 +_0,50	6,86 +_0,63*	x10,95 +_0,97*	x15,21 +_1,34*

Note: unit of measure is mmol/l; * - reliability in comparison to the control group ($p < 0,05$); x – reliability in comparison to isolated disease ($p < 0,05$).

Such results indicate that psoriasis, especially combined with hypertension, is accompanied by the release of excitatory mediators. As a consequence hyper stimulation of NMDA-receptors of N-metil-D-aspartate develops, that provokes dilatation of Ca-channels, massive entrance of Ca into the cell with consequent activation of proteases and phospholipase. Hyperenzymatic activity leads to interruption of integrity of the cell membrane and its organelles, first of all the internal membrane of mitochondria that significantly deepensenergetic disturbances.Glutamate receptor activation leads to synthesis of free radicals by activation of Ca-dependent arachidonic acid cascade, nitric oxide synthesis [10]. As previous studies have showed, psoriasis is accompanied by activation of glutamate receptors, that is one of launching mechanisms of free radical generation [13].

It is proved that under the normalconditions, there is a stable equilibrium between activity of Glutamatergic and GABAergic neurotransmitter systems. But in case of increased release of glutamate and aspartate the protectiveinhibition of CNS

increases, that is provided by such neurotransmitter amino acids as GABA and glycine.

The level of GABA and glycine in patients from isolated psoriasis group of mild severity practically did not differ from the control group.(Table 2). Patients from the same group but of moderate severity had reliable increase of these indicators in comparison to the control group, 23% and 35% respectively, and in case of severe course the patients had 21% and 23% decrease in these indicators.

In the group of psoriasis combined with hypertension the dynamic of these indicators was a bit different. In case of mild severity the level of GABA and glycine in blood plasma was reliably higher (on average on 28%) in comparison to the control. In case of moderate and severe course the level of inhibitory amino acids declined: GABA on 23% and 16%respectively, glycine on 34% and 27%.

Such dynamic of the level of neuroactive amino acids in blood plasma in patients with isolated and combined with hypertension psoriasis envisions significant changes of the effect that they make on the organism.

Table 2.

The level of GABA (γ-Aminobutyric acid) and glycine in blood plasma of patients with psoriasis depending on its severity (M +_ m).

Indicator	Control group		Severity of	disease
		mild	moderate	severe
		isolated	psoriasis	
GABA	46,8+_4,3	50,3+_4,9	57,5+_5,3*	37,1+_3,3*
glycine	5,23+_0,50	5,57+_0,52	7,06+_0,67*	4,03+_0,40*
	psoriasis	combined with	hypertension	
GABA	46,8+_4,3	59,7+_5,5*	x36,18+_3,8*	x30,9+_2,9*
glycine	5,23+_0,50	6,67+_0,63*	x4,38+_0,38*	3,84+_0,36*

Note: unit of measure is mmol/l; * - reliability in comparison to the control group ($p < 0,05$);

x – reliability in comparison to isolated disease ($p < 0,05$).

Thus, under the proper functioning of the cardiovascular system and metabolism, GABA concentration in the adrenal medulla is maintained on the constant level, that shows, on the one side, the high level of plasticity of the CNS metabolism, and, on the other side, it shows importance of the physiological role of GABA and its functions which are metabolic and transmitting. As a metabolic product of the adrenal medullar GABA has anti-hypoxic, vasodilating effect, under the normal conditions it almost does not go through the blood-brain barrier and acts mostly on the periphery.

During the compensation of disturbed cerebral circulatory dynamics the important role belongs to GABAergic system, that is one of the main elements of neuro-chemical regulation of cerebral blood flow under the normal and pathological conditions. Vascular effects of GABA are due to inhibition of sympathetic and activation of parasympathetic centers in the CNS, its effect on vascular GABA-receptors. Thanks to this GABA and its agonists decrease cerebro-vascular resistance, especially in case of increased arterial tonus [14 –16].

Concerning glycine, it is seen as possible regulator of autonomic nervous system disturbances [17]. There are data that glycine actively influences on hypothalamic mechanisms of vasomotor regulation. Moderate amount of glycine in autonomic ganglions and in tissues of some organs suggests the possibility of its participation in the peripheral regulatory mechanisms [18].

Having the results of decrease of the levels of GABA and glycine in blood plasma of psoriatic patients, especially in its severe course, allows us to make the conclusion about severe disturbance of the above mentioned effects of these mediators. We know that the main route of GABA synthesis in the cerebral tissue and in the walls of the cerebral arteries is its synthesis from glutamic acid. The increased glutamate level and decreased GABA level in blood plasma might show the inhibition of this metabolic route of glutamate and activation of others. Besides this, significant decrease of the level of inhibitory amino acids shoes ineffectiveness of inhibitory defense mechanisms. The raise of GABA and glycine levels in cases of

mild and moderate course of isolated psoriasis and mild course of psoriasis combined with hypertension indicates switching-on of the compensatory mechanisms of protectiveinhibition.

Conclusions

1. Severe course of psoriasis, especially combined with hypertension is characterized by excitatory and inhibitory mechanisms imbalance with signs of protective inhibition insufficiency; deficiency of GABAergic protective mechanisms along with increased release of excitatory amino acids determines the severity of psoriasis in this contingent of patients.
2. Psoriasis accompanied by Glutamate receptor activation, than is one of starters of free radical generation.
3. Changes of the level of excitatory and inhibitory amino acids in blood plasma of psoriatic patients indicate their obvious participation in formation of cerebral circulation disturbance and autonomic regulation of peripheral vessels disorder.
4. . Biochemical monitoring of the level of neuro active amino acids in blood plasma of psoriatic patients allows to monitor the effectiveness and validity of treatment.

References.

1. Huerta C., Rivero E., Rodríguez L. G. Incidence and Risk Factors for Psoriasis in the General Population// Arch Dermatol. -2007.-№ 143(12).-P.1559-1565.

2. Azfar RS, Gelfand JM. Psoriasis and metabolic disease: epidemiology and pathophysiology // CurrOpinRheumatol. -2008.- №20 (4).-P.416-22.

3. Ahdout J., Kim J., Chiu M.. Modifiable metabolic syndrome associated lifestyle factors in psoriasis patients // AcadDermatol.- 2009.- March.-P.3330

4. Zaghloul S. S., Goodfield M. J. Objective Assessment of Compliance With Psoriasis Treatment// Arch Dermatol.- 2004.-№ 140(4).-P.408-414.

5. Stern RS, Nijsten T, Feldman SR. Psoriasisis common, carries a substantial burden even when not expensive, and is associated with widespread treatment dissatisfaction // J.Investig.DermatolSympProc .- 2004.-№ 9(2).-P. 136-139

6. Davidovici B. B., Sattar N., Jörg P. C., Puig L., Emery P., Barker J. N.et al. Psoriasis and Systemic Inflammatory Diseases: Potential Mechanistic Links between Skin Disease and Co-Morbid Conditions// Journal of Investigative Dermatology.-2010.-№ 130,.-P.1785–1796.

7. Herron M.D., Hinckley M., Hoffman M.S., etal. Impact of obesity and smoking on psoriasis presentation and management // Arch. Dermatol. – 2005. – Vol. 141, № 12. – P.1527-1534.

8. Mallbris L., Granath F., Hamsten A., et al. Psoriasis is associated with lipid abnormalities at the onset of skin disease // J.Am. Acad. Dermatol. – 2006. – Vol. 54, № 4. – P.614-621

9. Ткаченко С.Г., Беловол А.Н., Кондрашова В.Б., Береговая А.А., Рыжкова Н.А., Штыров И.Н. Анализ международного опыта изучения коморбидности псориаза и метаболического синдрома // Український журнал дерматології, венерології, косметології.-№2(41).-2011.-С.29-36 Tkachenko S.G., Bilovol A.N., Kondrashova V.B., Beregovaya A.A., Ryshkova N.A., Shtyrov I.N. Analysis of international experience of psoriasis and metabolic syndromecomorbidity study // Ukrainian Journal of dermatology, venereology, cosmetology.-№2(41).-2011.-P.29-36

10. Hardingham N, Dachtler J, Fox K. The role of nitric oxide in pre-synaptic plasticity and homeostasis // Frontiers of Cellular Neuroscience. -2013.-V.7.-P. 1-19.

11. Wenner P. Mechanisms of GABAergic homeostatic plasticity //Neural Plast.-2011.-V.2011.-P.1-6.

12. Carmona E, Gomes C, Trolin G. Purification of GABA on small columns of Dowex 50W; Combination with a method for separation of biogenic amines// ActaPharmacolToxicol (Copenh).-1980.-№46(3).-P.235-240.

13. Cadet J.L., Brannock C.Invited Review Free radicals and the pathobiology of brain dopamine systems//Neurochemistry International .-1997.-Vol. 32. Issue 2.-P. 117–131.

14. Abboud F. M. The sympathetic system in hypertension. State-of-the-art review// Hypertension.-1982.-№ 4.-P.208-225.

15. Hamel E. Perivascular nerves and the regulation of cerebrovascular tone // Journal of Applied Physiology.- 2006.-Vol. 100(3).- 1059-1064

16. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease // Nature reviews. Neuroscience.-2004.- Vol. 5.-P. 347-360

17. Coote J. H. Landmarks in understanding the central nervous control of the cardiovascular system// Experimental Physiology.-2007.-Vo. 92. Issue 1.-P. 3–18.

18. Llewellyn-Smith I. J. Anatomy of synaptic circuits controlling the activity of sympathetic preganglionic neurons //Journal of Chemical Neuroanatomy.-2009.- Vol. 38. Issue 3.- P. 231–239

Received: 07.04.2014 *Accepted: 14.05.2014*