CORRELATIONS BETWEEN SERUM LEVELS OF HISTAMINE, DIAMINE OXIDASE, SUBSTANCE P IN PATIENTS WITH CHRONIC URTICARIA

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The onset and progression of various disorders, including chronic urticaria, are associated with stress. The gut-brain-skin axis is used to describe correlations among the nervous system, gastrointestinal tract states and systemic and skin inflammation. We have summarized inflammatory and immune mechanisms underlying chronic urticaria and stress in the context of the gut-brain-skin axis. The study was aimed to show the relationships between substance P, the neurotransmitter, and diamine oxidase, the enzyme disrupting histamine in the gut of patients suffering from chronic urticaria. A total of 165 adults aged 18–68 were enrolled; 97 patients had chronic urticaria, the comparison group was formed of 68 nominally healthy individuals. ELISA (Cloud-Clone Corp; China) was used to simultaneously estimate serum levels of substance P, diamine oxidase, and histamine. We revealed a significant positive correlation ($\rho = 0.5$; $p < 0.05$) between substance P and diamine oxidase in patients with chronic urticaria and in the comparison group, which confirmed the existence of the gut-brain-skin axis. The paper provides theoretical background and new targets for treatment of chronic urticaria. The possibility of prevention and treatment of these disorders by modulation of gut microbiota is discussed, the place of diet and the lifestyle modification contributing to improvement of general health are determined.

Keywords: substance P, diamine oxidase, histamine, chronic urticaria, stress, gut-brain-skin axis

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ВЗАИМОСВЯЗЬ УРОВНЕЙ ГИСТАМИНА, ДИАМИНОКСИДАЗЫ И СУБСТАНЦИИ Р В СЫВОРОТКЕ КРОВИ У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ КРАПИВНИЦЕЙ

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Возникновение и прогрессирование различных заболеваний, в том числе хронической крапивницы, связаны со стрессом. Ось кишечник-мозг-кожа используют для объяснения корреляций между состоянием нервной системы, желудочно-кишечного тракта, а также системным и местным воспалением в коже. В контексте оси кишечник-мозг-кожа мы обобщили воспалительные и иммунные механизмы хронической крапивницы и стресса. Целью нашего исследования было показать взаимосвязь между нейротрансмиттером субстанцией Р и диаминоксидазой, ферментом, разрушающим гистамин в кишечнике у пациентов, страдающих хронической крапивницей. В исследование было включено 165 взрослых людей от 18 до 68 лет, 97 пациентов страдали хронической крапивницей, группу сравнения составили 68 условно здоровых лиц. Методом ИФА (Cloud-Clone Corp; Китай) одновременно оценивали уровни субстанции Р, диаминоксидазы и гистамина в сыворотке крови. Была выявлена прямая заметная корреляционная связь ($\rho = 0,5$; $p < 0,05$) между субстанцией Р и диаминоксидазой у пациентов, страдающих хронической крапивницей, и в группе сравнения, что подтвердило наличие оси кишечник-мозг-кожа. В статье представлены теоретическая основа и новые цели для лечения хронической крапивницы. Обсуждена возможность предотвратить и лечить эти патологические состояния путем модуляции микробиоты кишечника, определены место диеты и изменения образа жизни, способствующие улучшению состояния здоровья в целом.

Ключевые слова: субстанция Р, диаминоксидаза, гистамин, хроническая крапивница, стресс, ось кишечник-мозг-кожа

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The fast-paced life of today's society and recent events starting from the pandemic of novel coronavirus infection cause severe anxiety and stress. This results in numerous adaptive physiological alterations of the cardiovascular, endocrine, nervous systems, thereby significantly disturbing the human body's allostasis. The essence of allostasis is that physiological systems continuously fluctuate to adjust to the environment [1]. Physical and psychological stress can be acute or chronic,

depending on the duration and intensity. Acute stress in associated with a sudden, short-term, isolated, unique incident, such as a traffic accident, surgical intervention [2]. Chronic stress results from the long-term and frequently repeated exposure to psychogenic or physiological stressors. This causes endocrine and behavioral responses regulated by various neurochemical systems. Strong association between stressful life events and disorders of the cardiovascular, endocrine, nervous, respiratory systems, cancer, gastrointestinal tract and skin disorders is well known [3].

The term "axis" was accepted as the one describing a two-way relationship between the nervous system and other systems, such as gastrointestinal tract, skin. The gut-brain axis is the best-studied one. The concept of the gut-brain axis includes not only classical autonomic nervous system pathways, sympathetic and parasympathetic, but also endocrine interactions (hypothalamic-pituitary-adrenal axis), connections between cognitive and emotional functions in the brain [4]. Communication involves the enteric nervous system, metabolic pathways [5]. Mast cells are important effector cells of the gut-brain axis. When exposed to stress, these cells release a broad range of neurotransmitters and pro-inflammatory cytokines capable of affecting the gastrointestinal tract physiology [6]. Activation of the vagus nerve by cytokines stimulates anti-inflammatory responses of neurons, since acetylcholine, the main neurotransmitter of the vagus nerve, impairs the release of such cytokines, as tumor necrosis factor alpha (TNFα), interleukin 1β (IL1β), IL6, and IL18. The immune cells produce various neurotransmitters, thereby affecting serotonergic systems, regulate mood and behavior. For example, leukocytes synthesize and release corticotropin and endorphins in response to bacterial lipopolysaccharides [4]. Stress and sadness modulate hunger and dietary habits. High calorie foods can improve the well-being. Food also represents an important factor affecting the gut microbiome [7].

Microbiome plays an important role in human health, homeostasis, immune system, and disease pathogenesis [7]. The disrupted link between microbiome and the host body has been actively studied in individuals with gastrointestinal tract disorders. The researchers have shown that chronic stress activates caspase-1, thereby affecting the gut microbiome composition, which results in the reduced abundance of *Akkermansia spp*. and *Blautia spp*. and the increase in the ratio of *Firmicutes/Bacteroidetes* [8], *Escherichia coli*, and *Bacteroides fragilis* [9]. The type I IL1 receptor and its ligands are expressed in the brain regions responsible for brain response to stress and transmission of IL1β signals, which is fundamental for mediating neurobehavioral and neuroendocrine responses to stress and adaptation. Various stressors activate inflammation via NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) or P2X7 (purinergic ligand-gated ion channel 7 receptor) receptors, which results in maturation of caspase-1 causing the IL1β and IL18 release. The levels of caspase-1 and NLRP3 mRNA are elevated in blood cells of patients with depression [8]. Depression and anxiety are the best understood mental disorders associated with the gut-brain axis. It has been confirmed that the tryptophan precursor suppression is associated with the gut microbiome. Considering the antimicrobial and anti-inflammatory effects associated with the gut microbiota restoration using antidepressants, it was proposed to treat depression and anxiety disorders through manipulation of microbiome and the gut-brain axis [4]. In the recent study, the relationship between the gut microbiome disruption severity and the severity of cognitive impairment was assessed in children with autism spectrum disorder [10]. The other study showed that gut microbiota composition alteration could contribute to the development of neurodegenerative process [11].

Diet plays an important role in determining the gut microbiota composition. Metabolites produced by gut microbiota not only modulate the mucosal immune response, but also affect lungs and the brain. Microaspiration of bacteria or travel of the sensitized immune cells through lymph and blood can also affect the immune response of other organs. Gut dysbiosis is associated with a number of lung diseases, including asthma and cystic fibrosis. The two-way relationships between the gut and lungs (gut-lung axis) are exemplified by the intestinal issues observed in individuals with lung diseases. The study has shown that mucosal immune cells can migrate through the lymphatic system, which determines the immune response of various organs (gastrointestinal tract, lungs, etc.). The T and B cells of Peyer's patches can travel through bloodstream and migrate to both intestine and extraintestinal sites (including bronchial epithelium and lymphoid tissues) [12]. It has been shown that immune cells (T and B cells that secrete sIgA and ensure mucosal immunity) found in the lamina propria of the gut and mesenteric lymph nodes neutralize the majority of translocating bacteria, however, fragments of dead bacteria travel from the mesenteric lymphatic system to systemic circulation. These bacterial fragments and metabolites can modulate immune response in the lung [13]. Perhaps, there is a similar pathophysiological pattern involving other systems of human body.

There is emerging research on the skin microbiome and its association with the gut [14]. There are papers describing the gut-brain-skin axis [15]. Thus, the correlations among gut mictobiota, emotional states and systemic and skin inflammation have been reported. Gut dysbiosis contributed to the Th17-mediated skin inflammation via the IL23, IL17 signaling pathway by increasing production of IL22 and interferon gamma (IFNγ), which resulted in hyperproliferation of keratinocytes [16]. The skin responses caused by stress primarily involve cytokine (for example, IL6, IL1, IFNγ) secretion and activation of peripheral corticotrophin-releasing hormone of the skin produced by sebocytes, keratinocytes, and mast cells [17]. The nervous, endocrine, and immune systems have many common mediators (for example, neurotransmitters, neuropeptides, hormones, cytokines) capable of modulating the nervous system activity during stress [18, 19]. Peripheral nerves in the skin mediate neurogenic inflammation by releasing neuropeptides (substance P (SP), brain-derived neurotrophic factor, and nerve growth factor). Thus, SP is a pro-inflammatory neuropeptide that is related to stress. The SP biological activity is mediated primarily by the neurokinin receptors (NK)-1. The SP/NK-1 receptor pathway can be activated in response to the stress stimulation of both autonomic and central nervous systems. The study has shown that NK-1 is expressed mostly in mast cells, which suggests the important role of the NK-1 receptor activation in the mast cell degranulation caused by stress [20]. Other researchers have shown that SP can be involved in the corticotrophin-releasing hormone-mediated mast cell degranulation during stress [21]. It has been also shown that SP can increase virulence of the skin microbiome due to alterations in bacterial cytoskeleton, which can represent one more mechanism contributing to its role in neurogenic inflammation [22]. High SP levels were observed in depression suggesting that the depression pathogenesis was associated with SP/NK-1 [20].

Great interest in the issue is indicative of its relevance, therefore, the study was aimed to show the relationship

Table. Correlations between the indicators Histamine — Diamine oxidase, Substance P — Diamine oxidase in patients included in the study on chronic urticaria

Indicator	Histamine — Diamine oxidase	Substance P — Diamine oxidase
Correlations in the comparison group (n = 68)	–0.4	0.5
Correlations in the group of patients with chronic urticaria (n = 97)	–0.4	0.5
Correlations for all people included in the study (n = 165)	–0.4	0.5

Note: ρ — degree of correlation.

between the SP neurotransmitter, and diamine oxidase, the enzyme disrupting histamine in the gut of patients suffering from chronic urticaria.

METHODS

The study involved assessment of substance P, diamine oxidase, and histamine in patients suffering from chronic urticaria. Enzyme-linked immunoassay (Cloud-Clone Corp; China) was used to simultaneously estimate three serum inducators in patients with chronic urticaria and in the comparison group. A total of 165 adults aged 18–68 were enrolled. Among them 97 patients with chronic urticaria had been receiving outpatient treatment at the Nikiforov's All-Russian Center for Emergency and Radiation Medicine, EMERCOM of Russia, in 2018–2023. Recurrent urticaria and/or angioedema occurring throughout 6 weeks or more were considered to be the inclusion criteria. The diagnosis of chronic urticaria was established in accordance with the Federal Clinical Guidelines on the Diagnosis and Treatment of Urticaria [23]. The comparison group consisted of 68 nominally healthy individuals matching those of the index group in gender and age with no signs of urticaria or allergic disorders.

Medical and social history of each subject was taken; great attention was paid to the triggers of chronic urticaria, the existing comorbidity. Food intolerance was a trigger in 46 patients suffering from chronic urticaria out of 97; 27 patients reported stress as a trigger of the disease.

The R program for Windows was used for statistical data processing, the correlations among the studied substance P, diamine oxidase and histamine were assessed using the Spearman's rank correlation coefficient. The Chaddock scale was used for more accurate assessment of correlation strength. The differences between the indicators compared were significant at p-value < 0.05.

RESULTS

We assessed correlations among the studied substance P, diamine oxidase and histamine using the Spearman's rank correlation coefficient. The correlations of diamine oxidase with histamine and diamine oxidase with substance P turned out to be significant (p < 0.05) (Table).

The correlation analysis yielded a moderate negative correlation between histamine and diamine oxidase, the enzyme ensuring histamine degradation. A significant positive correlation between substance P and diamine oxidase attracts attention (Figure).

DISCUSSION

The substance P neuropeptide can form an almost direct link between the skin and the brain. The diamine oxidase enzyme synthesized by apical cells of the intestine can be affected by various mechanisms, from genetic suppression of activity to the impact of microbiome [24]. Recently, diamine oxidase has been proposed as a marker of mucosal integrity [25].

When reviewing the literature, we have found only one paper reporting simultaneous assessment of substance P and diamine oxidase [26]. In 2023, the results of the experimental study, during which the authors studied irritable bowel syndrome (IBS) caused by stress in the rat model, were published. High expression of SP and diamine oxidase associated with IBS was reported. In recent years, it is believed that IBS is induced by a combination of factors, such as changes in visceral sensitivity, disturbances of the gastrointestinal function and the gut-brain axis, including microbiome alterations [27]. Diamine oxidase, as an enzyme produced in the villi of the intestinal mucosa, reflects disruption and repair of the epithelium, is released into blood or the intestinal lumen after the intestinal mucosa disruption and necrosis. Normal serum levels of diamine oxidase are very low, however, these increase with increasing inflammation due to the release of large amounts of the enzyme into blood. In our study we noted an upward trend in serum levels of diamine oxidase and substance P associated with exacerbation of chronic urticaria relative to the comparison group. However, we have revealed a significant increase in the levels of diamine oxidase and substance P in patients suffering from urticaria without exacerbation, which confirms persistence of inflammation during remission and requires further investigation.

CONCLUSIONS

The study has confirmed the correlations between the substance P neurotransmitter and diamine oxidase, the enzyme degrading histamine in the gut, in both patients suffering from chronic urticaria and comparison group. This confirms the existing hypothesis of the gut-brain-skin axis.

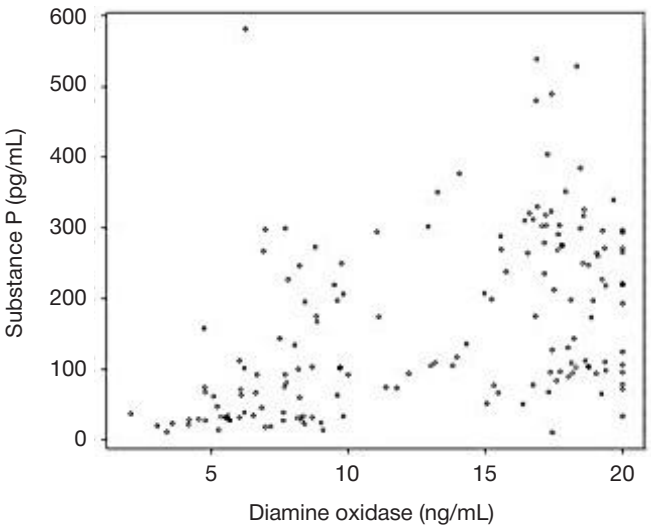

Figure. Scatter plot reflecting the correlation of substance P and diamine oxidase

However, the chronic urticaria pathogenesis represents a multifactorial complex of changes in the immune system and the gut-brain-skin axis signal transmission. The currently available approaches to treatment of urticaria are clearly defined, but not always successful. The today's guidelines on diamine oxidase deficiency are focused mainly on the diet and the use of dietary supplements. However, diet is not always effective; perhaps, in the future dietary treatment will be based on the features of human microbiome as well. The other targets of interest are represented by the effects on neurotransmitters, which will probably form the basis for treatment methods, along with the microbiome modulation following personalized profiling. It is recommended to use all the methods focused on stress correction and allostasis maintenance, including not only diet, but also adequate amount of quality sleep, positive social interactions. The effects on all the links of the gut-brain-skin axis contributing to allostasis can help recovery, since the innate adaptive plasticity of the brain can more effectively influence other systems [28].

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