EXPERIMENTAL PAPERS

Peculiarities of Endoplasmic Reticulum Stress Regulator XBP1 Expression in the Gut-Associated Lymphoid Tissue of Wistar Rats under Chronic Stress

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Abstract—Chronic social stress (CSS) can cause physiological disturbances, provoking the development of depression and anxiety, and stress-induced immune dysregulation is a trigger for the development of many pathological conditions, including inflammatory bowel diseases. New data in human and animal models suggest an intriguing relationship between endoplasmic reticulum stress, depression and inflammation. Under cellular stress, the number of protein folding disorders increases, which leads to the development of endoplasmic reticulum stress (ERS). The ERS, in turn, activates the "unfolded protein response" system (unfolded protein response, UPR), the IRE1—XBP1 signaling system is very important. The transcription factor XBP1 is responsible for regulating the expression of a large number of genes involved in the proper folding and maturation of proteins, the degradation of misfolded proteins and regulation of immune responses. In addition, changes in XBP1 expression can significantly affect the risk of developing the disease and the progression of inflammatory and autoimmune diseases, including inflammatory bowel disease.

The situation that has developed in recent years in modern society is characterized by a high level of social tension, in which stresses acquire a prolonged character. Activation of the reaction to stress leads to changes associated with the body's ability to adjust its homeostasis and thus minimize the potential impact of the threat. However, chronic social stress can cause physiological disorders not only in the neuroendocrine system, provoking the development of depression and anxiety, but also lead to changes in the functioning of innate and adaptive immunity, and stress-induced immune dysregulation is a trigger of the development of many pathological conditions, including inflammatory bowel diseases [1].

It is known that even under normal physiological conditions, up to 30% of proteins synthesized on ribosomes have disturbed tertiary and quaternary structure (so-called "defective ribosomal products") [2—4]. Under conditions of cellular

stress, the number of such proteins with impaired folding increases even more, leading to the development of endoplasmic reticulum stress (ERS) and functional overload of the molecular chaperone system and ubiquitin-proteasome system [2, 5]. This, in turn, disrupts the level of presentation of endogenous peptides to antigen-presenting cells and can lead to the development of autophagy, apoptosis or inflammation [6, 7]. The unfolded protein response (UPR) system, which is essential for preserving the functional integrity of cells, is activated as a counteraction to the development of ERS [3−5]. This process is protective and adaptive in nature, allowing cells to neutralize the disturbances associated with UPR. However, if protein synthesis, folding, transport and degradation are not normalized, apoptosis develops in the cell due to direct activation of proteases (endoplasmic reticulum-specific caspase 12), a number of protein kinases (Ask, JNK, p38 MARK) and transcription factors (ATF4, ATF6) [6−9].

Among the three canonical pathways regulating ER development, the IRE1−XBP1 signaling system is extremely important. Under ERS, the transmembrane kinase/endoribonuclease IRE1 is activated, which specifically recognizes the 5' and 3' splice sites of XBP1 mRNA and excises the 2nd nucleotide intron, a short sequence 26 bp long [2, 10]. This leads to a shift in the reading frame and translation of the active transcription factor XBP1, which is 376 amino acids long. The formation and accumulation of the splicing form of *XBP1* gene mRNA is a characteristic marker of IRE1−XBP1 signaling pathway activation of UPR system that coordinates metabolic and immune responses [11−14]. It is this alternative splice variant of the XBP1 transcription factor that is responsible for regulating the expression of hundreds of genes involved in proper protein coagulation and maturation, including the degradation of misfolded proteins [10].

As is known, the transcription factor XBP1 (X box-binding protein 1) was originally identified as a critical factor in the regulation of gene expression of the major histocompatibility complex (MNS) class II in humans in the early 1990s. Later, a number of studies on experimental rodent models showed the key role of XBP1 in the regulation of immune reactions, in particular the production of proinflammatory cytokines. And changes in the level of XBP1 transcriptional activity had a significant impact on the risk of inflammatory and autoimmune diseases, including inflammatory bowel diseases, since a decrease in its expression blocked the production of antimicrobial peptides by Paneth cells, caused the development of ERS, hyperactivation of IRE1 and could further lead to activation of proinflammatory cytokine genes, development of chronic inflammation and cell death (primarily, autophagy) [4, 6, 7, 10].

There is interesting data on the presence of a functional connection between ERS and chronic social stress, in particular, a number of works have shown the relationship of the "response to unconverted proteins" system with the development of stress-induced depression and cognitive disorders in rats [15−17], and changes in the expression level of key regulators PERK, IRE1a and ATF6a induced apoptosis development under chronic social stress [18, 19]. This, in turn, suggests the involvement of ERS in the development and progression of inflammatory and autoimmune diseases under conditions of chronic social stress (CSS).

Taking into consideration the literature data, we assumed that one of the possible mechanisms of changes in the functional state of immune structures associated with gastrointestinal mucosa under conditions of CSS was a decrease in the expression of the transcription factor XBP1, and as a consequence, impaired differentiation and survival of dendritic cells, B- and T-lymphocytes with subsequent activation of proinflammatory cytokine production by immune cells.

Therefore, the aim of the present work was to study the expression level of XBP1 mRNA, proinflammatory cytokines IL-1β, IL-17α in intestinal-associated lymphoid tissue in Wistar rats in experimental models of CSS.

MATERIALS AND METHODS

The researches were carried out on 60 mature female Wistar rats. All procedures performed in the studies involving animals were in compliance with ethical standards approved by legal acts of

Ukraine, principles of Basel Declaration and recommendations of the Bioethics Commission of the Institute of Physiology of NAS of Ukraine (from 21.02.2006 no. 3447-IV). The animals were randomly divided into 3 experimental groups of 20 rats each: control rats (group 1) kept under standard conditions with free access to water and food, such parameters as temperature and humidity were kept constant throughout the experiment. The rats simulated chronic social stress CSS1 through three weeks of social isolation and prolonged psycho-emotional exposure were kept under conditions of permanent living of females in an "aggressive environment", namely through a perforated partition in a cage with an aggressive male, daily confronted with another male placed in his cage (group 2). Group 3 consisted of rats that simulated CSS2 by keeping the animals in overpopulated cages with a daily change of grouping, with the experimental female being placed in a new balanced and overpopulated colony every day.

To obtain evidence that the rats really developed social stress, expressed by the manifestation of anxiety and depression, characteristic behavioral tests were performed. The level of emotional-behavioral and exploratory activity was studied in the "open field" and "partition" tests, where these parameters were assessed by the number of fecal boluses, rearing, sniffing, freezing, time and number of grooming, and seeking shelter [20]. In the Porsolt test ("forced swimming"), the level of animal depression was determined by the time of passive swimming and manifestation of the first immobility [21].

The objects for molecular genetic studies by reverse transcription-polymerase chain reaction (RT-PCR Real-time) were clustered lymphoid nodules of the ileum (Peyer's patches), which were placed in a Bouin solution, dehydrated in ascending concentrations of ethanol, and paraffinized.

Total RNA extracted from 15-μm-thick histological sections by preliminary deparaffinization in xylene followed by rehydration in descending concentrations of ethanol (100%, 96%, 70%) and homogenization using a mortar and pestle was performed using the Trizol RNA Prep 100 kit (Isogen Lab, LTD, Russia), which contained Trizol reagent (a lysis reagent containing the denaturing agent guanidine thiocyanate and phenol, pH 4.0) and ExTraGeneE (a suspension of a mixture of ion exchangers). The reaction was prepared and performed according to the kit protocol.

The concentration and quality of the isolated total RNA were determined on a LibraS32PC spectrophotometer (Biochrom Ltd., England). For the subsequent reverse transcription (RT) procedure, RNA samples were selected with the following parameters (according to the optical density ratio A260/A280): 260nm/280nm = 1.8–2.2.

To perform OT and obtain cDNA, 2 μL RNA and the OT-1 kit by Syntol (Russia) were used. A CFX96 Real-Time PCR Detection Systems amplifier (Bio-Rad Laboratories, Inc., USA) and Maxima SYBR Green/ROX qPCR MasterMix (2X) reagent kit (Thermo Scientific, USA) were used to determine the expression level of the studied genes. According to the manufacturer's instructions, the final reaction mixture for amplification included SYBR Green dye, Maxima HotStartTaq DNA Polymerase, 0.3 mM forward and reverse specific primers, and 1 μL matrix (cDNA). The reaction mixture was brought to a total volume of 25 μL by adding deionized H_2O. Specific primer pairs (5'−3') for the analysis of the studied and reference genes were selected using PrimerBlast software (www.ncbi.nlm.nih.gov/tools/primer-blast) and manufactured by Metabion (Germany) (Table 1). Amplification was performed under the following conditions: initiated denaturation at 95°C, 10 min; then 50 cycles: denaturation—95°C, 15 s; primer annealing—58–63°C, 30 s; elongation—72°C, 30 s. Fluorescence intensity was recorded automatically at the end of the elongation stage of each cycle using the SybrGreen automatic channel. The glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was used as a reference gene to determine the relative value of the change in expression level of the studied genes. The relative normalized amount of cDNA of the target genes was determined by the ΔΔCt method. The data were normalized to the mean of the control group and logarithmized on base 2 to result in a normal distribution. Negative controls were included in the

Table 1. Specific primers, which were used in real-time RT-PCR

Gene	GenBank accession	Primer
XBP1	NC_051349.1	F = 5'-ACACGCTTGGGA ATGGACAC-3'
		R = 5'-CCATGGGAAGATGTTCTGGG-3'
Il17a	NC_051344.1	F = 5'-CTGGACTCTGAGCCGCAATG-3'
		R = 5'-TGCCTCCCAGATCACAGAAG-3'
Il1b	NC_051338.1	F = 5'-TCTTTGAAGAAGAGCCCGTCC-3'
		R = 5'-GGTCGTCATCATCCCACGAG-3'
GAPDH	NC_051339.1	F = 5'-GCCTGGAGAAACCTGCCAAG-3'
		R =5'-GCCTGCTTCACCACCTTCT-3'

F, direct primer; R, reverse primer.
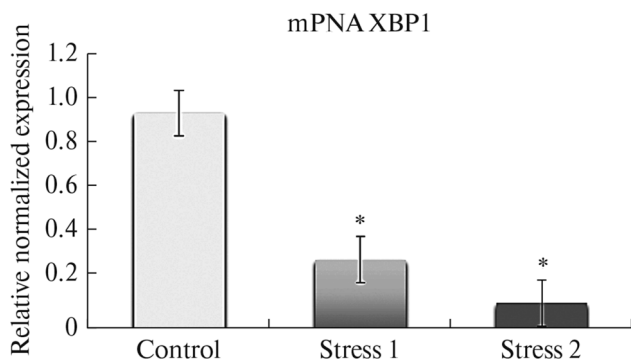
Fig. 1. Relative normalized amount of *XBP1* gene mRNA. Normalization by the $\Delta\Delta Ct$ method with the *GAPDH* reference gene. *—The differences between the control and experimental groups, $p < 0.05$.

experiment: no added cDNA matrix in the PCR reaction, no added mRNA matrix in cDNA synthesis, and no added enzyme in cDNA synthesis. All amplification reactions were performed on individual samples in three replicates. A total of 10 female rats from each experimental group were used in this experiment.

Statistical analysis of PCR data was performed using CFX Manager™ software (Bio-Rad, USA). The Kolmogorov−Smirnov test was used to test the hypothesis about the nature of the distribution of the data under study. To confirm the hypothesis of normal distribution we used parametric unpaired t-criterion, and to reject the hypothesis we used nonparametric unpaired Mann−Whitney U−criterion. Significance of the obtained results was assessed by means of a single-factor analysis of variance, Dunnett's criterion was used as an a posteriori criterion. The critical level of significance for statistical hypothesis testing was taken to be 0.05.

RESULTS

It is known that changes in XBP1 expression can significantly affect the level of proinflammatory cytokine production and further lead to the development of inflammatory and autoimmune diseases. In this regard, our work analyzed the transcriptional activity of XBP1/pro-inflammatory cytokine genes IL-1β, IL-17α in gut-associated lymphoid tissue.

According to our data, the level of XBP1 mRNA expression in the cells showed a downward trend. Thus, in experimental models, this index decreased 3.1-fold ($p < 0.05$) for CSS1 and 8-fold ($p < 0.05$) for CSS2 compared to the control group of rats (Fig. 1).

The development of chronic social stress was also accompanied by significant changes in the expression of *IL-1*β and *IL-17*α genes in the gut-associated lymphoid tissue of rats, more pronounced in the case of CSS1. In particular, this study found a unidirectional increase in the transcriptional activity of *IL-1*β (6-fold ($p < 0.05$) for CSS1 and 2.8-fold ($p < 0.05$) for CSS2); *IL-17*α (2.3-fold ($p < 0.05$) for CSS1 and 53% ($p < 0.05$) for CSS2) compared to the control group of animals (Figs. 2, 3).
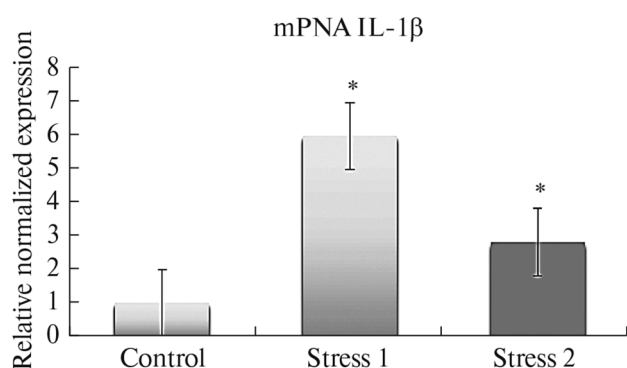
Fig. 2. Relative normalized amount of *IL-1*β mRNA in gut-associated lymphoid tissue cells. Normalization by the ΔΔ Ct method with the *GAPDH* reference gene. *—The differences between the control and experimental groups, $p < 0.05$.
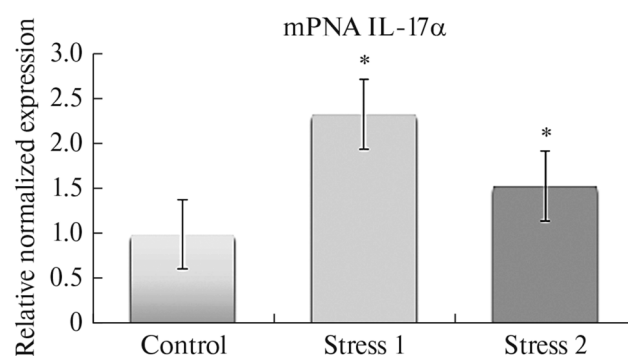
Fig. 3. Relative normalized amount of *IL-17*α mRNA in gut-associated lymphoid tissue cells. Normalization according to the ΔΔCt method with the *GAPDH* (glyceraldehyde-3-phosphate dehydrogenase) reference gene. *—The differences between the control and experimental groups, $p < 0.05$.

DISCUSSION

According to the literature data, XBP1 is one of the key transcription factors inducing response to unconjugated proteins and a powerful regulator of proinflammatory cytokine genes. Therefore, changes in its expression under conditions of stress factors of various nature, including chronic social stress, according to several authors, can significantly influence the level of proinflammatory cytokine production (IL-1β, IL-6, IL-17α and TNF-α) and further lead to the development of inflammatory and autoimmune diseases [22−27]. In the present study, we found that in all groups of animals against the background of experimental models of CSS1 and CSS2 there was a significant decrease in the mRNA expression level of XBP1. This, in turn, was accompanied by activation of IL-17α and IL-1β production by immune cells. Probably, the deficiency of XBP1, caused, according to our study, by social stress, was one of the mechanisms that led to the development of ERS and, as a consequence, contributed to the increased transcriptional activity of *IL-1*β and *IL-17*α genes. And this fact has been confirmed in a number of works [6, 18, 24, 26−28]. For example, the Lotrich study found that elevated levels of IL-6, TNF-α, IL-1β and their soluble receptors were mediated by UPR in patients with severe depression [28]. And the work of Liu et al. and Zhang et al. on animals demonstrated the relationship between changes in XBP1 expression and the development of inflammatory processes in chronic social stress [15, 29].

In addition, an important link between intracellular ERS and organ-specific inflammation in the intestine has recently been revealed [6, 30, 31]. In particular, studies showed that deletion of XBP1 in mouse epithelial cells led to the spontaneous development of inflammation in the small intestine, including formation of crypt abscesses, leukocytic infiltration, and overt ulcers. It is noteworthy that even the deletion of a single XBP1 allele was sufficient to cause the development of spontaneous enteritis in a large number of animals [6, 22]. Moreover, hypomorphic XBP1 with the loss of one allele also led to Paneth cell dysfunction and hypersensitivity to DSS-induced colitis in mice, and deletion of both alleles led to Paneth cell apoptosis [22]. Earlier studies in humans showed similar results. Moreover, ERS may be a major cause of intestinal inflammation (for example, as observed in XBP1$^{-/-}$ mice) or a consequence of inflammation (for example, as observed in IL-10$^{-/-}$ and IRE1β$^{-/-}$ deficient mice) [22], and patients with Crohn's disease and ulcerative colitis demonstrated reduced XBP1 levels [22, 23].

Also, several whole-genome studies have pointed to an association between inflammatory bowel disease and a region of the genome physically close to the *XBP1* and *IRE1*β genes [11, 12]. Sequencing has identified new rare single-nucleotide polymorphisms (SNPs) in XBP1 that, along

with other environmental and genetic risk factors, may give predisposition to or induce a pathological process in the intestine. For example, Kaser et al. found that XBP1 SNPs rs5997391, rs5762795, and rs35873774 are associated with inflammatory bowel disease [6]. However, despite the undoubted importance of changes in XBP1 expression by intestinal epithelial cells in the development of pathology, a number of studies have now shown the ability of this transcription factor to regulate innate and adaptive immunity responses [11, 12, 30−34]. Recently, signaling through TLR has been shown to activate the IRE1/XBP1 pathway, and this is crucial for the body's immune defense [12, 14, 34]. As noted, TLRs are highly conserved receptors that recognize pathogen-associated molecular patterns and danger signals. When macrophages are stimulated in vitro with TLR2 (Pam3CSK4) and TLR4 (LPS) agonists, the IRE1/XBP1 pathway is activated independently of other mechanisms of the UPR system and in the absence of ERS [12]. Interestingly, treatment of activated macrophages with lipopolysaccharide together with tunicamycin caused inhibition of tunicamycin-induced ERS. In a further study, the authors observed a TLR-mediated pathway of XBP1 activation. In turn, XBP1 promoted the production of proinflammatory cytokines, including IL-6, TNF, and IFN-β [12]. Thus, XBP1 deficiency increased bacterial infection in mice by reducing the levels of these cytokines. It was found that the XBP1 transcription factor interacted with the promoter regions of the IL-6 and TNF genes, which caused sustained production of proinflammatory cytokines (IL-6 and TNF-α) [12]. Therefore, we can consider that XBP1 plays an important physiological, including protective, role in both innate and adaptive immunity. This is not surprising, given that IRE1 has α- and β-domains of RNase, which are unique homologues to the similar domains of RNase L, an important component of the antiviral system [35, 36].

Dendritic cells are known to play a crucial role in pathogen recognition and in the initiation of innate and adaptive immune responses. Several studies have shown a high level of XBP1s expression in dendritic cells compared to inactivated T- and B-lymphocytes. IRE1α−XBP1 signaling pathway of the UPR system is also important for the development and survival of dendritic cells, including plasma dendritic cells [22, 37, 38]. Thus, XBP1-deficient mice showed a decrease in the number of these cells, especially plasma cells, and a corresponding decrease in the level of IFN-α secretion. Also, decreased expression or absence of XBP1 impaired dendritic cell differentiation and survival, while increased expression of the transcription factor enhanced their development [22, 30].

In addition, the changes in XBP1 expression detected under stress may also have a significant impact on the differentiation processes of the cells of the adaptive immune system. XBP1 has been shown to induce differentiation of activated B-lymphocytes into plasma cells [27, 30, 38]. It has been demonstrated that XBP1-deficient B cells showed normal proliferation and activation, but the level of J-chain expression necessary for Ig assembly was reduced [3, 30]. Therefore, these animals were more susceptible to infections, and restoration of XBP1 expression resulted in resumption of Ig production. It is known that XBP1-induced expression of IL-6 in spleen B-cells is a factor of their terminal differentiation [3, 38]. Thus, XBP1 expression in professional secretory cells possibly contributes to the development of additional functions allowing these cells to respond to physiological signals of the UPR system. The mechanism of activation of the UPR system and XBP1 during plasma cell differentiation is still an interesting and open question. And given the importance that B-cells play in the protection of the intestinal mucosa against pathogens, the possible consequences of the changes in XBP1 expression by intestinal-associated lymphoid tissue that we have identified become clear. In addition, these changes may also affect the final production of autoantibodies to cellular antigens by plasma cells, which explains the dramatic increase in the incidence of autoimmune diseases in people exposed to social stress. It is also known that the ERS response is a critical factor in the initiation of T-cell differentiation during antigen recognition [39−42].

Thus, the results reveal the role of ERS in the development of inflammatory and autoimmune diseases, including inflammatory bowel disease.

CONCLUSION

The present study showed that the events occurring in the Gut-Associated Lymphoid Tissue under conditions of chronic social stress clearly contradict the classical stress paradigm and provoke not immunosuppression, but a pronounced activation of the immune system with subsequent development of an inflammatory process. In our opinion, one of the possible mechanisms of such physiological changes in the structures associated with gastrointestinal mucosa was a decrease in the expression of the transcription factor XBP1, and as a consequence, the subsequent activation of proinflammatory cytokine production by immune cells. Our findings demonstrated a significant decrease in XBP1 mRNA expression level. This, in turn, led to increased production of proinflammatory cytokines such as IL-1β and IL-17α.

Thus, the results of the experiment suggest the involvement of endoplasmic reticulum stress in the development and progression of inflammatory bowel diseases under conditions of chronic social stress.

AUTHORS' CONTRIBUTIONS

Idea of work and planning of the experiment (K.A.M.), data collection (T.I.A., P.I.S., E.A.V.), data processing (T.I.A., P.I.S., E.A.V.), writing and editing the article (T.I.A., K.A.M.).

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CONFLICT OF INTEREST

The authors declare no apparent or potential conflicts of interest related to the publication of this article.

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