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Psychoneuroimmunological mechanisms of stress-induced mental and psychosomatic disorders

Abstract

Relevance. Psychosomatic disorders represent a significant medical and biological problem, as their development is linked to the chronic activation of stress-mediating systems, in particular the hypothalamic-pituitary-adrenal axis and immuno-inflammatory mechanisms, which contribute to the development and progression of somatic pathology. Despite a considerable body of research, the pathogenesis of psychosomatic disorders requires an integrative synthesis that takes into account the interaction of neuroendocrine, immunoinflammatory and metabolic mechanisms, in particular neuroinflammation, glucocorticoid resistance, activation of the kynurenine pathway and gut dysbiosis. The relevance of this study stems from the need to systematise these data and develop a comprehensive pathogenetic model that can serve as a basis for improving the diagnosis and treatment of psychosomatic disorders.

Aim. To systematise current scientific data on the psychoneuroimmunological mechanisms underlying the development of stress-induced mental and psychosomatic disorders by analysing the neuroendocrine, immuno-inflammatory, neurotransmitter and microbiome changes that arise under the influence of chronic stress and contribute to the development of psychosomatic pathology.

Materials and methods. The study involved a narrative analysis of current scientific publications in the PubMed, PMC and Scopus databases for the period 2015-2025 (187 identified, 26 included in the final analysis). Methods of systematic analysis, generalisation and comparison of scientific data were employed.

Results. This study systematises an integrative approach to the pathogenesis of psychosomatic disorders, uniting neuroendocrine, immune, metabolic and microbiome mechanisms into a single, interconnected cascade. Key points of convergence (the hypothalamic-pituitary-adrenal axis, indoleamine 2,3-dioxygenase 1, neuroinflammation) have been identified, and the concept of a pathological "vicious circle" that drives the chronicity of the process has been substantiated. It has been shown that chronic stress, via glucocorticoid resistance, neuroinflammation and kynurenine metabolism, forms a self-reinforcing pathological cycle, which underlies the chronicity of psychosomatic disorders.

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Conclusions. Psychosomatic pathology should be regarded as a systemic, multifactorial process in which the interaction of neuroendocrine, immune and microbiome regulation plays a key role.
Practical value. The findings presented here can be used to deepen the understanding of the pathogenesis of psychosomatic diseases and to identify promising therapeutic targets.
Keywords: hypothalamic-pituitary-adrenal axis; glucocorticoid resistance; neuroinflammation; kynurenine pathway; "microbiome-gut-brain" axis.

INTRODUCTION

Psychosomatic and stress-induced mental disorders are one of the most pressing issues in modern medicine. According to the World Health Organisation [1], depression is the leading cause of disability worldwide, whilst anxiety disorders affect over 280 million people. The prevalence of psychosomatic conditions – ranging from irritable bowel syndrome to cardiovascular and endocrine comorbidities – is steadily increasing in the context of chronic social stress, making an understanding of their pathogenetic mechanisms a clinical priority. The central component of the stress response is the hypothalamic-pituitary-adrenal axis (HPA axis). N.W. Churchill *et al*. [2] described glucocorticoids in their work as "final effectors of the stress response", which regulate the transcription of hundreds of genes and determine whether acute stress will progress to a chronic condition. It is precisely the prolonged hyperactivation of the HPA axis, leading to the development of glucocorticoid resistance – a condition in which cortisol loses its anti-inflammatory and inhibitory function – that is now regarded as the key pathogenetic mechanism linking psychological stress to somatic dysfunction. E. Knezevic *et al.* [3] examined how chronic hypercortisolism causes hippocampal atrophy, excitotoxicity via NMDA receptors and suppression of brain-derived neurotrophic factor (BDNF), thereby forming the neurobiological substrate of depression and post-traumatic stress disorder (PTSD). In parallel with neuroendocrine changes during chronic stress, the immune system is activated. C.M. Pariante [4] emphasised in his review that glucocorticoid resistance is a central link between stress and systemic inflammation: when cortisol loses its ability to suppress NF-κB, levels of IL-1β, IL-6 and TNF-α rise steadily, maintaining a chronic inflammatory state. D.L. Wong *et al*. [5] demonstrated that chronic catecholamine activation independently exacerbates oxidative stress in the endothelium and triggers cardiomyocyte apoptosis, which explains the cardiovascular comorbidity associated with depression and PTSD.

An important molecular link between inflammation and neurotransmitter disturbances is the kynurenine pathway of tryptophan metabolism. A.H. Miller & C.L. Raison [6] proposed a concept whereby cytokine-induced activation of indoleamine-2,3-dioxygenase (IDO1) redirects tryptophan away from serotonin synthesis towards the accumulation of neurotoxic metabolites – quinolinic acid and 3-hydroxykinurenine – which directly contributes to cognitive and affective disturbances. A.A. Badawy *et al*. [7] confirmed the clinical significance of this mechanism in a systematic review, noting an increased KYN/Trp ratio in patients with major depressive disorder, PTSD and chronic fatigue syndrome. In current discourse, understanding of the role of the "microbiome-gut-brain" axis (MGBA) in the pathogenesis of stress-related disorders has expanded significantly. In their review, J. Khlevner *et al*. [8] characterised this axis as a multi-level communication system comprising neural (vagus nerve), immune (cytokines, Toll-like receptors), endocrine and metabolic pathways. R.G. Xiong *et al*. [9] found that in depression and anxiety disorders, the microbiome is characterised by a reduction in anti-inflammatory producers of short-chain fatty acids (*Faecalibacterium prausnitzii*, *Roseburia*) and an increase in pro-inflammatory taxa (*Enterobacteriaceae*), whilst dysbiosis and increased intestinal permeability trigger a systemic inflammatory cascade that sustains neuroinflammation.

Despite a significant body of research, an integrative pathogenetic model that unites neuroendocrine, immune, metabolic and microbiome mechanisms into a single interconnected cascade remains insufficiently systematised. In particular, the points of convergence between HPA axis dysfunction, IDO1 activation and dysbiosis – as components of a single "vicious circle" that drives the chronicity of the process – have not been fully described. A. Warren *et al*. [10] emphasised the need to consider these mechanisms holistically, as an isolated analysis of individual links in the pathogenesis does not allow for the identification of optimal therapeutic targets. A. Verma *et al*. [11] also emphasise that stress-induced dysregulation of the microbiome, metabolome and hormonal axis forms a mutually reinforcing cycle that requires a comprehensive therapeutic approach. Thus, the systematisation of current data and the development of a comprehensive pathogenetic model of psychosomatic disorders is a pressing task, both for deepening scientific understanding of the problem and for justifying new diagnostic and therapeutic strategies. The aim of the study was to conduct a comprehensive analysis of current understanding of the psychoneuroimmunological basis of stress-induced mental and psychosomatic disorders, with a focus on determining the role of neuroendocrine dysregulation, the immuno-inflammatory response, neurotransmitter disturbances and changes in the gut microbiome in the pathogenesis of psychosomatic pathology.

MATERIALS AND METHODS

A narrative literature review incorporating elements of a structured search was conducted to identify relevant studies investigating the pathogenetic mechanisms of psychosomatic disorders induced by chronic stress. Three electronic databases were searched: PubMed, PMC, and Scopus. The search strategy was based on the following keywords: "stress-mediating systems", "hypothalamic-pituitary-adrenal axis", "glucocorticoid resistance", "neuroinflammation", "psychoneuroimmunology", "kynurenine pathway", "microbiome-gut-brain axis", and "psychosomatic disorders". These terms were used both individually and in combination using the Boolean operators AND and OR. The search was primarily limited to English-language publications published between 2015 and 2025, yielding an initial total of 187 publications. The selection process was carried out in two stages. In the first stage, the titles and abstracts of all the publications found were independently reviewed by two researchers to assess their relevance to the research question; based on the results of this stage, 64 publications were selected. Studies that clearly did not investigate the neuroendocrine, immune or metabolic mechanisms underlying the development of psychosomatic pathology were excluded. In the second stage, the full texts of 64 potentially suitable articles were obtained and also independently assessed; following a full-text analysis, 26 sources were included in the final dataset. Among the selected publications were: a fundamental review of cortisol physiology by J. Kaur *et al.* [12], as well as works by D.S. Goldstein *et al*. [13-14], devoted to the role of catecholamines in stress responses and their link to neurodegenerative processes. Disagreements regarding the inclusion or exclusion of individual publications were resolved through collegial discussion until a consensus was reached. Articles were included in the analysis provided they met the following criteria: direct investigation of the pathogenetic mechanisms of psychosomatic disorders in the context of the stress response; publication in a peer-reviewed journal indexed in Scopus. Publications with similar or duplicative content were excluded (preference was given to works of higher methodological quality or greater relevance), as were conference abstracts and proceedings, and articles that did not meet the criteria for an evidence base. Following the selection process, a corpus of 26 publications was compiled, on the basis of which an integrative pathogenetic model of psychosomatic disorders was developed using methods of systematic analysis, generalisation and comparison.

RESULTS AND DISCUSSION

A key factor in the development of psychosomatic disorders is the chronic activation of stress-mediating systems, in particular the hypothalamic-pituitary-drenal axis and the sympathoadrenal system [1, 6]. In response to prolonged psycho-emotional stress, the secretion of corticoliberin, adrenocorticotropic hormone and cortisol increases, which is initially of an adaptive nature [12]. Chronic hyperactivation of these systems leads to excessive production of cortisol and catecholamines. The first, immediate "line of defence" against stress is provided by the sympathetic-adrenal system (SAS). A perceived stressor, via the cortical associative areas and the amygdala, activates the hypothalamic preoptic and paraventricular nuclei, from where descending sympathetic pathways reach the adrenal medulla. Chromaffin cells are responsible for a massive release of adrenaline (80-85% of secretion) and noradrenaline (15-20%) into the bloodstream. This response develops within seconds and is known by the classic term "fight-or-flight" [13]. D.L. Wong *et al*. [5] demonstrated that adrenaline not only performs a short-term regulatory function, but, upon chronic activation, becomes a direct factor in tissue damage: it stimulates oxidative stress in the endothelium by increasing the production of reactive oxygen species (ROS), activates NF-κB-mediated inflammatory signalling, accelerates cardiomyocyte apoptosis and enhances platelet aggregation. Furthermore, via β2-receptors, adrenaline suppresses natural killer (NK) cells and alters the cytokine profile, which explains the immunosuppression observed during acute stress. Takotsubo syndrome (stress-induced cardiomyopathy) is an extreme example of the cardiotoxicity of catecholamines: following emotional trauma, a massive release of adrenaline causes transient dysfunction of the left ventricular apex, which clinically resembles acute myocardial infarction. The pathophysiological mechanism involves the direct toxic effect of supraphysiological concentrations of catecholamines and spasm of the small coronary vessels [5].

The second level of the stress response, the HPA axis, is activated more slowly but has longer-lasting effects. In response to stress, neurons in the paraventricular nucleus of the hypothalamus release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which stimulate the corticotropic cells of the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH acts on the zona fasciculata of the adrenal glands, activating the synthesis of cortisol [12]. At the cellular level, cortisol interacts with mineralocorticoid receptors (MRs, high affinity) and glucocorticoid receptors (GRs, lower affinity). MRs are active at basal levels and provide "proactive" inhibition, whilst GRs are activated during stress and provide "reactive" inhibition. In the brain, MRs have a neuroprotective effect, whereas excessive activation of GRs may contribute to neurotoxicity [3]. The genomic action of cortisol is mediated through binding to GRs, their translocation into the nucleus and interaction with glucocorticoid

response elements or transcription factors (NF-κB, AP-1), which alters gene expression (hours) and brings about a large-scale reprogramming of cellular metabolism, the immune response and neuroplasticity. Non-genomic effects occur more rapidly – via membrane receptors and signalling cascades (MAPK/ERK) [2-3]. Under conditions of chronic stress, glucocorticoid resistance develops, manifesting as a reduction in receptor sensitivity to cortisol. Prolonged hypercortisolism leads to a reduction in the density and sensitivity of glucocorticoid receptors in target tissues (the hippocampus, pituitary gland, hypothalamus and immune cells). "Glucocorticoid resistance" ensues – a condition in which, despite elevated cortisol levels, its anti-inflammatory and inhibitory effects on the HPA axis are attenuated. E. Knezevic *et al*. [3] described numerous pathological consequences of chronic hypercortisolism in a systematic review: in hippocampal neurons, excessive activation of the GR leads to hyperexcitation of glutamate NMDA receptors (excitotoxicity), oxidative stress, suppression of neurogenesis in the dentate gyrus, atrophy of dendritic spines and a reduction in hippocampal volume. These changes are well documented in patients with major depressive disorder and PTSD. Concurrently, chronically elevated CRH in the amygdala enhances fear memory and reactivity, forming the neurobiological basis of anxiety.

Another form of dysregulation – hypocortisolism associated with increased sensitivity of the GR – is characteristic of PTSD. C.M. Pariante [4] demonstrated that in PTSD, the number of lymphocytic GR is significantly elevated, whilst daily cortisol excretion is reduced compared with healthy individuals and patients with major depression. This phenomenon is interpreted as compensatory hypersensitivity of the GR following initial stress-induced exhaustion, or as an epigenetic adaptation that reprogrammes the HPA axis to a "conservative" mode following massive stress. It is of fundamental importance that, in PTSD and major depression, dysregulation of the HPA axis occurs in opposite directions, although in both cases it is pathogenic. Regulation of the stress response at the level of the central nervous system (CNS) is mediated through the interaction of the hippocampus, the amygdala and the medial prefrontal cortex (mPFC): the hippocampus is responsible for contextual processing and the inhibition of stress-related memories, the amygdala for the initial assessment of threat and the formation of a fear response, whilst the mPFC provides top-down cognitive control over its activity. Under chronic stress, this system becomes unbalanced: the hippocampus atrophies as a result of glucocorticoid-induced neurotoxicity, the amygdala hypertrophies and becomes hyperreactive, whilst the mPFC loses its ability to effectively inhibit it due to the weakening of inhibitory gamma-aminobutyric acid (GABAergic) projections. As a result, a state of chronic "readiness for danger" develops, characteristic of anxiety disorders, depression and PTSD. Cortisol inhibits the synthesis of brain-derived neurotrophic factor (BDNF), and its reduction in the hippocampus and BDNF is one of the most consistently observed molecular correlates of depression. BDNF is essential for neuronal survival, synaptogenesis and neurogenesis, and the restoration of its levels is considered one of the mechanisms of action of SSRIs, electroconvulsive therapy and physical exercise. Chronic hypercortisolism also disrupts neurotransmitter systems: it reduces the sensitivity of 5-HT1A serotonin receptors, inhibits tryptophan hydroxylase activity, decreases dopamine availability in the mesolimbic system – contributing to anhedonia – and enhances glutamatergic excitation in the hippocampus, leading to the development of excitotoxicity [3]. The interaction between glucocorticoid receptors and the noradrenergic system confers pronociceptive properties on hypercortisolism, which is significant in the development of psychosomatic pain.

As noted by A. Warren *et al.* [10] and D.S. Goldstein *et al*. [13], glucocorticoid resistance leads to a loss of cortisol's anti-inflammatory effect and the activation of systemic inflammation. This is accompanied by increased levels of pro-inflammatory cytokines, in particular interleukin-1β, interleukin-6 and tumour necrosis factor-α [14-16]. Systemic inflammation is associated with the development of neuroinflammation through the activation of microglia – the primary immunocompetent cells of the central nervous system [2, 7, 17]. Activated microglia produce pro-inflammatory mediators, as well as reactive oxygen and nitrogen species, which disrupt neuronal plasticity, synaptic transmission and neurotransmitter balance, as highlighted by H.Y. Tang *et al.* [18], N. Mourtzi *et al*. [19] and G. Turecki *et al.* [20]. It has been established that disruption of glucocorticoid signalling leads to a loss of control over the immune response and the development of systemic inflammation. Activation of microglia and elevated levels of pro-inflammatory cytokines give rise to a state of neuroinflammation, which is key to the development of psychosomatic disorders. Under conditions of chronic stress, cortisol, despite elevated blood levels, gradually loses its ability to suppress inflammation. This occurs through several mechanisms. Firstly, pro-inflammatory cytokines chemically modify the glucocorticoid receptor (GR) in such a way that it is less able to enter the cell nucleus and cannot perform its function. Secondly, cytokines stimulate the formation of an "inactive" form of the GR (the β-isoform), which blocks the function of the main form of the receptor. Thirdly, chronic inflammation activates the NF-κB signalling factor, which competes with the GR for the regulation of the same genes. The result is a pathological vicious cycle (Fig. 1).

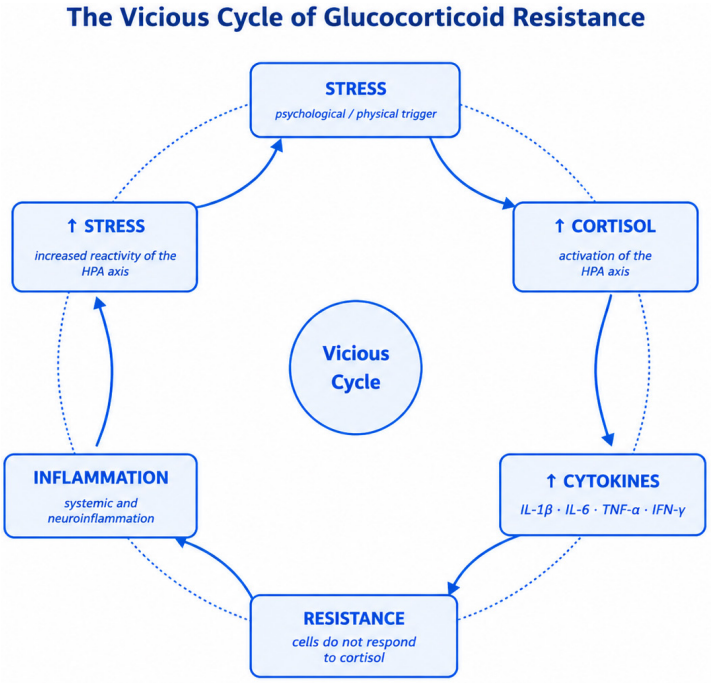

Figure 1. The pathological vicious cycle of glucocorticoid resistance
Source: compiled by the authors based on E. Knezevic *et al*. [3], C.M. Pariante [4], D.S. Goldstein *et al*. [13]

As shown in Figure 1, glucocorticoid resistance develops as a self-perpetuating pathological cycle, in which chronic stress and increased cortisol secretion are accompanied by the activation of pro-inflammatory cytokines, a reduction in the sensitivity of target cells to cortisol, and the subsequent maintenance of neuroinflammation. Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ) themselves also activate the HPA axis, stimulating further secretion of CRH by the hypothalamus. They increase the permeability of the blood-brain barrier (BBB) – a protective structure separating the blood from brain tissue – and enter the central nervous system (CNS), where they activate microglia – specialised immune cells of the brain. Activated microglia begin to release substances that damage neurons: excess glutamate (the main excitatory neurotransmitter), free radicals, nitric oxide and other pro-inflammatory molecules. At the same time, it inhibits the function of astrocytes – the "support" cells of neurons that provide them with nourishment and protection – in particular, reducing the production of the neurotrophic factor BDNF [21]. The accumulation of excess glutamate leads to excessive neuronal excitation via NMDA receptors – a process known as excitotoxicity, which is one of the key mechanisms underlying hippocampal neuronal death in depression. It is precisely this mechanism that underpins the action of ketamine: by blocking NMDA receptors, it rapidly eliminates excessive excitation, restores synaptic connections and increases BDNF levels – all within a few hours, significantly faster than conventional antidepressants [3]. The key mechanism linking immune and neurotransmitter changes is the cytokine-induced activation of IDO1, which causes a shift in tryptophan metabolism from the serotonin pathway to the kynurenine pathway [8]. This leads to a reduction in serotonin levels – which are important in the development of affective and somatoform disorders – and to the accumulation of neuroactive metabolites [5, 21-22]. The kynurenine pathway of tryptophan metabolism acts as a molecular link between inflammation and neurotransmitter disturbances. Upon activation of the IDO1 enzyme, tryptophan is redirected from serotonin synthesis towards the formation of neurotoxic metabolites, in particular quinolinic acid [7-6]. Table 1 summarises information on the main metabolites of the kynurenine pathway and their neurobiological role.

Table 1. Density and porosity of studied travertine samples

Metabolite	Mechanism of action	Effect	Clinical significance
Kinurenine (KYN)	Substrate for both branches of the kynurenine pathway (KP); competes with tryptophan (Trp) for transport across the blood–brain barrier (BBB)	Reduces the availability of Trp for serotonin	↑ in cases of depression, sepsis

Table 1. *Continued*

Metabolite	Mechanism of action	Effect	Clinical significance
Quinoline acid (QA)	NMDA receptor agonist; induces oxidative stress through Fe^{2+} chelation	Excitotoxicity, apoptosis of hippocampal neurons	↑ in the CSF of patients with depression, Alzheimer's disease, and Parkinson's disease
Kynurenic acid (KYNA)	NMDA receptor and α7 nicotinic acetylcholine receptor antagonist	Neuroprotection, reduced excitability	Reduced in depression; the primary target of new antidepressants
3-Hydroxykinurenine (3-HK)	Generates reactive oxygen species (ROS); activates neuronal apoptosis	Neurotoxicity	↑ in cases of PTSD and schizophrenia
Picolinic acid (PA)	Neuroprotective and antioxidant; chelates metal ions	Anti-inflammatory, anti-apoptotic	↓ in cases of Alzheimer's disease

Note: ↑ – an increase in the level or activity of the relevant metabolite/parameter; ↓ – a decrease in the level or activity
Source: compiled by the authors based on A.H. Miller & C.L. Raison [6], A.A. Badawy *et al*. [7], K. Ogyu *et al*. [16]

IDO1 represents a key point of convergence between the HPA stress response, immune activation, and neurochemical alterations. Pro-inflammatory cytokines, particularly IFN-γ and IL-6, stimulate IDO1 activity, whereas cortisol released during the stress response initially suppresses IDO1 as part of its anti-inflammatory action. However, under conditions of chronic inflammation and glucocorticoid resistance, this inhibitory effect is lost. Consequently, persistent IDO1 hyperactivation reflects the simultaneous dysregulation of both neuroendocrine and immune regulatory systems. A clinical study by A.H. Miller & C.L. Raison [6] confirmed that kynurenine concentrations and the KYN/Trp ratio – a recognised marker of IDO1 activity – are significantly elevated in patients with major depressive disorder, PTSD, chronic fatigue syndrome, and in patients with cancer receiving cytokine-based immunotherapy. Notably, administration of IFN-α for chronic hepatitis C induces a clinical syndrome resembling major depressive disorder in a proportion of patients, predominantly through activation of the IDO1-dependent kynurenine pathway. Quinolinic acid activates NMDA receptors and promotes excitotoxic neuronal injury, while 3-hydroxykynurenine possesses potent pro-oxidant properties that further enhance neuronal damage and sustain neuroinflammation [8,20]. Together, these mechanisms establish the pathological vicious cycle of "neuroinflammation–neurotoxicity" (Fig. 2).

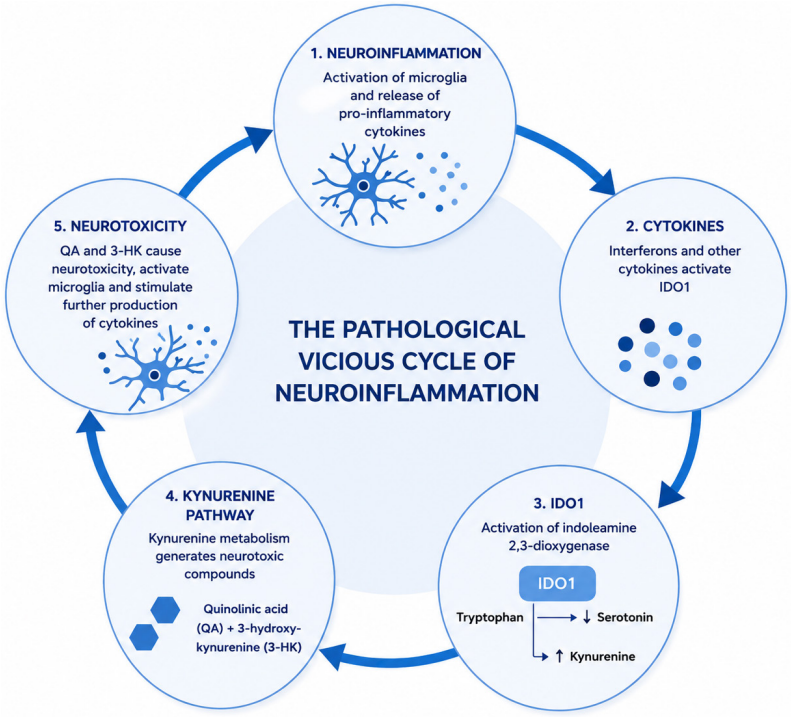

Figure 2. The pathological vicious cycle of "neuroinflammation–neurotoxicity"
Source: compiled by the authors based on A.H. Miller & C.L. Raison [6], A.A. Badawy *et al*. [7]

At the same time, it should be noted that activation of the kynurenine pathway is not a universal marker of depressive disorders: an increased KYN/Trp ratio and IDO1 activity are not observed in all patients with major depressive disorder, and their severity varies considerably depending on the degree of inflammation, comorbid somatic conditions and the study methodology. This limits the consideration of the kynurenine pathway as the sole or obligatory pathogenetic mechanism of depression and points to the need for further stratification of patients into biological subtypes [16-17]. The integrative model presented in Figure 3 illustrates the sequence of pathogenetic events from the primary trigger to the final clinical outcome.

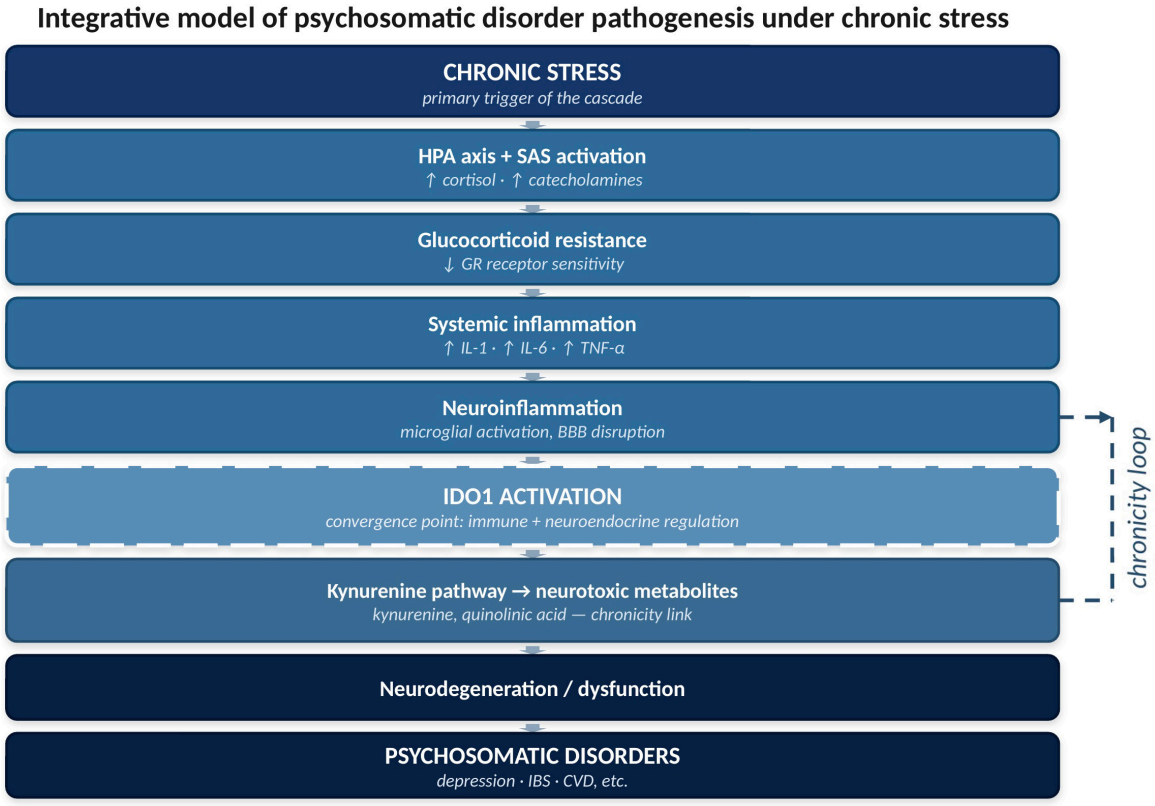

Figure 3. An integrative model of the pathogenesis of psychosomatic disorders in chronic stress
Source: compiled by the authors based on E. Knezevic *et al*. [3], C.M. Pariante [4], A.H. Miller & C.L. Raison [6]

The primary component of the model is chronic stress, which triggers a cascade through the activation of the HPA axis and the SAS, accompanied by increased levels of cortisol and catecholamines. The intermediate components of the model develop sequentially: glucocorticoid resistance (reduced receptor sensitivity to cortisol), loss of immune control, systemic inflammation (elevated IL-1, IL-6, TNF-α) and microglial activation with disruption of the blood-brain barrier, which together constitute a state of neuroinflammation. The key point of convergence in the model is the activation of IDO1, which integrates the immune (cytokine-dependent) and neuroendocrine (cortisol-dependent) signalling pathways, switching tryptophan metabolism to the kynurenine pathway. This forms an intermediate link in the chronicisation process: the accumulation of neurotoxic metabolites (kinurenine, quinolinic acid) sustains and exacerbates neuroinflammation, creating a self-reinforcing cycle – it is precisely this cyclical nature, rather than a linear sequence, that determines the chronic and progressive nature of the pathology. The final components of the model are neurodegeneration/dysfunction and the psychosomatic disorders themselves (depression, IBS, cardiovascular diseases, etc.). Based on the logic of the model, potential therapeutic targets include: glucocorticoid receptors (restoration of sensitivity), pro-inflammatory cytokines (anti-cytokine therapy), the IDO1 enzyme (IDO1 inhibitors) and the gut microbiome (probiotic correction of dysbiosis), as intervention at the convergence points is theoretically capable of breaking the self-perpetuating cycle of chronicity more effectively than targeting individual peripheral links in the cascade. An additional factor is the state of the gut microbiome [23-24]. Dysbiosis is accompanied by increased intestinal barrier permeability and the translocation of lipopolysaccharides into the bloodstream, which activates Toll-like receptors and enhances cytokine production, thereby sustaining systemic and neuroinflammation [4, 11, 25].

The concept of the MGBA axis has evolved from a hypothesis into a well-established neurobiological paradigm. It is a multi-level communication system comprising a neural channel involving the vagus nerve and the enteric nervous system, an immune channel involving cytokines, Toll-like receptors and microglial activation, an endocrine pathway involving hormones and neuropeptides, notably serotonin, peptide YY, GLP-1 and melatonin, as well as a metabolic pathway represented by short-chain fatty acids and other microbial metabolites [11]. The microbiome weighs approximately 1-2 kg, and the number of microbial cells is roughly equal to the number of cells in the body. Around 90-95% of the body's serotonin is synthesised in the gut by enterochromaffin cells – primarily under the regulatory influence of gut bacteria and their metabolites, but not directly by the bacteria themselves. The gut microbiome is also involved in the synthesis of GABA, acetylcholine, noradrenaline and dopamine in quantities sufficient for local neuroregulation. Furthermore, gut bacteria are the principal producers of short-chain fatty acids, which perform numerous systemic physiological functions and act as histone deacetylase inhibitors, thereby serving as important epigenetic regulators [23]. Psychological stress and elevated cortisol alter the composition of the microbiome through several mechanisms. Sympathetic activation reduces blood flow to the gut and the secretion of protective mucus, which suppresses the commensal microflora. Cortisol increases intestinal permeability by disrupting tight junctions in enterocytes, in particular by reducing levels of claudin-1 and ZO-1, as a result of which bacterial antigens, such as lipopolysaccharide, enter the bloodstream and activate Toll-like receptor 4, triggering systemic inflammation. Catecholamines further stimulate the growth of pathogenic bacteria, notably Escherichia and Salmonella [19].

The microbiome's feedback effect on the hypothalamic-pituitary-adrenal axis is mediated via microbial metabolites of tryptophan and short-chain fatty acids, which regulate serotonin secretion by enteroendocrine cells and influence signalling via the vagus nerve to the hypothalamus. Bacterial lipopolysaccharides are also capable of stimulating the secretion of corticotropin-releasing hormone. Certain strains of *Lactobacillus* and *Bifidobacterium* produce GABA and reduce cortisol levels during stress [23]. A systematic review by R.G. Xiong *et al.* [9] showed that in depression and anxiety disorders, the microbiome is characterised by a reduction in anti-inflammatory producers of short-chain fatty acids, such as *Faecalibacterium prausnitzii* and *Roseburia*, and an increase in pro-inflammatory taxa, particularly Enterobacteriaceae. A reduction in *Faecalibacterium* is one of the most consistently reported markers of depression. Increased intestinal permeability during chronic stress triggers a systemic inflammatory cascade, involving the activation of Toll-like receptor 4, the nuclear factor NF-κB, the production of pro-inflammatory cytokines and the subsequent activation of microglia, leading to the development of neuroinflammation. The "microbiota-inflammasome-brain" theory highlights the role of the NLRP3 inflammasome as an additional mechanism in depression, particularly in patients with inflammatory bowel disease. Therapeutic data from A. Icenhour *et al.* [23] demonstrated that probiotics, specifically *Lactobacillus helveticus* R0052 in combination with *Bifidobacterium longum* R0175, reduce cortisol levels and symptoms of anxiety and depression, whilst the use of *Lactobacillus plantarum* JYLP-326 and *Bifidobacterium breve* CCFM1025 enhances the efficacy of standard pharmacotherapy, accompanied by normalisation of the microbiome and tryptophan metabolism. However, the clinical evidence base regarding the efficacy of probiotics in psychiatry remains inconsistent: the results of individual randomised trials are contradictory, the effects are often strain-specific and not transferable to other probiotic preparations, and most studies have small sample sizes and short follow-up periods. Thus, the role of probiotics as an adjunctive therapy for mental disorders requires confirmation in larger-scale and methodologically sounder clinical trials before they can be recommended for widespread clinical use [9, 23].

Irritable bowel syndrome is the most common functional gastrointestinal disorder, with a prevalence of 10-15% and a higher incidence in women; it is characterised by chronic abdominal pain, bowel dysfunction and bloating without structural abnormalities. According to the Rome IV criteria and the DGBI concept, IBS is regarded as a disruption of the brain-gut axis, rather than a purely "psychological" or "organic" disease. Psychological stress is a trigger for flare-ups in over 70% of patients; at the same time, IBS itself perpetuates chronic stress via a bidirectional loop. Early childhood stress is associated with the development of IBS through epigenetic changes in the HPA axis, in particular NR3C1 methylation [18]. Studies by A. Icenhour *et al*. [23] and L. Fardet *et al*. [24] demonstrated hyperreactivity of the HPA axis in IBS: an increased ACTH response to CRH, reduced activation of the medial prefrontal cortex and an enhanced intestinal motor response, which is associated with visceral hypersensitivity. CRH and cortisol accelerate intestinal transit, activate mast cells, increase intestinal permeability and alter the microbiome, thereby promoting microinflammation. An increase in CRH-positive neurons in the submucosal plexus has also been observed, indicating local hyperactivation of the CRH system [18]. Thus, the pathogenesis of psychosomatic disorders involves an interaction of neuroendocrine, immune and metabolic mechanisms, at the centre of which lies a vicious circle of glucocorticoid resistance, chronic inflammation, activation of the kynurenine pathway and the neurotoxic effects of its metabolites [4, 6, 9]. This is consistent with

current concepts in psychoneuroimmunology, notably those of A. Farzi *et al*. [25] and X. Gong *et al.* [26], and justifies the need for an integrative approach to therapy. Chronic neuroinflammation also causes metabolic changes in the CNS through the activation of IDO1, which shifts tryptophan metabolism towards the kynurenine pathway, leading to the accumulation of neurotoxic metabolites that further activate microglia and perpetuate the pathological "vicious circle" of neuroinflammation and neurotoxicity.

CONCLUSIONS

1. Based on a review of the literature, this study systematises current understanding of the role of stress-mediating systems – the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal system – in the development of psychosomatic disorders, which manifest through neuroendocrine, immune and metabolic mechanisms.

2. A review of the literature has shown that a key link in the pathogenesis is the dysregulation of glucocorticoid signalling in the form of glucocorticoid resistance, which leads to a loss of control over the inflammatory response and the development of systemic inflammation.

3. According to the literature, neuroinflammation acts as a central pathogenetic mechanism, arising as a result of microglial activation, increased levels of pro-inflammatory cytokines and impaired blood-brain barrier permeability.

4. An analysis of current sources provides grounds for asserting that the kynurenine pathway of tryptophan metabolism, via IDO1 activation, is a key point of convergence between the immune and neuroendocrine systems, contributing to the accumulation of neurotoxic metabolites and the development of cognitive and affective disorders.

5. Based on a review of the literature, the role of the microbiome-gut-brain axis as an important modifier of stress-induced changes has been substantiated, through its influence on intestinal barrier permeability, the production of lipopolysaccharides and the activation of systemic inflammation.

6. Based on a synthesis of scientific data, an integrative pathogenetic model has been proposed that unites hyperactivation of the HPA axis, neuroinflammation, kynurenine metabolism, epigenetic changes and microbiome dysbiosis into a single interconnected cascade.

7. Based on a review of the literature, a pathological "vicious circle" has been identified, in which chronic stress, via glucocorticoid dysfunction and immune activation, sustains a self-reinforcing system of neuroinflammation that underlies the chronicity of psychosomatic disorders.

8. An analysis of the current scientific literature supports the need to view psychosomatic pathology as a systemic, multifactorial process in which the interaction of neuroendocrine, immune and microbiome regulation plays a key role.

Limitations of the study. The study has a number of limitations. Firstly, the narrative nature of the review, which incorporates elements of a systematic search, does not rule out subjectivity in the selection and interpretation of sources. Secondly, a significant proportion of the mechanisms analysed (in particular, the role of IDO1, the microbiome and epigenetic changes) have been studied predominantly in animal models or in small clinical samples, which limits the direct transfer of findings to clinical practice. Thirdly, the heterogeneity of the nosological groups (depression, PTSD, IBS, cardiovascular disorders), which were considered collectively within the psychosomatic model, complicates the formulation of universal pathogenetic patterns.

Prospects for further research. Promising areas for further research include: conducting systematic reviews and meta-analyses for individual nosological groups, taking into account the specific nature of their pathogenetic mechanisms; clinical validation of the proposed integrative model through multicentre cohort studies; investigating IDO1 and metabolites of the kynurenine pathway as potential biomarkers of severity and prognosis in psychosomatic disorders; and studying probiotic and targeted psychopharmacological interventions aimed at key convergence points in the described pathogenetic cascade.

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CONFLICT OF INTEREST

None.

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Психонейроімунологічні механізми стрес-індукованих психічних і психосоматичних розладів

Анотація
Актуальність. Психосоматичні розлади становлять значущу медико-біологічну проблему, оскільки їхній розвиток пов'язаний із хронічною активацією стрес-реалізуючих систем, зокрема гіпоталамо-гіпофізарно-надниркової осі та імунозапальних механізмів, що сприяють формуванню й прогресуванню соматичної патології. Попри значний обсяг досліджень, патогенез психосоматичних розладів потребує інтегративного узагальнення з урахуванням взаємодії нейроендокринних, імунозапальних і метаболічних механізмів, зокрема нейрозапалення, глюкокортикоїдної резистентності, активації кінуренінового шляху та дисбіозу кишечника. Актуальність дослідження зумовлена необхідністю систематизації цих даних і формування цілісної патогенетичної моделі, що може слугувати основою для вдосконалення діагностики й терапії психосоматичних розладів.
Мета. Систематизувати сучасні наукові дані щодо психонейроімунологічних механізмів розвитку стрес-індукованих психічних і психосоматичних розладів шляхом аналізу нейроендокринних, імунозапальних, нейромедіаторних та мікробіомних змін, які виникають під впливом хронічного стресу та беруть участь у формуванні психосоматичної патології.
Матеріали та методи. У дослідженні проведено наративний аналіз сучасних наукових публікацій у базах даних PubMed, PMC, Scopus за 2015-2025 роки (187 знайдених, 26 включено до фінального аналізу). Використано методи системного аналізу, узагальнення та порівняння наукових даних.
Результати. У роботі систематизовано інтегративних підхід до патогенезу психосоматичних розладів, що об'єднує нейроендокринні, імунні, метаболічні та мікробіомні механізми в єдиний взаємопов'язаний каскад. Виділено ключові точки конвергенції (гіпофізарно-надниркова вісь, індоламін-2,3-діоксигеназа 1, нейрозапалення) та обґрунтовано концепцію патологічного «порочного кола», що забезпечує хронізацію процесу. Показано, що хронічний стрес через глюкокортикоїдну резистентність, нейрозапалення та кінуреніновий метаболізм формує самопосилюване патологічне коло, яке є основою хронізації психосоматичних розладів.
Висновки. Психосоматична патологія має розглядатися як системний мультифакторний процес, де ключову роль відіграє взаємодія нейроендокринної, імунної та мікробіомної регуляції.
Практична цінність. Отримані узагальнення можуть бути використані для поглиблення розуміння патогенезу психосоматичних захворювань та визначення перспективних терапевтичних мішеней.
Ключові слова: гіпоталамо-гіпофізарно-наднирникова вісь; глюкокортикоїдна резистентність; нейрозапалення; кінуреніновий шлях; вісь «мікробіом – кишківник – мозок».