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REVIEW ARTICLE

Interplay of G-proteins and Serotonin in the Neuroimmunoinflammatory Model of Chronic Stress and Depression: A Narrative Review

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Abstract: ***Introduction*:** This narrative review addresses the clinical challenges in stress-related disorders such as depression, focusing on the interplay between neuron-specific and pro-inflammatory mechanisms at the cellular, cerebral, and systemic levels.

***Objective*:** We aim to elucidate the molecular mechanisms linking chronic psychological stress with low-grade neuroinflammation in key brain regions, particularly focusing on the roles of G proteins and serotonin (5-HT) receptors.

***Methods*:** This comprehensive review of the literature employs systematic, narrative, and scoping review methodologies, combined with systemic approaches to general pathology. It synthesizes current research on shared signaling pathways involved in stress responses and neuroinflammation, including calcium-dependent mechanisms, mitogen-activated protein kinases, and key transcription factors like NF-κB and p53. The review also focuses on the role of G protein-coupled neurotransmitter receptors (GPCRs) in immune and pro-inflammatory responses, with a detailed analysis of how 13 of 14 types of human 5-HT receptors contribute to depression and neuroinflammation.

***Results*:** The review reveals a complex interaction between neurotransmitter signals and immunoinflammatory responses in stress-related pathologies. It highlights the role of GPCRs and canonical inflammatory mediators in influencing both pathological and physiological processes in nervous tissue.

***Conclusion*:** The proposed Neuroimmunoinflammatory Stress Model (NIIS Model) suggests that proinflammatory signaling pathways, mediated by metabotropic and ionotropic neurotransmitter receptors, are crucial for maintaining neuronal homeostasis. Chronic mental stress can disrupt this balance, leading to increased pro-inflammatory states in the brain and contributing to neuropsychiatric and psychosomatic disorders, including depression. This model integrates traditional theories on depression pathogenesis, offering a comprehensive understanding of the multifaceted nature of the condition.

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1. INTRODUCTION

1.1. Stress-related Disorders and Inflammation

Stress-related disorders comprise a category of psychiatric conditions, including posttraumatic stress disorder, acute stress reaction, adjustment disorder, and depression, which manifest after stressful or traumatic life events [1].

Major depressive disorder (MDD) is a severe mental disorder that significantly affects an individual's quality of life. Although the exact etiology remains elusive, more emphasis is placed on the role of psychological stress in the onset of depression [2]. MDD is characterized by symptoms such as depressed mood (manifested as reduced motivation or hopelessness), anhedonia (the decreased capacity to derive pleasure from activities such as food, sex, and social interaction), energy, irritability, difficulties in concentration, disturbances of sleep and appetite, cognitive dysfunction, and suicidality [3].

Stress, which is inherently multifaceted, involves adaptive responses at the cellular, tissue, and organismic levels, the latter including psychoemotional aspects. In pathological states, these responses often show maladaptive traits, contributing to the development of a variety of diseases. This condition, which has been variably termed 'distress' or 'pathological stress' by researchers, essentially amalgamates adaptive and maladaptive functional systems. In particular, as pathological conditions evolve, there is a consistent increase in the severity of this maladaptive stress or distress. In particular, chronic psychological stress, also known as psychoemotional or mental stress [4-6], can induce a pro-inflammatory state in specific regions of the brain and the systemic environment. This condition is associated with hypothalamic-pituitary-adrenal axis dysfunctions and increased sympathetic nervous system activity [7]. Furthermore, stress plays a role in a variety of cardiovascular diseases, including hypertension, myocardial ischemia, and accelerated

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atherosclerosis [8], as well as in gastrointestinal dysfunction [9], irregularities of the immune system [10] and general allostatic load [11]. These physiological changes contribute to a pathogenetic cycle that implicates both the central nervous system (CNS) and peripheral tissues, thereby sustaining Major Depressive Disorder (MDD) and other stress-related diseases. Simultaneously, MDD and chronic stress are risk factors for the progression of neurodegenerative diseases, particularly those of a vascular nature [12]. The impact of stress on these health outcomes is especially pronounced in older populations [13].

To differentiate between pathological stress leading to disease and adaptive stress, some authors use the term "distress" to describe the former [14-16]. In subsequent discussions, we will refer to pathological stress as mental distress, distinguishing it, when necessary, from physiological stress and differentiating it both from pro-inflammatory cellular and tissue stress.

The association between MDD and neuroinflammation is now well-established [17]. Importantly, pro-inflammatory mechanisms, which extend beyond the traditional understanding of inflammation as a singular process, evidently contribute to both the maintenance of nervous tissue homeostasis and the borderline physiological states that are precursors to neuropathologies and certain stress-related somatic conditions [18]. This requires nuanced differentiation between various forms of neuroinflammation and the broader concepts of pro-inflammatory tissue and cellular stress, as well as the identification of qualitative transitions between these pro-inflammatory states.

In MDD and other stress-related pathologies, there is a disruption in the relationship between the hypothalamic-pituitary system, the limbic system, and the neocortex [19, 20]. At the molecular level, this relationship is mediated by various neurotransmitters, including serotonergic pathways. These pathways, although significant in their own right, also modulate other neurotransmitters involved in the pathogenesis of MDD [21, 22]. Furthermore, the association between serotonergic mechanisms and inflammation has been well documented [23, 24].

The evolving understanding of inflammation, now perceived as a generalized pathological process [25, 26], requires a systematic exploration of the interrelations between serotonin (5-hydroxytryptamine, 5-HT) signaling, other neurotransmitters, and cellular pro-inflammatory stress in both normative and pathological states.

This review seeks to elucidate the molecular mechanisms linking chronic psychological stress with low-grade neuroinflammation in key brain regions. Its primary objectives are outlined as follows:

- Exploration of Cellular and Tissue Stress: This entails a comprehensive examination of cellular and tissue stress within the framework of general pathology. It involves identifying connections between these stress types and both canonical and non-classical forms of inflammation, as well as other general pathological processes.

- Impact on the Central Nervous System and Depression: The review investigates how cellular and tissue stress affects the central nervous system's physiological state, psychoemotional stress, and depression. It encompasses an analysis of oxidative stress mechanisms, the significance of GPCR signaling pathways, other types of receptors, and additional pro-inflammatory mechanisms. A concise review of current theories and concepts regarding the pathogenesis of depression is also included.

- GPCRs and Pro-Inflammatory Functions: An in-depth exploration is provided on the pro-inflammatory roles of GPCRs, with a particular focus on 5-HT receptors and their significance in neuropsychiatric disorders. The major findings from this analysis are summarized in Tables **S1** and **S2**.

- Principal Characteristics of the Neuroimmunoinflammatory Concept of Stress and Depression (NIIS Model): The 'Conclusion' section of the manuscript presents a detailed characterization of the Neuroimmunoinflammatory Stress and Depression Model (NIIS Model), encompassing its fundamental aspects and implications.

1.2. Methodological Approaches and Limitations of the Review

This review is conceptual and includes a comprehensive literature review that combines systematic, narrative, and scoping review methodologies, as well as systemic approaches to general pathology. Notably, this work does not utilize a meta-analytical approach based on the Cochrane criteria, as it does not primarily focus on specific clinical or pharmacological problems. However, most of the systematic reviews we cited did employ this methodology.

In conducting this review, we evaluated a total of 1856 articles, comprising 1003 review articles and 853 original research papers. Out of these, 753 articles were selected, with a predominance of reviews. 527 articles were included in the main list, while the remaining 226 references are provided in Appendices **S2** and **S3**. It is noteworthy that a significant portion of the original research articles selected were dedicated to experimental studies.

This blend of methodologies and the range of sources reviewed provide a broad and diverse perspective on the subject. However, the potential limitations of this approach include the absence of meta-analysis and the possibility of selection bias, despite our comprehensive and systematic approach in selecting articles.

1.2.1. Principles of Inclusion and Exclusion

Recent Reviews: Review publications from the last five years were preferred, especially those with high citation frequency, reflecting widely recognized concepts about neurotransmitter receptor signaling pathways and their role in the pathogenesis of depression. We aimed to exclude redundant publications or those detailing specific mechanisms that, in our assessment, did not contribute significantly to understanding the broader patterns of the issue.

General Pathology Theory: For topics such as the general theory of typical pathological processes, classification of inflammatory processes, and basic mechanisms of cellular and tissue stress, we primarily referred to our own publications. These reflect a systematic and detailed perspective on general pathology, and thus may more prominently represent the authors' subjective viewpoints.

1.2.2. Operational Limitations

- Despite a systematic approach to literature selection, selection bias is a potential limitation. Relevant studies may have been overlooked inadvertently due to specific search criteria or unavailability in the databases accessed.

- The dynamic nature of research in neuroimmunoinflammation and psychoneuroendocrinology suggests that new findings might emerge shortly after this review's publication,

potentially altering the current understanding of the interaction between G proteins, serotonin, and chronic stress.

- Publications that were not accessible in their entirety were not considered, possibly omitting some relevant scientific information.

- The review's primary focus on English-language studies could limit its comprehensiveness, as significant research published in other languages could have been overlooked, introducing a potential bias.

- Finally, while striving for objectivity, the nature of conceptual descriptive reviews inherently poses a risk of subjective bias in data presentation, analysis, and interpretation.

2. CELLULAR AND TISSUE STRESS: ASSOCIATION WITH INFLAMMATION

Cellular pro-inflammatory stress (CS) is defined as a "complex of interrelated universal and specific (to particular cell populations) cellular processes in response to the action of factors causing real or potential damage" [26]. CS encompasses a variety of interconnected standard processes, regardless of cell type, including (1) oxidative stress; (2) DNA damage response; (3) mitochondrial stress, including mitochondrial unfolded protein response (UPRmt); (4) endoplasmic reticulum stress (ER), incorporating calcium-dependent mechanisms and UPRER; (5) response of inducible heat shock proteins (HSP), including their role in UPR; (6) modulation of autophagy processes during cell growth, or intensification for degradation of altered organelles and macromolecules; (7) formation of inflammasomes; (8) synthesis of stress-related noncoding RNAs; (9) formation of stress granules; (10) assembly of an intracellular signaling network for cellular stress; and (11) development of pro-inflammatory receptor and secretory cell phenotypes. The primary outcomes of cellular stress include (1) restoration of cellular physiological equilibrium; (2) apoptosis; (3) various forms of programmed necrosis; (4) transdifferentiation; (5) malignancy; (6) cellular aging; and (7) chronicity of CS with gradual accumulation of morphofunctional disorders [25, 26].

The induction of a pro-inflammatory phenotype in various cells results in tissue stress, characterized by the formation of an inducible cytokine network. Each individual CS process, as well as its integrative mechanisms, involves negative feedback loops that serve to spatially and temporally constrain tissue stress and prevent physiological imbalances associated with CS. Such mechanisms include the induction of antioxidants, antiapoptotic factors, proteasomal and autophagic degradation of damaged organelles and stress proteins, and the reversibility of stress-induced post-translational modifications and epigenetic changes, controlled by stress noncoding RNAs [25, 26]. In the context of tissue stress, these mechanisms involve the production of specialized pro-resolvent mediators and other anti-inflammatory factors by activated cells [27-29]. The balanced interplay between activation and resolution mechanisms dictates the adaptive capabilities of cellular and tissue stress, while any imbalance therein culminates in persistent pathology, exemplifying the transformation of "medicine (inflammation) into poison".

Indeed, it is imperative to recognize that many molecular mechanisms that constitute cellular stress (CS) are evolutionarily conserved, predating the development of complex inflammation programs at the tissue and systemic levels. For example, heat shock proteins (HSPs) with homologous functions are ubiquitously present in different subcellular compartments (*e.g.*, nucleus, mitochondria, endoplasmic reticulum, cytosol) in both prokaryotic and eukaryotic cells [30]. Primitive forms of immune memory and non-classical inflammation, such as phagocyte accumulation at injury sites, are evident in diverse invertebrate species [31-33]. Furthermore, immunity in these organisms not only aims to neutralize harmful factors but also to maintain tissue homeostasis and regeneration [34]. However, canonical inflammation appears to have evolved exclusively in vertebrates, accompanied by advances in the blood microcirculation system, facilitating directed leukocyte migration to injury sites and enabling classical adaptive immunity of the lymphocytic type [35, 36].

Recent advances in molecular biology and pharmacology have considerably broadened our understanding of CS and inflammation as general pathological processes [25, 26]. Canonical or classical inflammation has traditionally been conceptualized as a primarily localized tissue response to injury, marked by exudative vascular reactions and significant migration of leukocytes to the site of inflammation. In contrast, acute systemic hyperinflammation, a life-critical condition, is characterized by microcirculatory dysfunctions, cytokine storms, multiorgan failure, and shock states [37, 38]. This systemic inflammatory response often follows as a sequel or direct complication of localized classical inflammation, as exemplified in COVID-19 cases [39].

Certainly, low-grade chronic inflammation represents a non-classical form of inflammation, intricately linked with metabolic factors, often termed meta-inflammation [40] - and aging processes, known as inflammaging [41, 42]. This form of inflammation primarily involves resident cells such as stromal macrophages and other connective tissue cells, as well as parenchymal cells in a state of pro-inflammatory cellular stress (CS). Importantly, low-grade chronic inflammation lacks a typical barrier function, which presents a proclivity to delocalization. Consequent systemic manifestations include conditions such as morbid obesity [43], metabolic syndrome [44, 45], and type 2 diabetes mellitus [46]. Neurodegenerative processes associated with old age can also be considered local manifestations of this type of inflammation, although pathogenetically linked to low-grade systemic inflammation [47-50].

Interestingly, the transition from local low-grade chronic inflammation to classical-type inflammation is observable under increasing harmful influences, exemplified in conditions such as non-alcoholic fatty liver disease and diabetic kidney disease [51]. The complex etiopathology of atherosclerosis presents another case in which features of both low-grade and productive inflammation coexist, warranting its classification as a special mixed type of inflammation [52].

Recent insights extend the relevance of pro-inflammatory mechanisms to diseases not traditionally classified as inflammatory, such as cancer [53]. Cellular and tissue stress, in its pro-inflammatory forms, is involved in a variety of physiological functions, encompassing embryogenesis, cell proliferation and differentiation, immunogenesis, functions of the integumentary tissue barrier, and skeletal muscle contractility [26, 54-58].

In metaphorical terms, if cellular and tissue stress are compared to an iceberg submerged in water, canonical inflammation would correspond to the visible, above-water segment of this iceberg (Fig. **1**). The less explored "submerged portion" would house various non-classical forms of inflammation, as well as stress and distress of the neuroendocrine system, among other physiological processes interlinked with CS mechanisms. These hidden dimensions can be crucial in the transition from physiological to pathological states when they are imbalanced.

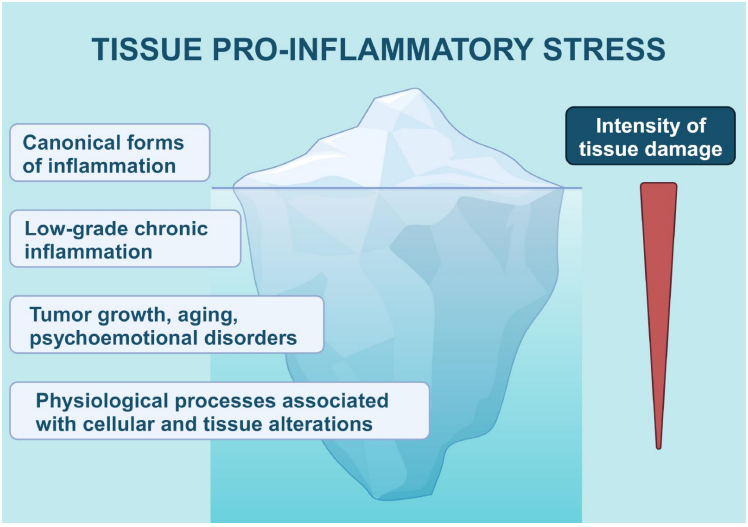

Fig. (1). The integrative role of tissue stress (the "Iceberg" Model) in various pathological and extreme physiological processes. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Hence, an in-depth understanding of the entire 'iceberg', that is, the totality of mechanisms related to cellular and tissue stress, both classical and non-classical forms of inflammation, is imperative for elucidating the intricate landscape of diseases and their pathogenesis.

Fig. (**1**) illustrates the crucial role of tissue stress, represented by the 'iceberg model', in various pathological and extreme physiological processes. This diagram emphasizes that cellular stress signaling pathways play a significant role beyond canonical inflammation. In fact, these mechanisms may contribute to the development of not only low-grade chronic inflammation and other forms of non-classical inflammation but also pathologies traditionally not classified as inflammatory diseases, such as cancer, aging, and neuropsychiatric disorders.

Qualitative transitions in the stress states of cellular and tissue depend on multiple variables. These factors encompass the type and strength of harmful agents, the magnitude, pervasiveness, and temporality of tension, and the particular milieus in which molecular pro-inflammatory pathways are involved. Furthermore, the involvement of "specialized" immune cells in these mechanisms is another factor that affects the environment of cellular and tissue stress. It is important to note that Fig. (**1**) intentionally omits the depiction of life-threatening systemic hyperinflammation. This is because the extent of the pro-inflammatory transformation of microvessels in this state surpasses that of canonical inflammation and has a significant impact on multiple organ systems. Therefore, it requires separate consideration as a state of pathological exigency.

Considering the comprehensive elucidation of cellular and tissue stress mechanisms and their intersection with various pathological and physiological processes, it is imperative to refine our classification systems. This differentiation would serve to encompass not only a spectrum of inflammatory responses but also a wider range of conditions, including those traditionally outside the scope of inflammatory diseases. This becomes particularly salient when considering the commonality of molecular and cellular pathways in states such as psychoemotional stress, which, although not conventionally categorized as inflammatory, exhibit analogous features at the molecular level (Fig. **2**).

This multidimensional framework aims to encapsulate both the pathological and extreme physiological processes that border pathology, thus providing a unified platform for future research and therapeutic intervention. Therefore, there is a pressing need not only to differentiate among types of inflammation but also to delineate the basic mechanisms that underlie pro-inflammatory cellular and tissue stress as a universal substrate for multiple physiological and pathological states.

Note that this common platform is applicable to multiple human pathologies. Cellular stress serves as the foundational systemic unit that underpins tissue stress, creating a shared pathogenetic platform that is relevant not only for a wide range of pathologies but also for various physiological conditions. The most notable manifestations of tissue stress, especially those that involve significant involvement of "professional inflammatory cells" from the immune system, are predominantly associated with classical forms of inflammation and potentially life-threatening systemic hyperinflammation. With a decrease in the intensity of these pro-inflammatory mechanisms, additional processes such as atherogenesis, low-grade chronic inflammation, and neoplastic diseases can be included in the spectrum, even though they are typically not categorized as inflammatory conditions. Therefore, these divergent pathologies have similar pro-inflammatory components at the cellular, tissue, and organismal levels, allowing their systemic conceptualization and the application of typical therapeutic methods for these conditions. Mental health conditions such as depression and other disorders linked to psychoemotional stress can further broaden this conceptual framework, providing a more thorough understanding of the usual pathological procedures. This integration will be discussed in the concluding section of the article.

3. THE ROLE OF TISSUE STRESS MECHANISMS IN THE PHYSIOLOGICAL STATE OF THE CNS, PSYCHOEMOTIONAL STRESS, AND DEPRESSION

The physiological thresholds for cellular, tissue, and organ structures, as well as for the organism as a whole, are not precisely defined. Surpassing these thresholds compromises both the functional integrity and the structural stability of these biological units over an extended period. However, a brief genetically programmed

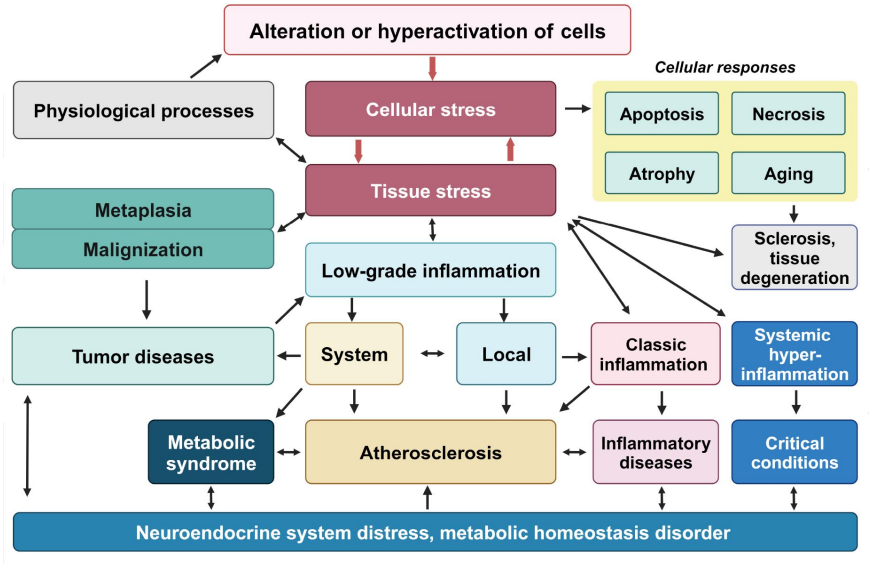

Fig. (2). Schematic model of cell and tissue stress as a common platform for various human pathologies. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

escalation in activity is essential for adaptive responses to adverse changes in both the internal and external environments. These adaptive responses were initially conceptualized by Selye as the "general adaptation syndrome," a notion that we now largely equate with stress [59-61].

It is pertinent to note that the adaptive stress phase can evolve into maladaptive stress during the exhaustion stage. Although stress predominantly implicates the neuroendocrine system, it exerts a secondary influence on other bodily systems. In particular, psychoemotional stress mainly facilitates adaptation to external environmental changes, both through nonspecific internal organ activity and through targeted neuromuscular actions [62-63].

Selye also classified inflammation as a form of localized adaptation syndrome, which can now be conceptualized as pro-inflammatory tissue stress. This expansive definition encompasses multiple forms of inflammation. As current understanding dictates, neuroendocrine stress manifests itself as a component of the systemic inflammatory response in various somatic pathologies, including, but not limited to, infections and trauma [64, 65].

Furthermore, the chronicity of psychoemotional stress, especially its transition to distress, can culminate in a variety of psychosomatic illnesses [66-69]. Interestingly, classical pro-inflammatory molecular pathways are actively involved in the pathogenesis of such psychosomatic conditions [70, 71]. Thus, a comprehensive understanding of stress requires an integrative perspective that accounts for its multifaceted interactions with inflammation and other pathological states.

In fact, the concept of stress has evolved, now encompassing both systemic and localized manifestations [72]. A sufficiently intense stressor can not only elicit localized stress but also trigger systemic responses by activating the hypothalamic-pituitary-adrenal (HPA) axis. When tissue damage occurs or molecular markers indicating the threat of damage are detected, localized or systemic pro-inflammatory tissue stress can manifest.

The complexity of psychoemotional stress and pro-inflammatory stress extends beyond their apparent external differences; both share fundamental attributes. That is, their adaptive mechanisms must be finely calibrated across specific parameters to retain adaptive functionality. Failing this balance, these mechanisms transition from serving adaptive purposes to instigating pathological development.

Turning our attention to the nervous system, the physiological importance of cellular and tissue stress mechanisms in this context, as well as their relationship with psychoemotional stress, deserves particular scrutiny. The nervous system serves as a nexus for interpreting both internal and external stimuli and responds through coordinated neurochemical and physiological actions. The relationship between pro-inflammatory tissue stress mechanisms in the nervous system and psychoemotional stress is bidirectional; the former can precipitate or exacerbate the latter and *vice versa*. Under normal conditions, these mechanisms function within tightly regulated limits to maintain homeostasis. However, in pathological states, dysregulated cell and tissue stress can precipitate a cascade of neuroinflammatory responses, and neurodegeneration, and contribute to neuropsychiatric disorders.

Therefore, an integrated understanding of the interaction between cellular and tissue stress mechanisms in the nervous system and psychoemotional stress is critical to developing targeted interventions for both physiological and pathological conditions.

3.1. Features of Cellular Stress in the Brain

The concept of a pro-inflammatory tone delineates the propensity of tissues to manifest pro-inflammatory mechanisms under physiological conditions. Tissues can be stratified into three primary categories based on their pro-inflammatory tone: (1) those with a high resting pro-inflammatory tone, such as integumentary tissues and immunocompetent organs; (2) those that exhibit intermittent, but significant surges in pro-inflammatory tone, exemplified by liver and skeletal muscle; and (3) those who maintain a relatively stable, low pro-inflammatory tone, highly sensitive to alterations in homeostatic parameters and vulnerable to biologically aggressive pro-inflammatory factors [26]. The central nervous system (CNS) belongs prominently to the third category.

The CNS exhibits unique physiological attributes, such as restricted blood flow due to the blood-brain barrier, that contribute to its specialized immunity privilege. Metabolically (at rest), the brain is unparalleled, consuming 20% of body glucose and oxygen, while having approximately 2% of body weight [73, 74]. This metabolic demand requires stable blood flow and efficient transport of oxygen and glucose. Furthermore, the high metabolic demand of the brain leads to the intensive production of specialized proteins crucial for cationic transmembrane transport, nerve impulse generation, and transmission. This metabolic environment makes CNS neurons particularly susceptible to oxidative stress and other damaging agents [75-77].

Another critical vulnerability lies in constant fluctuations in intracellular calcium and other cations in CNS neurons, attributable to neurotransmitter activity. In particular, cationic excitotoxicity is often mediated by glutamate ionotropic receptors, highly expressed in regions of the brain such as the limbic system, which are intimately involved in emotional disorders such as major depressive disorder (MDD), bipolar disorder, anxiety, and post-traumatic stress disorder [78-81]. Furthermore, neuronal damage and microglial activation can also be derived from dysfunctions in glutamate, monoamine, acetylcholine, and purine receptors [82-85], as well as inhibitory GABA-dependent neuronal deficiencies [86-88].

The unique metabolic and functional characteristics of neurons in the CNS require intricate regulatory mechanisms to control cellular stress (CS). Unlike other tissues, the brain is almost exclusively dependent on aerobic glycolysis, foregoing β-oxidation of fatty acids as an energy source [89]. This metabolic specialization mitigates the risk of lipotoxicity and concomitant mitochondrial dysfunction [90].

Moreover, the brain's energy-intensive activities and high protein biosynthesis rates must remain consistent throughout the neuron's lifetime. This persistent demand underpins the increased sensitivity of neurons to disruptions in mitochondrial and endoplasmic reticulum (ER) functions, manifesting as mitochondrial stress and ER, respectively [25]. In particular, mitochondrial stress often coincides with oxidative stress, where imbalanced overproduction of reactive oxygen species (ROS) results in genomic, proteomic, and lipid membrane damage. This accumulation of damage is involved in the formation of abnormal proteins, such as amyloids and prion-like proteins, which contribute further to cognitive aging and neurodegenerative diseases [91, 92]. Although traditionally associated with neurodegenerative disorders such as Alzheimer's, Huntington's, and Parkinson's disease, it is now recognized that oxidative stress is involved in neuropsychiatric conditions such as anxiety and depression [93-95].

In tissues characterized by high pro-inflammatory tone, such as integumentary tissues and the immune system, there exists an active cellular turnover of epitheliocytes and lymphocytes, with resting immune memory cells being the exception [96, 97]. On the contrary, neurons are postmitotic and have limited regenerative potential [98]. Aging neurons thus accumulate genomic and proteomic damage, instigating pro-inflammatory stress, which culminates in apoptosis and a resultant decrease in neuronal density within the CNS [99].

The DNA damage response (DDR) serves as a central regulator in the management of cellular stress, detecting genomic lesions, and activating a complex network of downstream factors, mediated by kinases such as ATM serine/threonine kinase. These factors ultimately dictate the fate of the cell, driving it toward survival, following DNA repair, or cell death as a result of apoptosis [100]. Key proteins such as ATM, p53, and p21 serve as integrators, evaluating various inputs to balance these dichotomous outcomes [100].

Given that neurons are postmitotic with limited regenerative capacity, DDR in these cells is geared toward promoting survival over apoptosis (regulating apoptosis in different directions, preventing its premature development). Specifically, activated ATM kinase in neurons stimulates autophagy and maintains the lysosomal-mitochondrial axis, thus dampening apoptotic pathways, although without forestalling neuronal aging [101]. Although ATM-mediated autophagy offers a temporary respite from apoptosis, it does not confer indefinite resistance to cell death. Ultimately, neurons succumb not only to apoptosis but also to programmed necrosis mechanisms such as pyroptosis, particularly when inflammasomes are hyperfunctional [102]. In this context, the release of damage-associated molecular patterns (DAMPs) from compromised cells exacerbates tissue stress and can induce neuroinflammation by binding to pattern recognition receptors (PRR) in glial cells [103].

Consequently, inflammasomes, particularly the NLRP3 variety, become a focal point, precipitating the secretion of pro-inflammatory cytokines such as IL-1β and IL-18 and further perpetuating CS. The triggers for inflammasome assembly range from molecular patterns associated with microbial pathogens (PAMPs) and endogenous DAMPs to chronic cerebral hypoperfusion, hypoxia, excitotoxicity of neurotransmitters, oxidative stress, and fluctuations in intracellular cAMP [25, 103].

Thus, CS in neurons is similar to navigating between Scylla and Charybdis; the cell must mitigate damaging factors without eliciting secondary harm from the very mechanisms designed to protect it. This is particularly pertinent in the context of autophagy, a double-edged sword. Depending on severity and context, autophagy can either resolve CS by degrading aberrant protein aggregates and dysfunctional mitochondria (as in mitophagy) or exacerbate neuronal damage and perpetuate chronic neuroinflammation [104, 105].

3.1.1. The Role of Calcium Cations in the Activation of Neurons

The role of calcium cations (Ca^{2+}) in neuronal function and activation is fundamental and intricate. In fact, normal neuronal functions require the continuous modulation of ion concentrations, including calcium, sodium, and potassium, as part of cellular homeostasis. This modulation is critical; dysregulation can result in cellular dysfunction and subsequent damage [106].

The endoplasmic reticulum (ER) serves as a key source of Ca^{2+} release into the cytoplasm, affecting the excitation of neurons and contractile tissues [106]. However, the same mechanism also precipitates ER stress, a widespread issue that affects nearly all cell types [107]. This calcium mobilization can activate calmodulin-dependent protein kinases (CaMK), which may contribute to CS [108].

Furthermore, the balance of neurotransmitter action is crucial in this context. An imbalance, specifically the hyperactivation of neurotransmitter receptors such as NMDAR1-3, can induce excitotoxicity, a toxic overstimulation of neurons. These receptors selectively bind to N-methyl-D-aspartate (NMDA) and are deeply involved in mediating excitotoxic damage [78, 109, 110].

Interestingly, a shared network of signaling pathways appears to be the basis for intracellular Ca^{2+} mobilization of intracellular Ca^{2+} in response to neurotransmitters and inflammatory mediators alike. These pathways involve mediators such as inositol-3-phosphate (IP3), phosphoinositide 3-kinases (PI3K), mitogen-activated protein kinases (MAPK), specifically ERK1/2, and members of the protein kinase C family (PKC) [111]. Common to the initiation of these signaling cascades are membrane proteins, such as G protein-

coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs), which often serve as upstream triggers.

In summary, calcium cations play a dual role in neurons: they are indispensable for normal function, but can contribute to CS and dysfunction if not tightly regulated. The pathways governing calcium mobilization are complex, involve a host of molecular players, and intersect with other signaling pathways that respond to various forms of cellular stress and damage. This makes control of calcium dynamics not only a matter of neuronal excitability but also a central issue in cellular health and pathology. More research is required to fully elucidate these complex interactions and develop targeted interventions for disorders characterized by calcium dysregulation.

3.1.2. Metabotropic Receptors GPCR and RTK in Nervous Tissue, Association with Cellular Stress

The canonical perspective posited G-protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs) as distinct and independent signaling machineries. However, this point of view underwent a paradigm shift following the seminal work by Daub *et al.* (1996), which revealed rapid tyrosine phosphorylation of epidermal growth factor receptors (EGFRs, ErbB-1) after stimulation with known GPCR agonists [112]. This key discovery established the concept of transactivation, in which the GPCR and RTK signaling pathways are not only parallel, but can directly influence each other.

The transactivation of RTK by GPCR can occur in both ligand-dependent and ligand-independent fashions [113]. In the ligand-dependent mechanism, Gβγ subunits of activated G proteins facilitate the activation of membrane proteases MMP and ADAM, which subsequently cleave the proformas of RTK ligands attached to the components of the extracellular matrix. These ligands are then liberated to interact with their corresponding RTKs. On the contrary, ligand-independent transactivation involves the activation of RTK through the phosphorylation of tyrosine residues at their C-termini by GPCR-activated effector proteins such as Src and PKC kinases. Additionally, second messenger molecules, such as reactive oxygen species (ROS), can directly initiate RTK activation.

Within the human genome, there are 90 tyrosine kinases, of which 58 are classified as RTKs. These RTKs are divided into 20 subfamilies [114]. Neurogenic RTKs encompass nerve growth factor receptors (NGFRs), tropomyosin receptor kinase receptors (TrkB, TrkA, TrkC), glial cell-derived neurotrophic factor receptor (GFR), fibroblast growth factor receptors (FGFR1-4), platelet-derived growth factor receptors (PDGFRα/β), and others such as EGF and neuregulin receptors (ErbB1-4), and receptors for insulin and insulin-like growth factor (IR and IGFR) [114-121].

Simultaneously, RTKs and GPCRs not only engage in mutual regulation but also utilize the same components of signaling pathways related to cellular pro-inflammatory stress (CS). Such components include Ras small GTPases, calcium mobilization from the endoplasmic reticulum, and specific kinases such as CaMK, PI3K, PKB (AKT), PKC, and MAPK.

On the other hand, most neurotransmitters interact through GPCRs. These neurotransmitters include catecholamines, serotonin, histamine, acetylcholine, GABA, endopioids, endocannabinoids, substance P, and neurokinin 1. Furthermore, glutamate acts *via* metabotropic receptors (mGluR), and purine mediators operate through AR (P1R) and P2YR receptors [122, 123]. Activation of GPCRs typically results in enhanced intracellular signaling aimed at both executing specific cellular functions and maintaining key aspects of homeostasis. However, hyperactivation of these receptors can lead to a loss of normal physiological properties of the cell and a disruption of cellular and tissue homeostasis [124].

Structurally, GPCRs are integral membrane proteins characterized by a signature arrangement of seven transmembrane helices and four intracellular and extracellular loops each [125]. Their pivotal role in cellular signaling has made them prime pharmacological targets [126]. However, their inherent promiscuity presents a challenge; GPCRs have the propensity to interact with multiple subfamilies of G proteins. Consequently, a single ligand has the ability to act on multiple G proteins, thus activating a network of signaling pathways through various GPCRs, some of which belong to different subfamilies of G proteins [127]. This complexity impedes straightforward analysis and predictions on the specificity of ligand-induced responses in the context of individual GPCRs (Fig. **3**).

Heterotrimeric G proteins associated with GPCRs comprise four different subfamilies (Gs, Gi/o, Gq/11 and G12/13), classified according to the functional and structural homology of their α-subunits [128]. In particular, the human Gq/11 subfamily extends beyond Gq and G11, including G14 (predominantly found in the kidneys, lungs, and liver) and G16 (exclusively expressed in hematopoietic cells) [129]. Each Gα subunit functions as a GTP binding protein with intrinsic GTPase activity, while the remaining subunits, Gβ and Gγ, form an integral and inseparable complex commonly called the Gβγ subunit.

Upon binding to the ligand, the activated GPCR facilitates the dissociation of the Gαβγ complex into its Gα and Gβγ components by catalyzing the exchange of GDP for GTP in the Gα subunit (Fig. **S1**). Subsequently, both the liberated Gα-GTP subunit and the membrane-associated Gβγ dimer orchestrate several downstream signaling events, the specifics of which are dictated primarily by the type of Gα subunit involved (Fig. **S1**). After fulfilling its GTPase function and hydrolyzing GTP to GDP and inorganic phosphate, the Gα-GDP subunit reassociates with the Gβγ complex, thus inactivating the GPCR. Concurrently, the activity of GPCRs can be modulated by pro-inflammatory cytokines such as TNF-α and IL-6, among other inflammatory mediators [130].

It should be noted that while the main ionotropic receptor for neuron activation, NMDAR, is not a GPCR, its activity can be modulated by various neurotransmitters acting through metabotropic GPCRs [131].

3.1.3. The Role of Phospholipase C (PLC) as Links in GPCR Signaling Pathways

GPCR activation has traditionally been evaluated through the production of second messengers such as cyclic adenosine monophosphate (cAMP), phospholipase C (PLC), inositol trisphosphate (IP3) and intracellular Ca^{2+} mobilization. The primary activator of PLC is the activated form of the Gq α-subunit (Gαq). However, certain PLC isoforms can also be activated by Gβγ dimers, notably those associated with Gi/o and Gq proteins [132-134]. On the α-subunits of Go proteins, they have been shown to inhibit PLC [135].

Once activated, PLC catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2) in the cellular membrane. This enzymatic activity produces two secondary messengers: diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3-1,4,5). DAG remains embedded within the lipid bilayer of the cell membrane, while IP3-1,4,5 is released into the cytosol. Subsequently, these messengers facilitate additional signaling pathways, primarily through activation of protein kinase C (PKC) and mobilization of intracellular Ca^{2+} reserves [136] (Fig. **S1**).

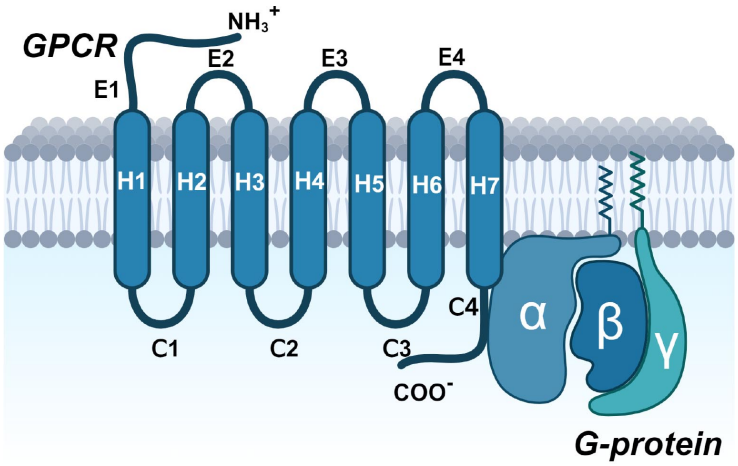

Fig. (3). Schematic structure of an unactivated GPCR bound to a trimeric G protein (Gαβγ). **Note**: The GPCR consists of seven domains or transmembrane helices (H1-7), four extracellular loops (E1-4), and four intracellular loops (C1-4). A trimeric G protein is associated with GPCR, which, upon activation and exchange of GDP for GTP in the α subunit of receptors, dissociates into Gα and Gβγ, triggering various signaling pathways. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

The role of PLC in GPCR signaling underscores its pivotal function as a link between receptor activation and downstream cellular responses. By serving as a catalyst in the formation of secondary messengers, PLC orchestrates a cascade of signaling events that have far-reaching implications for cellular physiology.

3.1.4. The Role of Protein Kinase C

The PKC protein family is an integral component of the expansive ABC protein kinase superfamily. This superfamily also includes Protein Kinase A (PKA), Protein Kinase B (PKB, also synonymous with AKT), and PKC [137]. Various isoforms of PKC are activated by a multitude of receptors, including those for growth factors, cytokines, eicosanoids, and hormones. Activation typically occurs *via* G-proteins, tyrosine kinases, and PLC. PKC plays a pleiotropic role in governing numerous physiological and pathological responses [138-140].

In particular, different PKC isoforms have been implicated in oxidative stress, regulation of cytokine-induced apoptosis, activation of the pro-inflammatory transcription factor NF-κB, and various mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase (ERK). These isoforms also influence the development of a secretory and receptor pro-inflammatory phenotype in both immunocompetent and other cell types. These actions are relevant not only during inflammatory responses, but also during normal physiological processes [141-146].

Furthermore, PKC modulates the signaling pathways of several neurotransmitters such as acetylcholine [147], N-methyl-D-aspartate (NMDA) [148], serotonin [149], catecholamines [150, 151], and substance P [152]. Consequently, PKC regulates the release and reception of many neurotransmitters at synaptic sites [153-155].

When activated by Gq, PKC can phosphorylate and activate L-type calcium channels in neurons, cardiac cells, and smooth muscle cells. This action often results in a vasoconstrictive effect [156]. PKC also enhances calcium mobilization by activating TRPC ion channels in vascular smooth muscle, TRPV1 channels in the CNS and immune system -particularly related to inflammation and pain perception - and TPRM channels in the nervous system [157].

Many regulatory effects of PKCs can be achieved by activating Src family kinases, including Src and Fyn [158-162]. In particular, Src kinases are also integral to cytokine signaling in various inflammatory processes [163-166]. Src kinases are involved in nervous tissue embryogenesis and, in the adult brain, modulate neuronal positioning memory and learning mechanisms by affecting synaptic mobility and promoting dendritic and axonal development [167-170]. Currently, Src kinases are involved in various neurological diseases. Moreover, both Src kinase and PKC can potentiate NMDAR expression, a process that can have adaptive or deleterious implications through NMDA excitotoxicity [171].

Some PKCs, mediated by Src kinases, can activate the PI3K/AKT and MAPK-ERK signaling pathways [172]. However, these actions can be bidirectional, depending on the specific isoforms of PKC involved [173]. Furthermore, PKC can activate ERK through the Raf/ERK1/2, pathway, as demonstrated in mechanically stressed endothelial cells [174].

In neurons, both excitatory (glutamatergic) and inhibitory (GABAergic), PKC has been shown to activate the pro-inflammatory transcription factor NF-κB [175, 176]. PKC can activate NF-κB *via* multiple pathways, including the PKC/ERK/NF-κB and PKC/MEK/ERK/NF-κB signaling cascades [177-179]. It should also be noted that neurotransmitter-induced activation through PKC can target not only ERK but also other MAPKs such as JNK and p38, particularly through the GPCR/Gq/PKC/Sc kinase/MAPK pathway. These pathways may result in more pronounced NF-κB activation of NF-κB compared to ERK [180]. Moreover, PKC can directly activate NF-κB *via* phosphorylation of IKKα [181].

PKC, which functions as a crucial element in neurons and glial cells, actively participates in the phenomena of brain aging, neurodegeneration, and various forms of neuroinflammation [182-184].

3.1.5. The Role of the Transcription Factor NF-kB in Normal and Neuroinflammation

The Nuclear Factor-κB (NF-κB/Rel) family, comprising NF-kB1, NF-kB2, RelA, RelB and c-Rel, which together form 15 distinct NF-κB dimers, serves as a critical set of transcription factors that are instrumental in modulating the expression of inducible

genes. These factors are particularly important when cells are endeavoring to restore homeostasis [185]. Situated at the core of cellular signaling during CS development, NF-κB plays a vital role in orchestrating cellular responses to oxidative stress. This is especially true in immunocytes and various other cell types, during the onset and progression of numerous inflammatory conditions [186, 187].

In the context of the immune system, NF-κB is indispensable for a wide spectrum of functions, ranging from acute inflammatory responses to the formation of secondary lymphoid organs. Beyond its immunological scope, NF-κB is vital for the survival, proliferation, and differentiation of nearly all types of human cells. Regarding neuroinflammation, the NF-κB pathways are instrumental in modulating the expression of pro-inflammatory genes, including cytokines, chemokines, and adhesion molecules [188].

Moreover, the role of NF-κB extends to the neural sphere, particularly in the regulation of synaptic plasticity. Activation of NF-κB signaling pathways through excitatory neurotransmission may well underlie the function of this transcription factor in cognitive behavior, both in healthy states and in pathological conditions [175]. Furthermore, the expression of NF-κB has been implicated in reducing the probability of apoptosis in aging neurons, acting as a protective mechanism against age-related neurodegenerative diseases [189, 190].

However, it is crucial to note that unbalanced overexpression of NF-κB in neurons and glial cells can have deleterious effects. Such dysregulation increases the propensity for pyroptosis and cell death, manifesting, for example, in depressive disorders [191]. This aberrant activity of NF-κB serves as a key driver in the pathogenesis of both neuroinflammation and neurodegenerative diseases [192, 193].

In summary, NF-κB serves a dual role, acting as both a guardian of cellular homeostasis and a potential harbinger of cellular dysfunction, depending on the context and balance of its expression.

3.1.6. Phosphoinositol 3-kinase Signaling Pathways (PI3K)

Most GPCRs activate PI3K, similarly to RTKs, through small GTPases. These GTPases are activated by the α subunit of various G proteins such as G12/13, Gi/o, Gq/11 and Gq, or directly through G βγ dimers (Fig. **S1**) [194-196]. Currently, Gq not only activates PI3K through protein kinase C (PKC) and small GTPases, but can also directly inhibit the catalytic subunit of the catalytic subunit PI3K p110a catalytic subunit *in vitro* [197]. Subsequent research confirmed the potential for Gq inhibition of PI3K [198]. This evidence underscores that CS activation pathways initiate negative feedback mechanisms aimed at resolving CS. Consequently, the pro-inflammatory and anti-inflammatory mechanisms of CS should not be considered in isolation; they are interconnected components of a unified system.

Class I PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate to form phosphatidylinositol-3,4,5-triphosphate. Upon hydrolysis of the ester bond between phosphate and inositol, inositol-3,4,5-triphosphate (IP3-3,4,5) is formed. This molecule, similar to IP3-1,4,5, facilitates the release of Ca^{2+} through the ionotropic receptors IP3 R1-3 (calcium channels). This process initiates a cascade of regulatory effects, including the activation of AKT, PKC, and small GTPases such as Ras, Rac, and Rho [199]. Activation of these enzymes subsequently triggers a wider array of downstream other CS inducers (Fig. **S1**).

The PI3K/AKT/mTOR pathway is highly versatile and prevalent in human cells. Regulation of processes that include prevention, growth, cell proliferation, DNA repair, and metabolism, primarily anabolism. It also inhibits macroautophagy and participates in various other CS processes [25]. This pathway is activated by insulin, multiple growth factors, cytokines, and most neurotransmitters [199, 200]. Inhibitors of this pathway have therapeutic potential in the treatment of autism and other neuropsychiatric and neurodegenerative disorders [201]. Interestingly, the PI3K/AKT/mTOR signaling pathway, while contributing to moderate manifestations of CS, can also enhance anti-inflammatory effects and limit neuroinflammation [202]. For example, the antidepressant-like effects of valproic acid may be linked to the activation of this pathway [203]. The pathway can also mitigate NMDA excitotoxicity associated with pathological autophagy hyperfunction [204]. However, overexpression of this pathway in an experimental model of intracerebral hemorrhage in rats exacerbates the production of pro-inflammatory cytokines and neuroinflammation [205].

Cytokines, growth factors, insulin, and numerous neurotransmitters can activate the more pro-inflammatory PI3K/AKT/NF-κB signaling pathway in a variety of cells, thus decreasing the probability of apoptosis, particularly in neurons [206-211]. Furthermore, the PI3K/AKT pathway triggers two critical DDR transcription factors, FOXO, and p53, which are important for neuronal survival or, conversely, apoptosis in the context of catastrophic DNA damage [212]. In general, the PI3K/AKT pathway can contribute in a variety of ways to pro-inflammatory and anti-inflammatory responses, depending on the context of CS mechanisms and neural cell types. Current paradigms suggest that PI3K/AKT is crucial in initiating the production of pro-inflammatory mediators in microglia, after stimulation of these stromal macrophages in the development of neuroinflammation [213].

3.1.7. MAPK - ERK Paths

Mitogen-activated protein kinases (MAPKs) serve as central components in various cell signaling CS pathways in virtually all eukaryotes [214]. A significant evolutionary surge in the duplication of the MARK gene occurred after the divergence of vertebrates from invertebrates [215]. This evolutionary advancement is closely correlated with the progressive maturation of the vertebrate immune system and intricate inflammation pathways [216-218].

The MAPK family in humans comprises three distinct subfamilies: extracellular signal-regulated kinases (ERK1/2), p38 kinases (p38α, p38β, p38γ, and p38δ), and N-terminal kinases of c-Jun (JNK1-3). Typically, growth factors, neurotransmitters, and other relatively mild inducers of CS are mediators of ERK signaling pathways. On the contrary, JNK and p38 are activated in response to more robust stress signals or intracellular damage [25, 219].

The ERK pathway is a complex and highly branched signaling cascade that regulates a myriad of cellular functions such as apoptosis and cell adaptation to low-intensity stressors. ERKs play a particularly significant role in neurotransmitter function, possessing minimal pro-inflammatory potential among MAPKs but are crucial for nerve cell survival under both normal and moderate stress conditions. The ERK cascade is a principal signaling pathway that affects a broad range of cellular processes, including, but not limited to, proliferation, differentiation, learning and memory, development, and synaptic plasticity. It maintains the functional stability of glial cells and neurons [220-222]. However, dysregulated activation of ERK and other pro-inflammatory pathways can contribute to neuronal damage and dysfunction [223-225].

ERK activation is modulated through various GPCR regulatory channels, including small GTPases that govern the Ras/Ras/MEK/ERK, PI3K/ERK, and PKC/MEK/ERK pathways [226-228] (Fig. **S1**). However, there exists conflicting evidence suggesting that the

PI3K/AKT pathway can phosphorylate Raf, effectively down-regulating its activity on downstream substrates, such as MEK/ERK [229]. This presence of multidirectional regulatory mechanisms ostensibly renders ERK activity more balanced and controllable.

Furthermore, activation of GPCR and RTK stimulates the formation of the β-arrestin/ERK signaling complex. This can occur independently of G proteins or involve the participation of the Gβγ dimer [230-233]. GPCRs can activate MAPKs (including ERK and JNK) through the recruitment of β-arrestin *via* the Raf/MEK/ERK and ASK/MKK/JNK pathways [234]. Concurrently, β-arrestin facilitates desensitization and internalization of the GPCR through a negative feedback mechanism [198, 234].

3.1.8. Cyclin-dependent Kinase-5 (Cdk5): Regulatory Mechanisms and Implications in Neurobiology

Cyclin-dependent kinase-5 (Cdk5), a prominent member of the cyclin-dependent kinase family, is ubiquitously expressed. Unlike other Cdks, Cdk5 exhibits unique functionalities specifically in postmitotic neurons, a context where other members of the cyclin-dependent kinase family are not expressed or inactive [235-238]. Cdk5 does not participate in cell cycle progression in proliferating cells. Instead, it plays a dual role: either contributing to genome stabilization and survival in postmitotic neurons or exerting aberrant effects when dysregulated. Deregulation of Cdk5 in postmitotic neurons can culminate in cell death.

During embryogenesis, Cdk5 is indispensable for brain development, and in the adult brain, it plays a crucial role in various neural processes, including, but not limited to, higher cognitive functions such as learning and memory formation. However, aberrant activity of Cdk5 is involved in the pathogenesis of several neurological disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease, leading to neurotoxic outcomes [237].

The regulatory mechanisms of Cdk5 are complex and multifaceted. Cdk5 can be activated by a multitude of neurotransmitters and pro-inflammatory factors through pathways such as PI3K and calcium ions. On the contrary, its activity is inhibited by the light chain enhancer NF-κB. Furthermore, Cdk5 is subject to multidirectional regulation by mitogen-activated protein kinases (MARKs), specifically ERK and JNK [235, 237].

In psychopathological conditions such as emotional stress, depression, and neuroinflammation, the role of Cdk5 can be paradoxical. It can serve as a neuroprotective factor or, in contrast, contribute to neurodegeneration, depending on the specific pathological context [237, 239-241].

3.1.9. Small GTPases: Key Regulators in Neural Development and Pathology

The G proteins are classified into two distinct subclasses: (1) heterotrimeric G proteins, comprising Gα, Gβ, and Gγ subunits, which are predominantly associated with GPCRs, and (2) small monomeric G proteins, also known as small GTPases [242, 243]. Small GTPases are evolutionarily conserved proteins, ranging in size from 20 to 25 kDa, and belong to the larger Ras superfamily, which is further divided into five primary subfamilies: Ras, Rho, Rab, Ran, and Arf. Similarly to other G proteins, small GTPases have the ability to bind and hydrolyze guanosine triphosphate (GTP) [242, 243].

The activation of small GTPases is often mediated by a variety of ligands, including pro-inflammatory cytokines, growth factors, and neurotransmitters. These ligands interact with membrane-associated G proteins, primarily through GPCR, RTKs, and non-receptor tyrosine kinases, facilitating downstream signaling events [244-247]. Furthermore, specific G proteins such as G12/13 and Gq also elicit signaling through small GTPases [128, 248, 249].

Small GTPases play a crucial role in numerous cellular processes essential for the comprehensive development and maintenance of the nervous system. They are involved in neurogenesis, cell differentiation, gene expression, cytoskeletal organization, membrane and protein transport, vesicular transport, synaptic plasticity, and neuronal survival [250-252]. Specifically, small GTPases function as integral enzymes that transduce extracellular signals into neural responses, facilitating the construction of neural networks and synaptic plasticity. They can act as independent activators of the ERK signaling pathway *via* the Ras /Ras/MEK/ERK cascade when neurotransmitters interact with GPCR [253].

Furthermore, small GTPases such as Ras, Rho, and Rab have been shown to activate PI3K and various signaling pathways related to PI3K [254-256]. Some Rab-GTPases also regulate the proper expression of GPCRs on the cell surface and are involved in multiple steps of GPCR biosynthesis and processing [257]. Small GTPases can also activate PKC, for example, through the Rho-GTPase/PKC pathway [258].

Given their wide range of functions, it is hardly surprising that abnormalities in small GTPase activity are linked to a myriad of cerebral diseases, including Alzheimer's disease, Parkinson's disease, intellectual disabilities, epilepsy, substance abuse, Huntington's disease, and amyotrophic lateral sclerosis, among others [250-252]. Importantly, small GTPases are intricately involved in the mechanisms of neuroinflammation, further underscoring their importance in neural pathophysiology [251, 252, 259].

3.1.10. The Role of Cyclic Nucleotides in GPCR-mediated Signal Transduction: Complex Modulators of Cellular Physiology and Pathophysiology

Cyclic nucleotides, mainly cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), serve as secondary pivotal messengers in GPCR signaling [260, 261]. The concentration of these nucleotides in the cytoplasm modulates various cellular activities, with some GPCRs stimulating adenylate cyclase (AC) through Gs proteins to increase cAMP levels, and others inhibiting AC through Gi and Go proteins (Fig. **S1**). Furthermore, the βγ subunits released after Gq-coupled GPCR activation play a multidirectional regulatory role in six of the nine membrane-bound AC isoforms [262].

Cyclic nucleotides govern a wide variety of cell functions, including cell growth and differentiation, gene transcription, protein expression, synaptic plasticity, neurotransmission, and the maintenance of cellular homeostasis. Although the AC/cAMP/protein kinase A (PKA) and guanylate cyclase (GC)/cGMP/protein kinase G (PKG) signaling axes are not explicitly categorized as pro-inflammatory pathways, their ubiquitous role in metabolic processes, cell cycle regulation, and ion channel activity makes them intersect with cytokine signaling pathways, especially in the CNS [263-265].

At elevated concentrations, cAMP generally exerts anti-inflammatory and tissue-protective effects, primarily by sequestering cytoplasmic calcium [263-265]. However, the function of cAMP in cellular processes is far from straightforward. For example, PKA phosphorylates various proteins that regulate ion flux through the L-type calcium channel (LCC) and the ryanodine receptor (RyR), thus modulating excitation-contraction coupling [266]. Furthermore, cAMP production is inhibited in the Gi/o G protein pathway, as well as by voltage-gated calcium channels (VGCC) [266].

In particular, the signaling mechanisms for cAMP and calcium are not isolated, but rather often interact in an antagonistic, synergistic or redundant manner [262]. The complexity of the cAMP/PKA pathway extends to its multiplicity of interacting components: nine membrane-associated ACs, one cytosolic Ca^{2+}-sensitive AC, eight phosphodiesterase families, multiple PKA subunits, and up to six cAMP-dependent ion channels [267, 268].

Furthermore, all isoforms of membrane AC can be modulated by calcium, either directly or indirectly, through calcium-binding proteins such as calmodulin (CaM), CaM kinases (CaMK), calcineurin (CaN), PKC or Gq-linked activation [267, 268]. This intricate network of interactions adds layers of complexity to cAMP-mediated cell responses, making its effects highly context-dependent. For example, cAMP can both inhibit and stimulate cell proliferation depending on cell type and can influence cell outcomes through ambiguous interactions with the Ras/Ras/MEK/ERK pathway [267, 268].

In certain cellular contexts, PKA exhibits a multifaceted role in modulating signaling pathways. Not only does PKA modulate ERK, but it also phosphorylates and activates p38 MAPK [269]. Furthermore, PKA can stimulate NMDAR expression in synapses by activating CaMKII and ERK, in collaboration with mobilized calcium, PKC, and Src kinase [270]. This synergistic action can amplify excitotoxicity mediated by NMDA under specific conditions. Furthermore, cAMP regulates various phosphodiesterases, thus offering negative feedback mechanisms that control both the duration and intensity of cAMP signaling [271]. These observations do not unequivocally categorize the cAMP/PKA pathway as an inhibitor of cell signaling during the pro-inflammatory CS development. Instead, they suggest that the cAMP/PKA pathway exerts a complex modulatory impact on several mechanisms with potential pro-inflammatory implications.

The cGMP signaling pathway, initiated primarily through nitric oxide (NO), serves as another pivotal component in cell signaling with a wide range of physiological implications [272, 273]. Constitutive neuronal NO synthase (nNOS) is activated directly *via* calcium/calmodulin (Ca^{2+}/CaM) or indirectly through the Ca^{2+}/CaM/CaMK pathway [274, 275]. However, the role of these activating pathways is dual-faceted.

For example, CaMKII can redirect nNOS from NO to superoxide anion (O^{2-}) production, which can exacerbate oxidative stress and decrease the protective role of the NO/cGMP pathway [276]. Conversely, direct action of Ca^{2+}/CaM on nNOS competitively inhibits CaMKII through NO formation. CaMKII hyperactivity can therefore lead to excitotoxicity in neurons, which is further amplified by increased oxidative stress (O^{2-}) and reduced NO/cGMP-mediated protection. Furthermore, reactive oxygen species (ROS) further activate CaMKII in a positive feedback loop, serving as an additional stimulus for NF-κB activation of NF-B and the progression of CS [277].

In neurons, the main physiological NO receptor is soluble guanylate cyclase (sGC), which is activated by NO to produce cGMP [278]. The NO/cGMP/protein kinase G (PKG) pathway is the main effector through which NO exerts its influence. Elevated levels of cellular cGMP activate PKG and other cGMP-dependent kinases, phosphodiesterases (PDEs), and ion channels that affect various cellular processes [279]. These range from calcium sequestration to cytoskeletal changes, vascular smooth muscle cell relaxation, improvement in tissue oxygenation, inhibition of leukocyte adhesion and migration, reduction of platelet aggregation, and even repair of damaged endothelium. Additionally, this pathway regulates gastrointestinal motility and exerts an inhibitory effect on the proliferation and migration of vascular smooth muscle cells (VSM-C).

In the context of the central nervous system (CNS), the NO/cGMP/PKG pathway plays a particularly crucial role in modulating neuroinflammation [280-283]. This modulation is context-specific and agonists targeting this pathway have shown therapeutic promise in neurodegenerative diseases [283, 284].

In summary, the NO/cGMP pathway constitutes a complex but vital component of cellular signaling, with specific relevance for neuroinflammation and neurodegenerative diseases. Its modulation by the calcium and CaMK pathways adds an additional layer of complexity, making it a topic of significant interest for therapeutic intervention strategies. The dual roles of the pathway in both anti-inflammatory and pro-oxidative processes underscore the need for nuanced understanding and targeted pharmacological modulation.

The intricate relationships between Ca^{2+}, NO, and cGMP in the CNS present an elaborate signaling network with multifaceted functional implications. Calcium mobilization is known to increase NO production, thus activating soluble sGC. This chain of events also influences calcium ion concentrations within the cell by modulating (predominantly inhibiting) both intracellular reserve release and membrane transport [285].

From a neurophysiological perspective, activation of the sGC/cGMP/PKG pathway has been associated with increased excitatory potentials in midbrain neurons mediated by glutamate and acetylcholine receptors [286]. However, the pathway is susceptible to inhibition under conditions of chronic stress, resulting in impaired memory and learning functions, particularly in the hippocampus [287, 288]. Currently, evidence suggests that sGC stimulation could be neuroprotective by attenuating inflammatory responses and apoptosis in models of neuroinflammation [283].

Within cellular metabolic processes, the cGMP/PKG pathway activates a multitude of anabolic reactions, including those integral to cell cycle regulation. In particular, guanylate cyclase has been implicated in the activation of various (RTK-related and G-protein-mediated growth factors, such as platelet-derived growth factor (PDGF) [284].

However, the role of cGMP/PKG in the development of inflammation and neuronal excitation remains unclear [285-287]. For example, the activation of NLRP3 inflammasomes in endothelial cells by tobacco smoke has been mediated by the cGMP/PKG/-TACE/TNF-α signaling pathway [289]. Furthermore, gaps persist in our understanding of the precise mechanisms that activate sGC, including its post- translational modifications, allosteric regulation, and interactions with partner proteins [278].

Therefore, the sGC/cGMP/PKG signaling network in the CNS represents a complex modulatory system with varying implications for cell physiology, neuroinflammation, and neuronal functions. Despite considerable advances in our understanding, unresolved questions and poorly understood mechanisms require further rigorous investigation for a more systematic understanding of the roles of this pathway. This could potentially offer new avenues for targeted therapeutic interventions in the CNS.

3.1.11. The Multifaceted Role of CaMKII in Stress-induced Pathologies in Nervous Tissue

Calcium/calmodulin-dependent protein kinase II (CaMKII) is a crucial mediator in the CNS, involved in the complex interplay of calcium signaling, neurotransmitter release, and neuroinflammation. It is abundantly expressed in the brain, where it has been estab-

lished as a key molecular player in learning and memory [290-292]. Comprising mainly α and β isoforms, CaMKII influences a range of cellular activities, including exocytosis of neurotransmitter vesicles, ion channel activity, synaptic plasticity, and intracellular transport [293, 294].

In the context of cellular stress, CaMKII plays a critical role in the activation of neuroinflammatory pathways. This includes interactions with Ras and Rho GTPases, MAPK, activator protein 1 (AP-1) and NF-κB transcription factors, as well as the generation of eicosanoid *via* the COX-2/PGE2 pathway [295, 296]. Kinase has been associated with the development of excitotoxicity and oxidative stress, conditions that are frequently exacerbated under psychoemotional stress and depression [297-299].

Furthermore, the role of CaMKII in NO signaling adds another layer of complexity to its multifunctionality. For example, CaMKII-mediated phosphorylation of nNOS decreases [299-301] NO and cGMP production while increasing superoxide generation [276]. On the contrary, CaMKII can inhibit phosphodiesterase 1 (PDE1), which is responsible for the degradation of cGMP and cAMP, thus activating the cGMP/PKG pathway [298]. Furthermore, CaMKII can modulate the activity of inducible NO synthase (iNOS) vascular smooth muscle cells (VSMC) and endothelial cells, leading to the redistribution of iNOS from the cytosol to the membrane and nuclear compartments [300, 301].

The broad impact of CaMKII is particularly notable in the context of inflammation. The enzyme can influence the angiotensin II vasopressor mechanisms in VSMC [302] and mediate vasodilation and exudative responses through iNOS during inflammation [303-305]. These roles fit the broader paradigm that associates low-grade systemic inflammation with hypertension and inhibition of constitutive NO synthase (cNOS) [37].

Together, the actions of CaMKII in the CNS are multifaceted and context-dependent, making it an enigmatic but essential participant in cellular stress responses. Its influence is broad, reaching from cellular signaling pathways to systemic responses in stress-related pathologies.

3.2. Pro-inflammatory Factors in Normal Central Nervous System Function

The CNS has long been considered an immune-privileged site, largely due to the presence of the blood-brain barrier and a relative scarcity of immune cells within the brain parenchyma. However, understanding the CNS as an immunologically active environment has gained considerable attention, mainly attributed to the role of resident immune cells such as microglia and perivascular macrophages [306].

Microglia serve as primary immune sentinels in the CNS, where they adopt a relatively quiescent phenotype under physiological conditions [307-316]. This phenotype is functionally aligned with the neuroprotective state M2, which facilitates CNS homeostasis through efferocytosis, clearance of metabolic waste, and modulation of synaptic plasticity [309-312]. The M2 state contrasts with the pro-inflammatory M1 state, which is associated with neuroinflammation and pathological conditions [311].

According to complement pathways C1q, C3, and CR3 - designated as the “Eat Me” pathways - as well as the CD47 and SIRPα “Don't Eat Me” pathways, among others, such as CX3CR1 signaling, quiescent microglia orchestrate the regulation of synaptic plasticity. This physiological process is essential to facilitate the genesis of new synapses [310]. Furthermore, microglia can modulate synaptic architecture modulate synaptic architecture either directly or indirectly. Direct modulation occurs through intimate neuron-microglia contact, while indirect modulation is achieved through the secretion of various cytokines and growth factors [315]. Furthermore, microglia are involved in the regulation of neurotransmission and contribute to the metabolic sustenance of astrocyte-neuronal networks, as well as the remodeling of the extracellular matrix within the CNS [316].

In several studies, evidence has been presented to suggest that neurons within an unimpaired cerebral environment not only habitually express mRNA from the Major Histocompatibility Complex Class I (MHC-I), but also that this expression is susceptible to modulation by neuronal activity. Moreover, this expression is temporally and spatially correlated correlated with recognized locations of synaptic plasticity [317].

Recent evidence suggests that even under normal conditions, pro-inflammatory mediators like IL-1β, IL-6, and TNF-α serve critical role in neuronal plasticity, learning, and memory [313]. Specifically, IL-6 demonstrates a dual nature; while predominantly known for its role in immune responses, it also has substantial effects on neurogenesis and cellular responses under both normal and pathological conditions [318].

This dual role of pro-inflammatory cytokines mirrors that of other key elements in the CNS, such as major histocompatibility complex class I (MHC-I) molecules, which are not only involved in immune responses, but also play a role in synaptic plasticity [317]. Intriguingly, in the nervous system, the association between the glutamate receptor—NMDAR—and cell signaling factors such as NF-κB, JAK/STAT, and p53 is discernible even in lower vertebrates, specifically in zebrafish (Danio rerio) [319]. This observation underscores the evolutionary conservation of these signaling pathways and their potential significance in neural functioning across diverse taxa.

In particular, the importance of these pro-inflammatory pathways becomes more pronounced under conditions that tread the fine line between physiological normalcy and pathological states. For example, ethanol-induced neuroimmune responses in the CNS have been associated with key pro-inflammatory cytokines and chemokines [320].

In conclusion, the existing literature provides compelling evidence for the intricate involvement of pro-inflammatory factors in the maintenance of physiological processes in the CNS. Their role extends beyond simple pathological implications, serving functional functions in synaptic plasticity, learning, and memory. As research progresses, a nuanced understanding of these dual functions will provide vital insight into both the normal physiology and the pathophysiology of the CNS.

3.3. The Role of Cellular Stress Mechanisms in Morbid Psycho-emotional Stress and Depression

The etiology of psycho-emotional stress is multifactorial and is influenced by various triggers. These include the imposition of self- isolation protocols during the COVID-19 pandemic [321, 322], psychogenic and physical traumas such as post-traumatic stress disorder [323, 324], and unresolved psychological conflicts that lead to anxiety and the perception of unattainable life goals [325, 326]. Furthermore, the presence of somatic symptoms can exacerbate stress-induced asthenia and depression [327], as well as social maladaptation [328, 329].

Depression often emerges as a sequel to chronic stress or distress [330, 331]. In particular, MDD is one of the leading causes of global disability and shares numerous pathogenetic mechanisms with chronic stress [332].

3.3.1. Hypotheses Exploring the Relationship between Stress and Depression

Morphofunctionally, stress and depression manifest through the presence of hyperexcitable foci in specific neural regions, including the cortex, the limbic-reticular complex, and the hypothalamic-pituitary-adrenal axis (HPA) [330]. When these foci become chronic, they evolve into allostasis loci, disrupting not only the functions of the CNS but also peripheral tissues [330-334]. Various neuro transduction mechanisms, susceptible to excitotoxicity, neuronal damage, and pro-inflammatory activation of glial cells, play a role in these processes.

Existing hypotheses such as the "monoamine hypothesis" [335], the "Glutamate and Neuroplasticity Hypothesis" [336-338], and the "Neurotrophic Hypothesis" primarily focus on isolated molecular pathways and neurotransmitter systems.

The "monoamine hypothesis" posits that the pathogenesis of stress and depression is primarily due to the depletion of brain monoamine neurotransmitters, such as serotonin, norepinephrine, and dopamine [335].

The "Glutamate and Neuroplasticity Hypothesis" contends that depressive disorders result from reduced neuroplasticity and dysregulation triggered by glutamate excitotoxicity. Significant clinical and experimental evidence accumulated over the last three decades substantiates the role of the glutamatergic system in the pathophysiology of stress and depression [336-338].

Two additional hypotheses have been proposed to elucidate the observed reduction in hippocampal volume in depressive disorders: (1) the "Neuroplasticity Hypothesis", focused on morphological changes in hippocampal neurons; and (2) the "Hypothesis of Impaired Neurogenesis in the Dentate Gyrus of the Hippocampus" [339].

The 'Neurotrophic Hypothesis' attributes a change in synaptic plasticity in depression to impaired neurotrophic support [340, 341]. Neurotrophins, as growth factors, are integral to the formation, maintenance, and plasticity of neural networks.

To extend our understanding of these interrelated complexities, we introduce the NIIS Model. This framework posits that pro-inflammatory signaling pathways and neurotransmitter pathways, specifically those involving G-proteins and 5-HT, form an integrated regulatory network even under physiological conditions. Chronic stress disrupts this balance, serving as a pathogenetic platform for a spectrum of neuropsychiatric and psychosomatic disorders, including depression. Our model integrates multiple facets of neuroimmunoinflammation and psychoemotional stress, and offers a comprehensive view that considers the synergistic interactions between the CNS and peripheral systems.

Another hypothesis concerns the disruption of the "long neuronal chain of monoamines". According to this model, both monoaminergic mechanisms (such as 5-HT neurons in the raphe nuclei) and nonmonoaminergic mechanisms (Glu/GABA neurons in the prefrontal cortex) are critical components of fast-acting antidepressant mechanisms. These two systems form an extensive neural circuit responsible for rapid synaptic plasticity in various regions of the brain, including the prefrontal cortex [342].

A seminal systematic review by Brigitta B. (2002) provides compelling evidence that chronic stress not only influences behavior, but also exerts broad effects on the endocrine, immune, and neurotransmission systems [343]. These findings suggest an intricate interplay between psychoemotional stress and altered relationships between the neuroendocrine and immune systems at the organismal level. As a consequence, depression may arise from dysfunctions in specific regions of the brain, such as the frontal cortex, hippocampus, amygdala, and basal ganglia, which are modulated by these systems in a feedback loop [344].

The complexity and integrative nature of the NIIS Model make it an essential addition to current academic discussions surrounding the pathology of stress-induced disorders. It aims to fill the existing gaps in our understanding by amalgamating insights from diverse biochemical pathways and molecular mechanisms.

3.3.2. The Nexus Between Oxidative Stress and Psychoemotional Stress

In normally functioning neurons, there is a consistent formation and utilization of reactive oxygen species (ROS) taking place [345]. Furthermore, the coenzyme NADPH -generated through the pentose phosphate pathway of glucose catabolism - is actively involved in microsomal oxidation processes, including the synthesis of NO from arginine in neurons and other brain cells [346]. During psychoemotional distress, an imbalance occurs in favor of oxidant activities over antioxidant defenses, resulting in oxidative stress within hyperactivated brain regions [345, 347]. Moreover, localized cerebral changes instigated by distress contribute to systemic pathologies, primarily of cardiovascular nature [348, 349].

This phenomenon can also be amplified into a systemic response to oxidative stress, considering the integrative role of the cardiovascular system [350]. Hence, a vicious cycle is established that perpetuates neurodegenerative processes in the brain and low-grade chronic inflammation in peripheral tissues [351, 352]. In cases of severe depression, there is an intricate association between oxidative stress, pro-inflammatory responses to psychoemotional stress, serotonergic pathways, neurogenesis, and dysregulated synaptic plasticity [95].

The adaptive or maladaptive consequences of oxidative stress are contingent on its equilibrium, notably at the level of transcription factors with either pro-oxidant or antioxidant functions. This balance can be represented by the expression ratio of NF-κB to NRF2 [25]. Clinical and experimental evidence indicates that pharmacological agents targeting NRF2-dependent pathways can confer protection against depression, whereas NF-κB signaling pathways exacerbate depression-like behavior [353]. Concomitantly, a dysfunctional pro-oxidant/antioxidant balance leads to variable impairments in the function of constitutive nOS and NO bioavailability in brain regions implicated in distress and affective disorders. These include the cortex, hippocampus, amygdala, hypothalamic nuclei, striatum, and dorsal raphe nucleus (DRN) [354]. Interestingly, both inhibitors and activators of NO formation have been implicated in antidepressant effects [354, 355].

3.3.3. The Implications of DNA Damage Response (DDR) in Stress and Depression

Potentiation of pro-oxidant enzyme activity, particularly in the cell nucleus, together with other factors related to CS, intensifies genomic damage and compromises the intricate epigenetic mechanisms that govern cellular homeostasis [356]. This escalation typically triggers the activation of DDR defense mechanisms, specifically in neuronal structures that respond to stress and depression. As delineated in Section 3.1.6, neurotransmitters interfacing through G-proteins act on key DDR transcription factors that maintain neuronal homeostasis. However, these DDR processes can be detrimentally disrupted under stress and depression conditions.

Given that the turmoil in the neuroendocrine system is not only localized, induced genomic damage extends its scope to peripheral tissues as well. For example, chronic stress has a direct impact on

cell physiology through sustained or recurrent activation of the sympathoadrenal system, along with the discharge of neuroendocrine mediators. This cumulative action is postulated to exacerbate genomic damage, particularly affecting pivotal pathways associated with biological aging and cellular stress, such as in peripheral blood leukocytes [5, 357].

Persistently activated DDR correlates with oxidative neuronal damage, even in patients who manifest mild cognitive impairment [358]. Moreover, sustained DDR significantly modulates the neuronal transcriptome, potentially accelerating the senescence phenotype in neurons [358]. Another ramification of DDR malfunction is its association with mitochondrial stress and the ensuing apoptosis in pathologically activated postmitotic neurons. This scenario can cause focal neurodegeneration within the brain [359]. Although autophagy could serve as a regulatory mechanism, dysregulated autophagy can induce autophagic cell death and alternative forms of programmed necrosis. At the tissue level, this translates into the onset of neuroinflammation with the involvement of microglial cells [359].

Although these molecular mechanisms have been extensively investigated in the context of neurodegenerative disorders [360], they have been relatively underexplored in conditions with subtler morphological and functional changes of the brain. However, the potential role of DDR dysfunction in posttraumatic stress disorder and depression is supported by the existing literature on genetic risk factors and intricate epigenetic malfunctions that contribute to the etiology of these disorders [361-363].

3.3.4. Interplay of Mitochondrial Stress and Endoplasmic Reticulum (ER) Stress in Depression

The current body of evidence firmly establishes a connection between mitochondrial dysfunction in various regions of the brain and a variety of psychiatric disorders, particularly depression [364]. Mitochondria are instrumental in ATP synthesis, intracellular Ca^{2+}-dependent signaling, and ROS regulation, thus facilitating complex neurophysiological processes such as neurotransmission and neuroplasticity. However, excessive Ca^{2+} uptake by mitochondria disrupts ATP synthesis, triggers mitochondrial swelling, releases cytochrome c, and activates the intrinsic apoptosis pathway [25]. Postmortem brain proteomic studies in depressed individuals, corroborated by animal models, reveal that approximately 20% of mitochondrial proteins exhibit significant deviations from normative levels [365]. This mitochondrial dysfunction, manifested through mtDNA mutations, aberrant protein expression, mitochondrial unfolded protein response (UPRmt), ROS imbalance, and ATP deficits, culminates in apoptosis, inflammation, and compromised neurogenesis and neurotransmission within key areas of the brain, namely the cortex, hippocampus, and striatum [366-368]. Therefore, reducing oxidative stress and improving mitochondrial function can serve as viable strategies to ameliorate depressive symptoms [369].

Endoplasmic reticulum (ER) stress shares mechanistic links with mitochondrial stress, including calcium mobilization and UPR, largely mediated by inducible heat shock proteins (HSP). Both are also involved in CS signaling pathways and are involved in autophagy, with adaptive or maladaptive outcomes [25]. ER stress, manifested through proteomic aberrations such as the accumulation of abnormal, amyloid, and prion-like protein complexes in neurons and extracellular matrixes, is a hallmark of neurodegenerative diseases [370-372]. In particular, evidence of ER stress, proteomic imbalances, and other ER-related anomalies have been documented in multiple regions of the brain affected by depression and conditions related to chronic stress (distress) [373-376]. This cumulative evidence substantiates that ER stress indexes and initial neurodegenerative changes exist already in depressive and posttraumatic stress disorders, well before the clinical onset of canonical neurodegenerative diseases typical of advanced age [377-379].

3.3.5. Formation of a Receptor and Secretory Pro-inflammatory Phenotype in CNS Cells in Stress and Depression

The emergence of a pro-inflammatory secretory and receptor phenotype is a characteristic feature of CNS cells, including neurons. Consequently, neurons participate in the formation of a cytokine network during instances of neurogenic stress, pain, migraine, neurodegenerative disorders, and mental illness [380-384]. Prolonged psychoemotional stress stimulates the production of pro-inflammatory cytokines, particularly in the hippocampus and other components of the limbic system, implicating them in the pathogenesis of psychotraumatic anxiety and depression [385].

Chronic exposure to elevated levels of inflammatory cytokines and persistent changes in neurotransmitter systems can lead to neuropsychiatric disorders, including depression. The mechanistic underpinnings of these behavioral effects involve the activation of inflammatory signaling pathways, leading to modifications in the monoamine, glutamate, and neuropeptide systems and reductions in growth factors such as brain-derived neurotrophic factor [386]. Furthermore, both acquired and congenital risk factors for depression can stably modulate the expression of inflammatory cytokines within the CNS [386].

In their seminal review, Miller AH *et al.* (2009) showed that the activation of inflammatory pathways diminishes neurotrophic support and impairs glutamate reuptake mechanisms, thus inducing oxidative stress and excitotoxicity. These changes are consistent with the neuropathological hallmarks of depressive disorders [387].

More evidence supports the connection between pro-inflammatory stress and depression comes from studies showing that psychosocial stress stimulates inflammatory signaling molecules, such as NF-κB, in neurons [387]. A considerable body of animal literature indicates that cytokine administration significantly affects serotonin, norepinephrine, and dopamine metabolism [388, 389]. Specifically, pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α activate indoleamine 2,3-dioxygenase (IDO), diverting tryptophan metabolism away from serotonin and towards the kynurenine pathways, thus contributing to the molecular mechanisms underlying depression [390].

Cytokines and their signaling pathways also influence the reuptake of monoamines at synaptic junctions. Pathways such as MARK (p38, ERK1/2), which mediate cytokine effects, have been observed to increase the activity of serotonin, DOPA, and norepinephrine membrane transporters [387]. Furthermore, pro-inflammatory cytokines like IL-1β, IL-2, IL-6, and TNF-α are recognized by neurons and induce various cellular responses, including pain perception [391].

As indicated previously, imbalances in activation neurotransmitters, particularly NMDA hyperfunction, can precipitate excitotoxicity, neuronal damage, and dysfunction in conditions such as MDD and Alzheimer's disease [392, 393]. These processes accelerate with aging and chronic cerebral ischemia [394]. Hence, neurotransmitter actions typically involve a balance between activation and inhibitory mechanisms, complemented by negative feedback loops. These actions may activate pro-inflammatory stress signaling pathways to mitigate harmful effects [395-397].

The formation of a cytokine network under conditions of distress and depression is intrinsically linked to the activation relationships between neurons and glial cells, particularly microglia, resi-

dent macrophages of the CNS. During periods of stress and depression, microglia activate the PI3K/AKT/NF-κB signaling pathway, a characteristic feature of cellular stress [398]. Chronic stress also induces the formation of DAMP such as HMGB1, as well as extracellular nucleosomes and histones, capable of activating microglia in affected CNS structures [399].

Microglia activation is markedly enhanced in suicidal individuals (based on autopsy data) and patients with depression, as well as in animal models of depression. This activation is associated with a shift towards a pro-inflammatory M1 phenotype, increased NLRP3 inflammasome formation, and increased production of pro-inflammatory cytokines like IL-1β, IL-6, IL-8, IL-12, and TNF-α [400]. Interestingly, TNF-α is produced by various types of CNS cells, including neurons, astrocytes, microglia, and endothelial cells [401]. However, M1 microglia are the predominant targets of TNF-α in neuroinflammatory processes, including MDD [401, 402]. In these contexts, TNF-α may promote neuronal death by activating the extrinsic pathway of apoptosis (TNF-α/TNFR1/caspase-8) or more pro-inflammatory mechanisms such as pyroptosis (TNF-α/NF-κB/NLRP3) [400, 401].

Tissue stress in the CNS can be propagated by microglial cells and astrocytes through extracellular vesicles containing non-coding stress RNAs [403]. The key role of microglia in the pathogenesis of neuroinflammation in progressive neurodegeneration is incontrovertible [404-408].

A study by Guo *et al.* demonstrated that chronic five-week stress in experimental mice can induce not only a pro-inflammatory response but also a compensatory anti-inflammatory response in the hippocampus [409]. This combined response was associated with microglial apoptosis, reduced microglial cell numbers, and decreased production of pro-inflammatory cytokines in the hippocampus of chronically stressed mice. However, a prevailing trend observed in most experimental models of depression and clinical observations in humans involves pro-inflammatory activation and increased numbers of microglial cells in various brain regions, including the limbic system (hippocampus, amygdala, among others) and the frontal cortex [387, 399, 400, 410-412].

Notably, the activation relationship between microglia and neurons in depression is bidirectional. Microglia and pro-inflammatory astrocytes significantly influence multiple aspects of neuronal function and dysfunction. Similarly, stressor-affected neurons influence microglial functions and dysfunctions primarily through soluble factors such as chemokines, cytokines, and neurotransmitters.

It is worth emphasizing that cytokines and other inflammatory mediators in neurons and glial cells activate the same pro-inflammatory signaling pathways as neurotransmitters acting through GPCR and RTK, including PI3K/AKT [413], various NF-κB pathways [414] and p53 [415], as well as MAPK-ERK [416] and MAPK-p38, among others [417-420]. However, pro-inflammatory mediators elevate the activation of these mechanisms to a new qualitative level of cellular signaling (CS). Moreover, pro-inflammatory cytokines can stimulate more CS-specific signaling pathways in neurons and glial cells, particularly those related to the non-receptor tyrosine kinases JAK and a broad spectrum of associated downstream pathways, including JAK/STAT and JAK/MAPK/NF-κB [421-423].

From this perspective, the connection between NMDA and the JAK/STAT pathway seems to be a natural phenomenon, as is the role of this connection in the pathogenesis of depression, neuroinflammation and neurodegenerative diseases [421, 424-427].

However, it is important to consider that not all cases of stress and depression necessarily involve neuroinflammation, especially in the absence of morphological signs of this process. The adaptive role of pro-inflammatory cellular and tissue stress in the development of extreme physiological processes should also be considered. Therefore, the concept of pro-inflammatory tissue stress in the CNS should be broadly interpreted to include not only neuroinflammation, but also borderline states and adaptive extreme physiological processes, not to mention the presence of a pro-inflammatory tone that maintains tissue homeostasis. It is also important to note that cytokine production, unlike neurotransmitters, occurs exponentially in the area of tissue damage; therefore, the specific contribution of specialized inflammatory mediators in the development of progressive tissue stress and neuroinflammation will assume a dominant role at a certain stage.

3.3.6. The Role of Acquired Immunity Mechanisms in Stress and Depression

Adaptive immunity, characterized by the specialized functions of T lymphocytes and myeloid antigen-presenting cells (APCs), such as dendritic cells and inflammatory macrophages, plays a nuanced role in the context of chronic low-grade neuroinflammation, compared to its function in classical inflammation. Although its role is conventionally considered less significant than that of innate immunity, emerging evidence suggests that subsets of adaptive immune cells actively participate in neural-immune interactions during neurodegenerative and neuropsychiatric conditions, including stress and depression [428, 429].

Normally, certain subpopulations of T lymphocytes can cross the blood-brain barrier (BBB) through parenchymal and leptomeningeal blood vessels, as well as through the choroid plexus, as part of immune surveillance [428]. During periods of neuroinflammation and neurodegeneration, the permeability of the BBB to these immune cells is notably increased [429]. Studies in experimental animal models and postmortem human brains have shown that effector and regulatory $CD4^+$ and $CD8^+$ T cells that infiltrate the CNS are typically found in proximity to blood vessels or near melanized dopamine neurons, particularly in the substantia nigra, a region commonly affected in Parkinson's disease [430].

Regulation $CD4^+$ T cells (Tregs), which are known for their immunosuppressive functions, have been reported to play a protective role in depression by suppressing chronic inflammatory responses [431]. In contrast, in a mouse model of chronic stress, migration of monocytes through a compromised BBB into the hippocampus was observed to exacerbate depressive behavior [432].

Thus, the role of acquired immune mechanisms in neuroinflammation related to stress and depression is complex and not yet fully elucidated. Migration of canonical immunocytes to the CNS appears to have both neuroprotective and neurodegenerative effects, depending on the context. For example, while Tregs can act to dampen inflammation and protect neuronal integrity, monocytes can potentially exacerbate depressive symptoms by increasing inflammation [431, 432].

Further comprehensive research is required to understand the multifaceted role of adaptive immunity in the pathogenesis of stress and depression. Given that immune cells such as T lymphocytes can interact with various types of CNS cells, including neurons, astrocytes, and microglia, a detailed mechanistic understanding is crucial for the development of targeted therapies. Furthermore, considering that stress and depression are associated with neuroinflammation and disruptions in neurotransmitter systems, it is imperative to understand how adaptive immune cells modulate these processes [387, 390, 401].

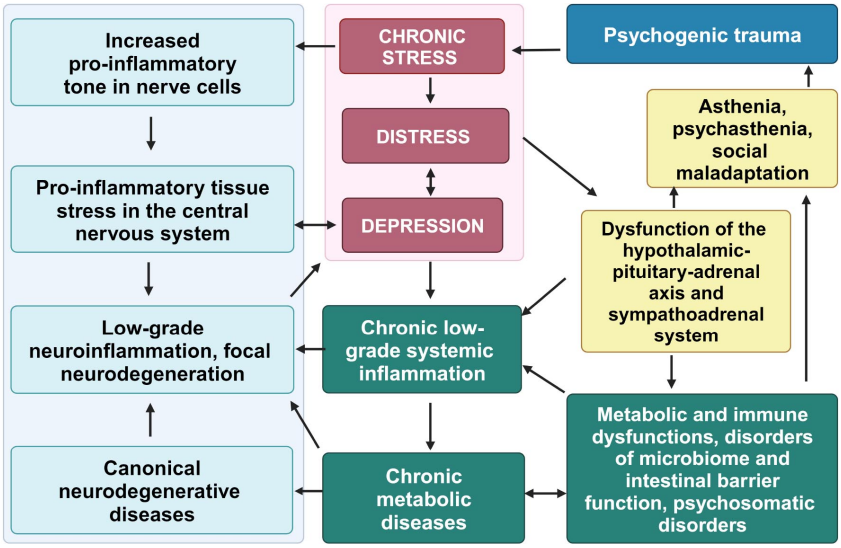

Fig. (4). The relationship of stress, depression, systemic, and low-grade inflammation. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

In summary, the involvement of adaptive immunity in stress and depression is an evolving field of study that warrants further in--depth investigation to unravel its complexities and implications for therapeutic interventions.

3.3.7. Systemic Inflammatory Response in Stress and Depression

Stress and depression are not merely localized phenomena within the CNS, but exert systemic effects that permeate various bodily tissues. Several key mechanisms underline the complex relationship between stress, depression, and systemic inflammation (Fig. **4**).

- Neuroendocrine Dysregulation: Dysfunctions in the HPA axis and the aldosterone-renin-angiotensin system manifest themselves either as hyperproduction of stress hormones or functional deficiency of cortisol due to adrenal atrophy. Furthermore, there is hypertonicity in the sympathoadrenal system and dysfunction in the parasympathetic nervous system [433-439].

- Gastrointestinal Dysbiosis: Disturbances in the intestinal microbiome and barrier function facilitate feedback mechanisms between microbial pathogen-associated molecular patterns (PAMP) and various intestinal neurotoxins affecting the CNS, thus creating a detrimental feedback loop [440-443].

- Immunotropic Complications: Stress-induced systemic immune dysfunctions contribute to a range of complications including infectious, autoimmune, allergic, and tumorous diseases [444-449].

- Metabolic Allostasis: Stress and depression can accelerate tissue aging and cause metabolic dysfunctions through mechanisms of low-grade systemic inflammation, upregulated damage-associated molecular patterns (DAMPs), aberrant metabolites, and disproportionate immunomodulatory effects of extracellular vesicles [450-455].

Psychosomatic Disorders: The emergence and progression of psychosomatic disorders further complicate the systemic nature of distress and depression [456-459].

Proinflammatory Mediator Accumulation: The systemic inflammatory response itself is associated with increased levels of pro-inflammatory cytokines, acute phase proteins, and other inflammatory mediators in the blood [387, 460-465].

The CNS contributes to these systemic effects through abnormal neuroendocrine regulation of homeostatic processes, including the disruption of gastrointestinal barrier functions. On the contrary, low-grade systemic inflammation - along with the presence of DAMPs, PAMPs, and toxic metabolites - impacts the CNS through afferent autonomic pathways, creating a vicious cycle of pro-inflammatory cascades within stressed brain structures.

Complementing these issues is the compromised integrity of the blood-brain barrier (BBB), which serves as an aggravating factor in the stabilization and progression of distress-related complications [466-470].

Given this complex interplay, it is not surprising that distress and depression are frequently comorbid with clinical manifestations linked to chronic low-grade systemic inflammation, such as morbid obesity, insulin resistance, nonalcoholic fatty liver disease, hypertension, rapidly progressive atherosclerosis, sarcopenia, and aging [471-499].

Thus, an interdisciplinary approach to understanding the multilayered relationship between systemic inflammation, distress, and depression is paramount for the development of targeted therapies and interventions.

4. PRO-INFLAMMATORY FUNCTIONS OF GPCR AND SPECIALIZED FUNCTIONS OF 5-HT RECEPTORS IN THE CNS

4.1. Involvement of GPCRs and their Ligands in Inflammation and Immunity

G protein-coupled receptors (GPCRs), the most extensive family of membrane proteins, play a crucial role in enabling the ner-

vous system to respond well to both external stimuli and internal states. However, this adaptability comes at the cost of fluctuations in cellular ionic composition and other homeostatic parameters within the CNS. Such perturbations carry the risk of cellular dysfunction and damage. This risk is evidenced by the intersecting signaling pathways that involve neurotransmitters and specialized CS signaling cascades, such as MAPK, NF-κB, Protein Kinase B (AKT), PKC and p53.

Cytokines and other specialized inflammatory mediators, although primarily associated with inflammation, are involved in low concentrations in a wide range of physiological processes, including metabolism, cell turnover, tissue growth, and cell differentiation. Intriguingly, as previously discussed, pro-inflammatory cytokines also play a role in maintaining the normal function of neurons.

The functional duality of GPCRs extends beyond their role in neurotransmitter signaling. This assertion is confirmed by the data in Table **S1**, which succinctly illustrate the immunotropic and pro-inflammatory roles of GPCRs mediated by specific types of G proteins. The ligands that bond to these GPCRs are not limited to well-known pro-inflammatory mediators such as chemokines, purines, bradykinin, histamine, eicosanoids, thrombin, C5a, and platelet-activating factor (PAF). They also include most classical neurotransmitters and hormones, as well as various other homeostatic factors. In particular, nearly all of these ligands, along with the GPCRs to which they bind, possess some degree of immunotropic activity, acting as regulators within the cellular signaling CS framework.

This expansive role of GPCRs and their ligands implies that understanding their function requires an interdisciplinary approach that integrates insights from immunology, neurobiology, and cell signaling. Their multifaceted roles in both normal physiological processes and pathological conditions make them promising targets for therapeutic interventions, although they have the complexity of potentially pleiotropic effects (Table **S1**).

It would be a mistake to equate "professional" and non-specialized participants in immune response and inflammation, at both cellular and molecular levels. Specialized pro-inflammatory factors show an exponential increase in their concentration during the course of inflammation, along with a corresponding increase in the expression of their inducible receptors. The signaling pathways of these specialized factors are primarily geared toward promoting pro-inflammatory tissue stress and fostering cellular interactions among various immunocytes.

On the contrary, non-specialized signaling CS regulators primarily aim to maintain homeostasis and execute specialized physiological cellular functions. It is also erroneous to posit that metabotropic GPCR of neurotransmitters serve as more potent inducers of CS in various cells compared to ionotropic receptors. For example, ionotropic 5-HT3 receptors can exert substantial pro-inflammatory activity [500-502], while the cholinergic system modulates mobilization, differentiation, secretion, and antigen presentation in adaptive and innate immunity cells, predominantly through ionotropic α7-nicotinic receptors (α7nAChR) [503].

4.2. The Role of the Serotonergic System in the Pathogenesis of Neuropsychiatric Disorders

Dysfunction in the serotonergic system has been implicated in the pathogenesis of various neurological and psychiatric disorders, notably including depression [504]. Conditions that are amenable to pharmacological intervention targeting 5-HT and its receptors encompass MDD, schizophrenia, generalized anxiety disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, migraine, and Dravet syndrome [505].

Treatment modalities for depression and anxiety disorders frequently utilize 5-HT reuptake inhibitors in synaptic junctions. Recent advances have also included the deployment of selective agonists and antagonists for specific subtypes of 5-HT receptors, including 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C, 5-HT3, 5-HT4, 5-HT6, and 5-HT7 receptors [499, 506].

However, the efficacy of these therapeutic approaches is limited, to some extent, by inherent complexity and internal inconsistencies within the serotonergic system. This complexity is evident even in a cursory overview of the functional functions and pathologies associated with various 5-HT receptors (Table **S2**).

The complexity of the pharmacological modulation of the serotonergic system can be attributed to several key factors.

- The 5-HT autoreceptors, as described in Table **S2**, are not only localized on the postsynaptic membrane, but also on the presynaptic membrane, where they act as a negative feedback loop after activation of the postsynaptic 5-HT receptors.

- Serotonin receptors can form heterocomplexes with other receptor types, thereby gaining new functionalities. For example, these heterocomplexes can include D2R-5-HT2A, D2R-5-HT1A, GalR1-GalR2-5-HT1A, FGFR1-5-HT1A, 5-HT1A-FGFR1-mAChR1.3, 5-HT2A-OXTR, and 5-HT2C-OXTR [500]. Additional complexes involving 5-HT1A are delineated in Table **S2**.

- A single 5-HT receptor can interact with multiple Gα subunits, some of which may have divergent functionalities (Table **S2**).

- Mutual activation can occur between 5-HT receptors and certain RTK, such as the epidermal growth factor receptor (EGFR).
- The impacts of individual 5-HT receptors can vary significantly depending on their location, either within different brain structures or between the CNS and peripheral tissues.

- Receptor functions often exhibit functional complementarity while also displaying redundancy in their most salient features, thus rendering them resilient to external perturbations.

- Receptor functions can be profoundly influenced by various pro-inflammatory factors, particularly under conditions of tissue stress and neuroinflammation, as commonly observed in chronic mental stress and depression.

- Serotonin levels, strongly implicated in depression, are prone to decline under conditions of elevated circulating and intracerebral pro-inflammatory cytokines, and decreased levels of tryptophan precursors due to cytokine-induced activation of the kynurenine pathway for tryptophan degradation in both the liver and CNS [507-510].

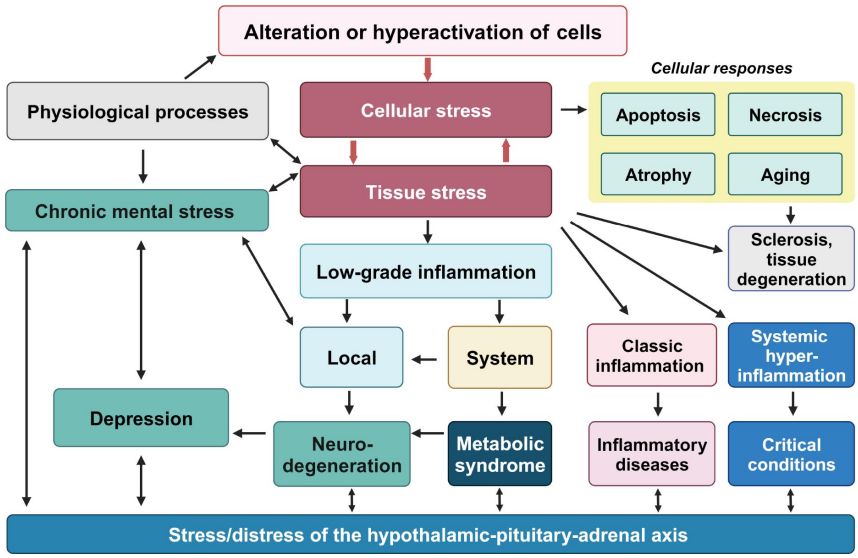

Fig. (5). Role of Pro-Inflammatory Stress in Chronic Mental Conditions. Chronic mental stress and depression are seamlessly integrated into the overarching framework of typical pathological processes. This integration is facilitated by the central role of pro-inflammatory tissue stress and cellular stress, which serve as fundamental functional units underlying various pathological processes of various etiologies. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Given these last two points, the utility of anti-inflammatory medications as adjunctive therapy for depression has gained attention. Meta-analysis of clinical trials indicates that anti-inflammatory treatments can ameliorate depressive symptoms and increase remission rates [511]. However, making definitive recommendations remains premature due to heterogeneity in study designs, patient populations, treatment protocols, and outcome measures, coupled with limited scientific rigor [512]. Furthermore, effective treatment of depression cannot be limited only to pharmacotherapy, but also requires psychotherapy and social rehabilitation to mitigate chronic patterns of aberrant psychogenic excitability in the CNS, linked to excitotoxicity, pro-inflammatory tissue stress, and neuroinflammation.

Furthermore, 5-HT affects numerous parameters of CS, including mitochondrial responses [513]. Serotonin is also evolutionarily related to the induction of HSP production [514] and controls the onset of oxidative stress in various cell types [515, 516].

In conclusion, pro-inflammatory mechanisms exert systemic control over serotonergic effects, and serotonin reciprocally influences cellular stress. The intricate balance, crucial for normal neuronal function, becomes disrupted under conditions of chronic psychoemotional stress and depression.

CONCLUSION

The emerging insights into the molecular underpinnings of various diseases challenge the conventional dichotomy between somatic and mental illnesses. A potential unifying element in these diseases could be cellular and tissue stress. This encompasses universal mechanisms like oxidative stress, stress kinases, and inducible transcription factors, which are integral not only to normal physiological processes but also to para-inflammatory processes in tumor growth, and both canonical and non-classical inflammation. This understanding invites a reevaluation of the pathogenesis of depression and psycho-emotionally linked diseases from the vantage point of general pathology.

Contemporary theories on depression primarily concentrate on neurotransmitter imbalances, hormonal fluctuations, and trophic and morphological neuronal changes. However, the absence of a central pathogenetic “core” or system-forming factor in these models may limit their capacity to fully encapsulate the complex pathogenesis of such conditions. Our proposed neuroimmunoinflammatory concept of depression and stress-related disorders seeks to amalgamate these diverse theories into a cohesive framework, extending to the general molecular mechanisms at the cellular level that underpin both mental and somatic diseases.

The Neuroimmunoinflammatory Stress Model (NIIS Model) posits that pro-inflammatory signaling pathways, in concert with neurotransmitter systems—particularly those involving G-proteins—constitute an integrated regulatory network active even under normal physiological conditions [517]. Specifically, 5-HT receptors associated with G-proteins play a pivotal role in initiating a range of cellular stress responses. These responses are fundamental to the functioning of various neuron types across both normal and pathological states. Chronic mental stress disrupts this balance, culminating in a state of distress that serves as the pathogenic foundation for a variety of neuropsychiatric and psychosomatic disorders, with depression being especially prominent [518]. The model is characterized by aberrant excitatory and inhibitory neural activity in specific brain regions, resulting in excitotoxicity and enduring shifts in homeostasis [519]. One salient consequence of such allostasis is pro-inflammatory tissue stress. If these compensatory mechanisms are inadequate, an imbalance between neurotransmitters and inflammatory mediators ensues [518, 519]. This prolonged tissue stress ultimately leads to brain atrophy, potentially indicative of low-grade neuroinflammation [517-519].

In contrast to extant models like the Monoamine Hypothesis or the Neuroendocrine Model, which primarily concentrate on neurotransmitter imbalances or hormonal alterations respectively, our NIIS Model integrates these aspects to provide a holistic understanding of the pathophysiology [335-344]. By underscoring the roles of G-proteins and serotonin receptors, this framework intro-

duces new perspectives into the convergent mechanisms underlying both neuroinflammation and depressive disorders [335, 340, 341].

This multi-faceted approach sets the NIIS Model apart from other prevailing models and enriches the scholarly discourse surrounding the pathology of stress-induced disorders [343, 344]. Furthermore, the comprehensive nature of our model offers the prospect of developing more precisely targeted therapeutic interventions for both neuroinflammatory and neuropsychiatric conditions [344] (Fig. **5**).

As mentioned above, our study does not strictly adhere to the format of a systematic review. Rather, it integrates a wide array of systematic reviews that focus on more specific aspects of the problem at hand. In the context of the neuroimmune-inflammatory concept of stress and depression, our work meticulously examines the roles of 5-HT receptors, other GPCRs, and G proteins. Our earlier publication delved deeper into the role of cytokine-dependent mechanisms, especially the JAK-STAT signaling pathways, in the pathogenesis of depression and other outcomes of pathological stress [421].

Moreover, our conceptual syntheses are in line with other researchers' findings regarding the role of pro-inflammatory mechanisms in the pathogenesis of classical mental illnesses, particularly schizophrenia [388, 520, 521]. This broader viewpoint facilitates the interpretation of the neuroimmune-inflammatory concept across a more extensive range of neuropsychiatric disorders.

Additionally, we acknowledge that transforming the NIIS Model into a comprehensive theory requires resolving many challenges. Notably, there is compelling evidence highlighting the involvement of classical hormones and neurotransmitters in the regulation of immune and pro-inflammatory processes. There are also studies focusing on classical inflammation and immunity mediators as quasi-neurotransmitters [421, 518, 522, 523]. However, this area of neurophysiology and neuropathology, in our opinion, demands more rigorous molecular research and syntheses.

From a practical standpoint, the NIIS Model emphasizes the potential effectiveness of using immunomodulatory and anti-inflammatory treatments in managing stress-associated neuropsychiatric diseases, taking into account their side effects on physiological processes in the brain and other areas.

LIST OF ABBREVIATIONS

AC = Adenylate Cyclase

ADAM = A Disintegrin and Metalloproteinase

PKB = Protein Kinase B

AR = Adenosine Receptor

ASK = Apoptosis Signal-regulating Kinase

ATM = Ataxia-telangiectasia Mutated

BBB = Blood-brain Barrier

CaM = Calmodulin

CaMK = Calmodulin-dependent Protein Kinases

cAMP = Cyclic Adenosine Monophosphate

CaN = Calcineurin

Cdk = Cyclin-dependent Kinase

cGMP = Cyclic Guanosine Monophosphate

CNS = Central Nervous System

COX-2 = Cyclooxygenase 2

CS = Cellular Pro-inflammatory Stress

DAG = Diacylglycerol

DAMP = Damage-associated Molecular Pattern

DDR = DNA Damage Response

EGF = Epidermal Growth Factor

ER = Endoplasmic Reticulum

ERK = Extracellular Signal-regulated Kinases

FOXO = Forkhead Box Protein O1

GC = Guanelate Cyclase

GDP = Guanosine Diphosphate

Glu = Glutamic Acid

GPCRs = G Protein-coupled Receptors

GTP = Guanosine Triphosphate

HMGB1 = High-mobility group Protein B1

HSP = Heat Shock Protein

5-HT = 5-hydroxytryptamine (serotonin)

IDO = Indoleamine 2,3-deoxygenase

IKKα = Inhibitor of Nuclear Factor Kappa-B kinase Subunit Alpha

IL = Interleukin

IP3 = Inositol 3-phosphate

JAK = Janus Kinase

JNK = c-Jun N-terminal Kinases

MAPK = Mitogen-activated Protein Kinases

MDD = Major Depressive Disorder

MHC-I = Major Histocompatibility Complex Class I

MMP = Matrix Metalloproteases

mTOR = Mechanistic Target of Rapamycin

NADPH = Nicotinamide Adenine Dinucleotide Phosphate

NF-κB = Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells

NLRP3 = Nod-like Receptor Protein 3

NMDA = N-methyl-D-aspartate

NO = Nitric Oxide

NOS = NO Synthase

NRF2 = Nuclear Factor Erythroid 2-related Factor 2

PAF = platelet-activating Factor

PAMP = Pathogen-associated Molecular Pattern

PDE = Cyclic Nucleotide Phosphodiesterases

PGE2 = Prostaglandin E2

PKA = Protein Kinase A

PKC = protein Kinase C

PKG = Protein Kinase G

PLC = Phospholipase C

PR = Purine Receptor

PRR = Pattern Recognition Receptor

ROS = Reactive Oxygen Species

RTK = Receptor Tyrosine Kinases

STAT = Signal Transducer and Activator of Transcription

TACE = TNF-α Converting Enzyme

TNF-α = Tumor Necrosis Factor Alpha

Treg = T Regulatory Cells

UPR = Unfolded Protein Response

VSMC = Vascular Smooth Muscle Cells

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Supplementary Material

Interplay of G-Proteins and Serotonin in the Neuroimmunoinflammatory Model of Chronic Stress and Depression: A Narrative Review

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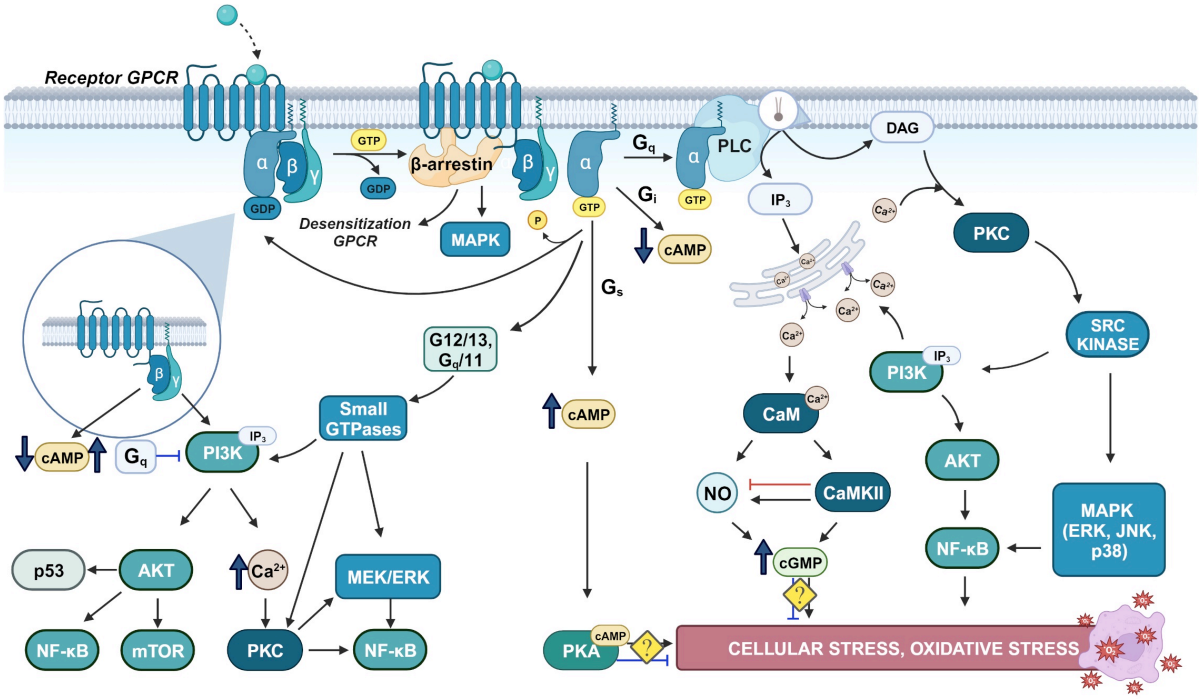

Fig. (S1). The Role of GPCR Receptors in Cellular Stress Development. Technical term abbreviations are explained in their first usage.

The GPCR receptor is associated with the trimeric (αβγ) G protein (G). Upon attachment of the ligand to the GPCR, the G α-subunit undergoes the replacement of GDP by GTP, leading to its dissociation from the G αβγ trimer and activation of the released G α. G protein signaling is disrupted by internal phasic Gα activity, which hydrolyzes GTP to GDP. This is followed by the reassociation of Gα with Gβγ and subsequent inactivation of the G protein. GTP is then dephosphorylated and converted to GDP, leading to inactivation of the Gα subunit that reattaches to the G-protein dimer-βγ. The Gαβγ trimer is formed, leading to the inactivation of the G protein. The G-proteins are separated into four families based on the α-subunit composition.

Gs stimulates adenylate cyclase to produce cyclic AMP (cAMP) from ATP. In addition, PKA is activated by cAMP, which can phosphorylate many downstream targets. On the contrary, Gi inhibits the formation of adenylate cyclase and cAMP, while activating several cation channels. Gq primarily stimulates calcium mobilization by activating PLC and forming inositol-3-phosphate (IP3) and diacylglycerol (DAG).

G12/13. All G proteins can activate small GTPases, predominantly G 12/13 and Gq. Once activated, GPCRs mediate their neurotropic and pro-inflammatory effects through various types of G proteins through the following principal signaling pathways:

(1) Activation of Phospholipase C (PLC) occurs mainly through the α-subunit Gq/11 (Gq greater than G11) and to some extent through the dimers of βγ G proteins. Active PLC catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate, generating inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). Subsequently, IP3 induces calcium (Ca2+) release from the endoplasmic reticulum and, together with DAG, activates protein kinase C (PKC). PKC then triggers various stress pathways, such as PKC / MEK / ERK, PKC / Sc / MAPK (ERK, JNK, p38)/NF-κB, as well as PKC / Sc / PPI3K / AKT. At the same time, calcium ions in the cytoplasm can activate numerous signaling pathways through CaMK.

(2) The regulatory effects of numerous GPCRs are largely determined by the PI3K Trunk and Fork track. Upstream, activation of various PI3K isoforms can be associated with Gα/PKC, Gα/small GTPases, and Gβγ. Downstream, most of the key mechanisms of GPCR are associated with PI3K signaling pathways. Specifically, PI3K can initiate several essential pathways for cell stress. The PI3K/AKT signaling pathways play crucial roles in cellular processes such as cell cycle regulation, cell proliferation, and apoptosis. They also have significance in the activation of the important DNA factors, FOXO and p53, for the response to damage. Furthermore, PI3K and Ca2+ activate the cyclin-dependent kinase Cdk5, which is vital for neuron survival. Meanwhile, not only does Gq activate PI3K through PKC and small GTPases, it can also directly inhibit the catalytic subunit of PI3K through a negative feedback mechanism.

(3) Adenylate cyclase is activated through Gs or inhibited through Gi/o, but more via Gi, which leads to the formation of cyclic adenosine monophosphate (cAMP) and the subsequent activation of various protein kinase A (PKA) signaling pathways. The regulatory effects of PKA are markedly pleiotropic. However, in general, the effects of cAMP, according to multiple authors, are anti-inflammatory and relaxing toward neurons and myocytes. However, due to its pronounced pleiotropy, the effects of cAMP on particular cellular stress signaling pathways remain ambiguous and controversial. Therefore, we must determine the role of cAMP in the development of particular variants of cellular stress in neurons, as well as in the nervous tissue as a whole.

(4) Activation by calcium, calmodulin (CaM), and CaM kinases has a multidirectional influence on NO production and cGMP formation. These versatile pleiotropic regulatory effects, similar to those of cAMP, generally affect the balance of neurotransmission and cellular stress mechanisms.

(5) Furthermore, small GTPases activated on the G12/13 and Gq sides - primarily Ras, Rho, and Rab - activate multiple signaling pathways, including through PI3K, ERK, and AKT (protein kinase B).

(6) GPCRs can activate MAPR MAPK (ERK and JNK) through the recruitment of β-arrestin. It is important to note that this process is objective and free from subjective evaluations. Technical term abbreviations are explained when first used for clarity purposes. At the same time, β-arrestin facilitates desensitization and internalization of the GPCR via a negative feedback mechanism.

Table S1. Immunotropic and pro-inflammatory effects GPCR, with established types of Gα subunits.

Ligands	Receptors	Gα	Immunotropic Effects, Role in Inflammation
5-HT (serotonin)	5-HT1	Gi, Go [1]	5-HT1A: Enhances macrophage phagocytosis, increases B cell proliferation, increases NK cell cytotoxicity, and modulates mast cell responses [2-4]. 5-HT1B: Promotes CD4+ T cell proliferation and mediates Ca^{2+} mobilization and chemotaxis in immature DC [2]. 5-HT1E: Mediates Ca^{2+} mobilization and chemotaxis in immature DCs [2]. $CD4^{+}$ T cells in multiple sclerosis: Show elevated 5-HT1A receptor expression [5].
	5- HT2	Gq, G11 [1]	5-HT2C: Enhances monocyte chemotaxis [2]. 5-HT2A: Increases pro-inflammatory activity and migration of eosinophils [6]. 5-HT2B: Expressed in monocytic-origin DCs; modulates the immune response [7].
	5- HT4	Gs [1]	5-HT4: Expressed in DCs, monocytes, macrophages, and mast cells [8].
	5-HT5A	Gi, Go [1]	5-HT5A: Expressed in microglial cells [9].
	5-HT6	Gs [1]	5-HT6: Expressed in eosinophils and mast cells [8].
	5-HT7	Gs [1]	5-HT7: Expressed in DCs, monocytes, macrophages (including microglia), T cells, and mast cells. Promotes T cell proliferation and naive T cell activation, enhances DC chemotaxis. A selective 5-HT7 agonist reduces macrophage inflammation by modulating cytokine production [8-10].
Adrenaline, norepinephrine	β_1 - AR	**Gs** , Gi [11]	β1-AR: Increases pro-inflammatory cytokine production in LPS-activated monocytes through cAMP elevation; suppresses host defenses against Listeria monocytogenes [12,13].
	β2 - AR	**Gs** , Gi [11, 14]	β2-AR: Reduces NF-κB in activated monocytes and macrophages; suppresses the secretion of inflammatory cytokines in response to LPS, and IFN-γ and TNF-α in CD8+ T cells. Enhances NK cell and Treg function; interferes with antibody production [15-18].
	α_1 -AR	Gq [19]	α1-AR: Enhances monocyte migration, complement synthesis, and pro-inflammatory cytokine production in LPS-activated monocytes; inhibits these functions in activated microglial cells. Increase neutrophilia and mast cell histamine release; inhibit T-cell proliferation. Enhances cytokine production in phagocytic cells [12, 16].
	α2 . AR	**Gq** , Gi/o [20,21]	α2-AR: Reduces IL-2 production; enhances Treg immunosuppressive function; inhibits phagocyte and NK cell activity; decreases the probability of neutrophil netosis [22].
Dopamine	DR1	Gq, Gs [23,24]	DR1: Regulates the development and function of bone marrow stem cells and is expressed in various immune cells. Mediates IL-6-dependent Th17 differentiation; contributes to M2 microglia differentiation; enhances NK cytotoxicity [24, 25].
	DR2-4	Gi/o [20]	DR3: Contributes to Th1 and Th17 mediated immunity [25]. DR2: Attenuates NK cytotoxicity [25].
Glutamate (via metabotropic mGluR)	mGluR2 -4, mGluR 6-8	Gi/o [20]	mGluR4c: Contributes to suppression of antitumor immunity by affecting NK and $CD8^{+}$ T cells [26].
	mGluR1, mGluR5	Gq [27]	mGluR5: Involved in LPS-induced microglial activation, specifically increasing NF-κB expression [28].
γ-Aminobutyric acid (GABA)	GABABR	Gi/o [20, 29]	GABABR: Enhances neutrophil chemotaxis to the inflammation site [30].
Acetylcholine	mAChR2, mAChR 4	Gi/o [20]	mAChR1 and mAChR5: Highly expressed on Th2 cells. mAChR4: Dominant on Th1 cells [31]. NK cells: Preferentially express mAChR1-3 [32].
	mAChR 1, mAChR 3, mAChR 5	Gq/11 [19]	
Substance P	NK1R	Gs, Gq [33]	Expressed on various immunocytes. Promotes autoreactive Th1 and Th17 cell formation, CNS migration. Activates leukocyte chemotaxis, T cell and monocyte proliferation, inflammation development [34].

Ligands	Receptors	Gα	Immunotropic Effects, Role in Inflammation
			The interaction of substances P-NK1R results in NF-κB activation, increased production of pro-inflammatory cytokines (IL-1, IL-6, TNF-α, MIP-1β, IFN-γ) [35].
Neurokinin 1	NK1R	Gq [33, 36]	Acts through the same receptor as substance P. Does not activate the Gs signaling pathway.
Melanocortins: adrenocorticotropic hormone, melanocyte-stimulating hormones (α, β, γ)	MC3R, MC4R	Gs [37]	Melanocortins (ACTH, α, β, γ-MSHs): Possess independent anti-inflammatory and immunomodulatory effects of glucocorticoids. Activate melanocortin receptors in the brain or immune cells. MC3R agonists have potential as new anti-inflammatory agents for chronic conditions [38,39].
Neuropeptide Y	YR1, YR3, YR5	Gi/o [40]	Up-regulated YR expression in immune cells after antigen or inflammatory stimulation [41]. Multiple roles in immune cells: inhibition of activation (Y1R), regulation of cytokine proliferation, differentiation, secretion; Y1R/Y2R/Y5R mediating phagocytosis and leukocyte migration [41]. Y1R has bimodal effects on the immune system, showing both anti-inflammatory and specific pro-inflammatory properties.
	YR2, YR4	Gi/o, Gq [40]	
Endoopioids	Opioid receptors-δ, κ, μ	Gi/o [20, 21]	Expressed by blood spleen cells, lymphocytes, and macrophages. Analgesic effect mediated by TLR4 signaling and leukocyte-dependent opioid peptide release [42]. Exogenous opioids induce immunosuppressive effects *in vitro* and *in vivo* immunosuppressive effects [43].
Endocannabinoids	CB1 R , CB2 R	**Gi/o** , Gq/11 [20, 44]	CB1R mainly on neurons, CB2R mainly on immune cells. CB2R activation leads to anti-inflammatory effects in various conditions. Including inflammatory pain, myocardial infarction, stroke, liver damage, gastrointestinal tract disorders, atherosclerosis [45]. Peripheral CB1R and CB2R agonists under testing for inflammatory diseases and cancer [46].
Corticotropin- releasing hormone (CRH)	CRH1R, CRH2R	Gq/11, Gs [47]	Lymphocytes in inflammation: Produce and possess CRHR. CRH acts as autocrine and paracrine factor. Implicated in the activation of the Fas/FasL system. Human mast cells synthesize and secrete CRH, acting in autocrine and paracrine manners. Particularly relevant in allergic inflammatory diseases [48,49].
Gonadotropin-releasing hormone (GRH)	GnRHR	Gq/11 [19]	Suppresses NO production and NF-κB expression in mouse macrophages [50].
Thyrotropin-releasing hormone (TRH)	TRHR	Gq/11 [19]	TRH: *In vivo* data suggest both stimulatory and inhibitory interactions with the immune system [51].
Calcitonin	CTR	**Gs** , **Gq,** Gi [52,53]	?
Parathyroid hormone (PH)	PTHR	**Gs** , Gq, Gi/o G12/13 [54]	Expressed in neutrophils, B-cells, and T-cells. PH increases lymphocyte proliferation and IL-2 production. The impact on the immune response remains contradictory [55].
Follicle Stimulating hormone (FSH)	FSHR	**Gs** , **Gq,** Gi [56]	Potentially negatively regulates the immunosuppressive function of decidual mesenchymal stem cells. Reduces IL-6 secretion [57].
Melatonin	MTR1/2	Gi/o [58]	Stimulates progenitor cells of granulocytes-macrophages. Stimulates NK cells and CD4+ cells; inhibits $CD8^+$ cells [59]. Potentially regulates immune system activation, reducing chronic and acute inflammation [60].
Somatostatin	SSTR1-5	Gi/o	Suppresses immune functions: lymphocyte proliferation, immunoglobulin production, and pro-inflammatory cytokine release (e.g., IFNγ).

Ligands	Receptors	Gα	Immunotropic Effects, Role in Inflammation
		[20]	Effective in various *in vivo* models of chronic autoimmune diseases and inflammation when treated systemically or topically [61].
Oxytocin	OXTR	Gq/11 [20]	Blocking OXTR: Inhibits mouse thymic T cell differentiation. Increases inflammatory cytokine expression and secretion. Immunocytes can secrete oxytocin as a histohormone [62].
Vasopressin	V2R	Gs, Gi/o, Gq/11, G12/13 [63]	Activation of V2R in kidneys: Inhibits PRR-mediated NF-κB activation (TLR4). Reduces pro-inflammatory activity of innate immune cells [64].
Glucagon	GCGR	**Gs,** G i, G q [65,66]	*In vivo*, causes suppression of cellular and humoral immune response [67-69].
Glucagon-like peptide 1 (GLP-1)	GLP1-R	**Gs** [70]	Regulate innate immune cells, particularly macrophages. Activate human monocyte-derived macrophages toward M2 polarization [71].
Short-chain fatty acids (SCFAs)	FFA2	Gi, Gq [72]	May contribute to immune homeostasis, tissue integrity, and pathogen responses. Widely expressed by immune cells in mice. Implicated in inflammatory tissue processes linked to metabolic disorders [73].
Vasoactive interstitial peptide	VIPR1	**Gs** [74]	Generated by T cells, promotes Th2 development, inhibits Th1 differentiation. VPAC1 constitutively expressed in lymphocytes, macrophages, monocytes, DCs, microglia, mast cells. VPAC2 induced upon stimulation, particularly in T cells [76].
	VIPR2	Gs, Gi, Gq [75]	
Adhesion molecules (ADGRL)	ADGRs _	Gi, Gq, G12/13 [77]	Participate in cell-cell and cell-extracellular matrix interactions. Critical in nervous system development, embryogenesis, immune response, endocrine functions, and tumorigenesis [78].
C5a complement	C5aR	Gi, G16 [79]	Expressed on various immunocytes: mast cells, phagocytes, platelets, endothelial cells, lymphocytes. Complement anaphylatoxin C5a action on C5aR initiates multiple pro-inflammatory effects.
Prostaglandin E_2 (PGE_2)	EP1R	Gq [80]	Most commonly expressed in neurons, not in astrocytes or microglia. EP1R inhibition after brain damage in mice improved cerebral edema, neuronal degeneration, neuroinflammation, and neurobehavioral problems. EP1R activation worsened these outcomes.
	EP 2R	Gs [80]	Expressed on T cells. Activation of EP2R inhibits cellular immune response [81].
	EP 3R	Gq, Gi [80]	Key receptor inducing fever during inflammation [82].
	EP4R _	Gs, Gi [80]	Modulates macrophage function through EP4R activation. Inhibits cytokine release and antigen presenting function in macrophages [81].
Histamine	HR1	Gq	Expressed in various cell types: neurons, endothelial cells, adrenal medulla, muscle cells, hepatocytes, chondrocytes, monocytes, neutrophils, eosinophils, DCs, T cells, and B cells. H1R signaling results in: prostacyclin synthesis, platelet factor activation, NO and eicosanoid synthesis, smooth muscle cell contraction. Activation of H1R increases eosinophil and neutrophil chemotaxis, enhances antigen-presenting cell function, activates Th1 lymphocytes, reduces humoral immunity, and stimulates IgE production [83].
	HR2	Gs [84]	Expressed in muscle, epithelial, endothelial, neuronal, hepatocyte, and immune cells. Counteracts some H1Rs, causing vasodilation through GMCC relaxation. Functions as a suppressor molecule in DC by increasing IL-10 production. Induces inhibition of leukotriene synthesis in human neutrophils through cAMP signaling [85].
	HR3-4 _	Gi/o	Inhibits acetylcholine release in cerebral cortex.

Ligands	Receptors	Gα	Immunotropic Effects, Role in Inflammation
		[83]	Controls neurogenic inflammation by inhibiting cAMP formation and Ca2+ accumulation [85, 86]. HR3-4 Activation: Induces chemotaxis in mast cells and eosinophils, accumulating inflammatory cells. H4R:Involved in increased IL-31 secretion by Th2 cells.
Bradykinin	B1R _ _	Gq, Gi [87,88]	B1R: Minimal expression in healthy tissues. Expression induced under special conditions like injury and inflammation [89]. B1R Agonists: Increase pro-inflammatory cytokine and adhesion molecule secretion on brain microvessel endotheliocytes. Reduce occludin expression in tight junctions, with no change in VE-cadherin expression [90].
	B2R	Gq/11, Gi [87, 91, 92]	Ubiquitously expressed, mediates vasodilation. Expression elevated in tissue damage pathologies due to oxidative stress and pro-inflammatory stimuli [89].
Thrombin	PAR1	Gq, G12/13 [93]	Predominantly expressed on the microvascular endothelium and platelets. Critical for the coactivation of coagulation and inflammatory responses [94].
Thromboxane (TxA2)	TxA_{2R} _	Gq, G12/13 [95, 96]	Priority activation: thrombosis/hemostasis and microvessel inflammatory responses. Expressed in microglia, capable of pro-inflammatory activation [95].
Prostacyclin (PGI_2)	IP	**Gs** [96]	IP Receptor for PGI2: Found on various cell types. Signaling leads to diverse physiological effects. PGI2 inhibits platelet aggregation, induces vasodilation through smooth muscle relaxation, and affects inflammatory responses through increased cAMP levels [97].
Platelet activation factor (PAF)	PAFR	Gq/11, Gi/o [98]	Expressed by vascular and innate immune cells. Activates pathways related to inflammation, oncogenic transformation, tumor growth, angiogenesis, and metastasis. Participated in various physiological processes. Possible role in neuroinflammation development [99].
Angiotensin II	A G T1R	Gi/o, Gq/11, G12/13 [20, 47]	Promotes CS development through MAPK and NF-kB activation. Expression includes immunocytes [100, 101].
	A G T2R	Gi/o [102]	Highly expressed in pulmonary fibroblasts. Their hyperfunction linked to pulmonary fibrosis [103].
Endothelins	ETAR	**Gq/11** , Gi/o [104, 105]	Main function: vasoconstriction. Also act as pro-inflammatory factors via ETAR [106,107].
	ET B R	Gs, Gi/o, Gq/11 [104]	ETBR Activation: Promotes activation of astrocytes. Induces the production of pro-inflammatory factors that cause BBB disruption [107].
ADP	P2Y1R	Gq/11 [93, 108]	Induces immunotropic and pro-inflammatory effects. Associated with Th17 activation in colitis [109].
ATP , UTP	P2Y2R	**Gq** /11, Gi/o, G12 [108, 110]	Involved in the development of inflammation, including glomerulonephritis [111] and alcoholic hepatitis [112].
UTP	P2Y4R	**Gq** /11, Gi/o [108,110]	Participated in the positive feedback loop in HIV-1 neurotoxicity. Activates PI3K/AKT and ERK pathways [113].
UDP	P2Y6R	Gq/11 [108]	Expressed in immune cells, including microglia. Implicated in neurological disorders. Ligand UDP acts like DAMP in cell death signaling. Binding of UDP binding to P2Y6R activates distinct biochemical pathways based on the disease context [114].

Ligands	Receptors	Gα	Immunotropic Effects, Role in Inflammation
ATP	P2Y11R	Gq/11 , Gs [108]	ATP Release and P2Y11 Activation: The inflammation process triggers massive ATP release. Activates purinergic receptors, including P2Y11. Recent data suggest a potential anti-inflammatory role: dendritic cell immunosuppression, inhibition of fibroblast proliferation, cytokine and ATP secretion [115].
ADP	P2Y12R , P2Y13R _	Gi/o [20, 108]	P2Y12R: Key role in platelet activation, targeted by antithrombotic drugs. Also present in immune cells and vascular smooth muscle cells, potentially involved in the inflammatory response [116]. P2Y13R: Possibly involved in various types of inflammation [117, 118].
UDP , UDP -glucose	P2Y14 R	Gi/o [108]	Functions as a pro-inflammatory mediator. Inhibition may hold promise for the treatment of inflammation-related diseases [119].
Adenosine	AR1	Gi/o [20, 21]	Expressed in all immune cell types. Regulate immune and inflammatory responses, often with anti-inflammatory effects. AR1 promotes neutrophil chemotaxis, while AR2 inhibits neutrophil activation [120].
	AR2	Gs [21]	
Leukotriene (LT) B 4 (LTB_4)	LTB4R1 _	Gq/11, Gi/Go [20]	LTB4 is a pro-inflammatory eicosanoid. LTB4R1a expressed in various inflammatory and immune cells: granulocytes, eosinophils, macrophages, Th1, Th2, Th17 cells, CD8 T cells, DCs [121].
LTD4 and $_{LTC4}$ _ > LTE_4	$CysLT_1R$	**Gq/11** , Gi/Go [122]	Actively involved in exudative-vascular reactions. Strongly implicated in allergic processes, particularly. CysLT1R antagonists reduce pro-inflammatory activation of endotheliocytes [123, 124].
Formyl Peptides	FPR1, FPR2	Gi/o [125, 126]	FPR1: Recognizes PAMPs, expressed by various immunocytes. Transmits chemotactic signals, triggers adhesion, migration, ROS formation, tissue repair, and angiogenesis [127]. FPR2: Lower affinity for bacterial N-formyl peptides compared to FPR1. Binds a wide range of agonists.Can promote or suppress inflammation based on expressing cell type [128].
Lysophosphatidic acid (LPA)	LPA R1-6	G α 12/13, G α q/11, G α i/o and G α S [129, 130]	Glycophospholipid with diverse functions. Stimulates cell reproduction, cytoskeleton recombination, cell survival, DNA synthesis, and ion transport [130].
Sphingosine-1-phosphate (S1P)	S1P R1-5	Gi [129]	Metabolic product of cell membrane sphingolipids. Secreted by erythrocytes, endothelial cells, and platelets. Binds to extracellular chaperones, acts through S1PRs on various cells. S1PRs interact with signaling pathways in embryonic development, inflammation, host defense, and homeostasis [131].
Chemokines	CXCR 1-6 _	**Gi/Go** [20, 132-134]	Chemokine Receptor Specificity: Complex, with multiple chemokines binding to many receptors. Inflammation-related chemokines show greater complexity. Homeostatic chemokines have fewer ligands. Chemokines vary in affinity for specific receptors. Biased signaling or functional selectivity is a key feature. Activated pathways depend on ligand and cellular context [140-142].
	CXCR4	Gq, G12/13 [135, 136]	
	CX3CR1	**Gi/Go** [133]	
	CCR1-10	**Gi/Go** [133, 137, 138]	
	CCR2	Gq [138,139]	

Note: The dominant forms of G proteins are highlighted in bold. Table 1 does not show the large group of GPCRs of peripheral sensory neurons responsible for vision, taste and smell. In total, about 800 GPCRs are encoded in the human genome [143, 144].

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Table S2. Brief characteristics, function and pathology of 5-HT receptors

Receptor (Gene)	Cell Transduction Factors	Localization	Function	Pathology	Literature
5-HT1A* (HTR1A)	Gi, Go, PKC, PI 3, ERK, Src kinases , ↓ cAMP, modulate Ca^{2+}. All 5-HT receptors that activate Gi / o multidirectionally modulate the activity of Ca^{2+} channels, open K^{+} channels (via G βγ), which leads to hyperpolarization and decreased excitability of neurons.	CNS: Predominantly localized in the neocortex, hippocampus, entorhinal cortex, olfactory bulb, raphe nuclei, septum, thalamus, interpeduncular nucleus, amygdala, and hypothalamic subnuclei, as well as in the dorsal and anterior horns of the spinal cord. Found on cholinergic neurons, and on cortical and hippocampal glutamatergic pyramidal neurons and granule cells. PNS: Also present in peripheral nervous system structures. Additional Localization: Detected in blood vessels and genital tissues.	Regulates various physiological processes including blood pressure (via medulla oblongata centers and vagus nerve activation), memory, sociability, appetite, cognitive functions, mood, nociception, penile erection, mydriasis, respiration, sexual behavior, sleep, and thermoregulation. Enhances dopamine release in the medial prefrontal cortex, striatum, and hippocampus. Forms heterodimers with multiple receptors such as 5-HT1B, 5-HT1D, 5-HT7, LPA R 1/3, GABA R 2, and S1P R 1/3. Influences hormone secretion, including cortisol, ACTH, oxytocin, prolactin, and somatotropin. Downregulates NMDA R expression in synapses by inhibiting the cAMP/PKA pathway.	Deficiency in receptor (R) is associated with conditions such as anxiety, autism, hyperphagia, nausea, vomiting, and impulsivity. Overexpression of autoreceptors can lead to depressive-like behavior, whereas activation of postsynaptic receptors exerts an antidepressant effect and pronociceptive effects (notably in the dorsal horns of the spinal cord). Additionally, the receptor is implicated in tissue regeneration processes, including liver and spinal cord motor neurons, as well as in wound healing. However, it may negatively impact certain memory and learning functions. Also plays a role in inhibiting the release of glutamate and acetylcholine in various brain regions.	[1-17]
5-HT1B* (HTR1B)	Gi, Go , β -arrestin/ERK, ↓ cAMP Ras-Raf/ERK , PI3K/AKT	Is primarily localized presynaptically, predominantly at axon terminals. In terms of tissue distribution, it is present in blood vessels, the CNS—including the cortex and basal ganglia—and the genitals.	Serves diverse physiological functions including learning, movement, memory, mood regulation, penile erection, sexual behavior, and pain management. Additionally, it contributes to vasoconstriction through its actions in the central nervous system and vascular endothelium. Mechanistically, presynaptic inhibitory autoreceptors are situated at axon terminals, while activation receptors are localized on the postsynaptic membrane.	Is implicated in various psychiatric and behavioral conditions such as addiction, anxiety, depression, schizophrenia, attention deficit hyperactivity disorder (ADHD), and antisocial behavior. Notably, the receptor interacts with the p11 protein (S100A10), the levels of which are observed to decrease in the brain during depressive episodes. A reduction in heteroreceptors is associated with the manifestation of a depressive-like phenotype.	[1, 3-9, 17-24].
5-HT1D* (HTR1D)	Gi, Go , PKC, ↓ cAMP , PI3K/AKT	In the CNS, it is primarily localized in the basal ganglia, specifically in the globus pallidus, substantia nigra, and caudate putamen. It is also present in the hippocampus and neocortex, as well as in the gamma motor neurons of the spinal cord. Moreover, the receptor is found in the peripheral nervous system (PNS), blood vessels, and genital tissues.	It is implicated in the regulation of movement, often through its localization in basal ganglia structures like the globus pallidus, substantia nigra, and caudate putamen. In the cardiovascular system, it contributes to vasoconstriction. Additionally, the receptor serves as an inhibitory regulator of atrial norepinephrine release, thereby affecting autonomic control of cardiac function.	Anxiety disorders have been associated with its dysregulation, suggesting a role in affective disorders. Importantly, interaction with the adapter protein p11 (S100 A10) has been reported. Notably, p11 levels are found to be reduced in the brains of individuals with depression, linking receptor function to mood disorders. Additionally, the receptor has been shown to promote pancreatic cancer, indicating its involvement in oncogenic processes. Therefore, the receptor emerges not only as a modulator of physiological functions but also as a critical player in diverse pathological conditions.	[1-3, 25-27]
5-HT1E (HTR1E)	Gi, Go , β -arrestin/ERK, ↓ cAMP	Is predominantly found in the CNS, specifically in the cortex and limbic system, implicating it in the regulation of cognitive and emotional functions. Beyond the CNS, the receptor is also localized in blood vessels and genital tissues, suggesting a role in vascular and reproductive physiology.	Is implicated in a variety of physiological processes, including memory enhancement and vasoconstriction. Moreover, the receptor plays a neuroprotective role in the central nervous system by defending neurons from oxidative and excitotoxic stress via the β-arrestin/ERK signaling pathway. Genetic consideration indicates that the HTR1E gene exhibits minimal polymorphism in human populations, suggesting a	Altered stress responses in individuals are potentially associated with the risk of developing mental disorders, but also play a role in the development of adaptive stress responses.	[1-3, 28, 29]

Receptor (Gene)	Cell Transduction Factors	Localization	Function	Pathology	Literature
			consistent function across individuals.		
5-HT1F (HTR1F)	Gi, Go , ↓ cAMP ,	Located in the CNS, specifically in the frontal cortex, hippocampus, and olfactory bulb, as well as in the peripheral nervous system. Additionally present in genital organs, mesentery, blood vessels, and kidneys.	Induces vasoconstriction and inhibits glucagon production in the alpha cells of the pancreatic islets. Facilitates mitochondrial biogenesis in the proximal tubules of the kidneys.	Mitigates migraine symptoms, inhibits dural inflammation.	[1-3, 30-32]
5-HT2A (HTR2A)	Gq, G11 , Gi, Go, PLC, IP3 , Ca^{2+}, Ras GTPases , Ras-Raf/MEK/ERK. ↑cGMP, Src kinases β -arrestin/ERK, JAK/ STAT3 PI3K/AKT/mTOR	CNS (cortex, hippocampus, olfactory bulbs, basal ganglia, dopaminergic and GABAergic neurons), PNS, gastrointestinal tract, platelets, fibroblasts, lymphocytes, myocytes, genital organs, blood vessels, heart.	Appetite, imagination, cognition, learning, memory, mood, perception, sexual behavior, sleep, thermoregulation. Regulates metabolic changes during neurostress. Exhibits pronociceptive effects through Gq/11 signaling pathway. Vasoconstriction, enhanced myocardial contractility, platelet aggregation, adipocyte differentiation. Notably, 5-HT2A may exhibit constitutive activity in the absence of a ligand.	Addiction, anxiety, schizophrenia, hallucinations. The receptor is implicated in the pathogenesis of epilepsy and hypertension. May exert ambivalent effects on depression. Reduced expression of the receptor is observed in the cortex in Alzheimer's disease. Facilitates cardiac hypertrophy through AKT/mTOR signaling. Augments synaptic release of NMDA via the PLC/PKC pathway.	[1-3, 33-41].
5-HT2B (HTR2B)	Gq , G11 , _ G 13, PLC _ IP 3 , Ca 2+ , ERK , NO / cGMP , GTPases Ras , c - Yes , Src and Fyn kinases , PI 3 K / AKT / NF - κ B	CNS (cortex, hippocampus, thalamus, pituitary gland, pons, medulla oblongata, cerebellar nuclei, lateral septum, dorsal hypothalamus and medial amygdala, expressed in neurons and microglia), PNS, platelets, blood vessels, gastrointestinal tract, Kupffer cells of the liver, kidneys , Pancreatic β-cells, adipocytes, spleen, lungs, uterus, heart, bone marrow, adipocytes , genitals.	Memory, learning, appetite, sleep; exerts an anxiolytic effect and modulates deep (slow-wave) sleep while inhibiting impulsive behavior. In cellular and systemic physiology, it modulates microglial function, cardiovascular activity, and gastrointestinal motility. Facilitates vasodilation but induces vasoconstriction in the pulmonary artery during hypoxic conditions. Stimulates the production of TNF-α in fibroblasts and TGF-β1 in hepatic stellate cells, thereby promoting megakaryocyte proliferation, erythropoiesis, and myelopoiesis. Catalyzes lipolysis in adipocytes and fortifies the IL-6/STAT3 signaling pathway. The expression of this receptor is upregulated in response to IL-4 and IL-6 via the JAK/STAT pathway.	Engages in the pathogenesis of various conditions, notably migraine (in cases of hyperfunction) and schizophrenia (in instances of receptor deficiency), and contributes to visceral pain. Exhibits a dual role in certain neoplastic conditions. In macrophages, it curtails the release of pro-inflammatory cytokines and fosters a shift towards the M2 phenotype at the expense of the M1 phenotype. Facilitates hypertrophy of cardiomyocytes and is implicated in heart failure. Involved in fibrosis of internal organs. Possesses pro-inflammatory activity and exacerbates insulin resistance.	[1-3, 42-49].
5-HT2C (HTR2C)	Gq , G11 , _ G 12, G 13 , Gi , Go , PLC , _ IP 3 , Ras GTPases , Src kinases , PKC , ERK , $Ca2^{+}$, NO / cGMP , ↓ cAMP (via Gi / o)	CNS (present in large quantities in the choroid plexus (plica choroidea), hippocampus , prefrontal cortex, and in the subthalamic and lateral habenular nuclei. predominantly localized on GABAergic, glutamatergic, dopaminergic, neuropeptidergic and cholinergic neurons) , gastrointestinal tract, platelets. Blood vessels, genitals.	Regulates deep sleep, appetite, and gastrointestinal motility. Functions as a heteroreceptor for norepinephrine and dopamine, inhibiting their release in the limbic system. Influences movement, mood, sexual behavior, sleep, and thermoregulation. Involved in energy homeostasis, particularly in aspects of nutrition and glucose metabolism, by acting on the hypothalamus and brainstem. Serves as a mitogen that controls cellular proliferation and differentiation across various cell types. Modulates the hypothalamic-pituitary-adrenal axis. Notably, 5-HT2C may exhibit constitutive activity in the absence of a ligand.	Addiction, anxiety, depression, epilepsy, schizophrenia, and antisocial behavior are associated with 5-HT2C receptor dysregulation. Overactivity of the 5-HT2C receptor may exacerbate symptoms of depression and anxiety. Genetic knockout studies in mice have shown that the absence of 5-HTR2C leads to increased food intake, insulin resistance, and obesity. Paradoxically, activation of 5-HT2C in Sim1 neurons in the paraventricular nucleus of the hypothalamus stimulates food consumption. Numerous human polymorphisms of the 5-HT2C receptor have been identified as risk factors for neuropsychiatric diseases as well as obesity.	[1-3, 50-58].

Receptor (Gene)	Cell Transduction Factors	Localization	Function	Pathology	Literature
5-HT3 (HTR3)	Ionotropic receptor, which is a Na^+ and K^+ channel	In the CNS, it is predominantly found in regions such as the cortex, medulla oblongata, hippocampus, caudate body, putamen, and brain stem, including the area postrema and the dorsal motor nucleus of the vagus nerve. Additionally, this receptor is present in the PNS and the gastrointestinal tract. Notably, 5-HT3 is also expressed in various inflammatory cells, encompassing monocytes, macrophages, dendritic cells, T cells, B cells, and mast cells.	Plays a pivotal role in learning and memory processes. Activation of this receptor opens a channel that facilitates an excitatory response in neurons. This excitation occurs due to the influx of sodium (Na+) and potassium (K+) ions, and, to a lesser extent, divalent cations like calcium, as well as low molecular weight organic cations. Furthermore, subunits A and E of the 5-HT3 receptor are localized on the inner mitochondrial membrane. The action of serotonin on these subunits has been shown to influence changes in the mitochondrial membrane potential and the rate of oxygen consumption. This suggests a multifaceted role for the 5-HT3 receptor, extending beyond neurotransmission to cellular bioenergetics.	Is implicated in a variety of neuropsychiatric conditions, including addiction, anxiety, depression, and schizophrenia. Its activation is also associated with gastrointestinal disturbances such as vomiting and nausea. Importantly, the receptor plays a role in immune modulation, promoting the production of pro-inflammatory cytokines and contributing to inflammatory processes. Certain polymorphisms in the HTR3 gene have been identified as risk factors for obsessive-compulsive disorder and irritable bowel syndrome. This underscores the receptor's multi-systemic influence, from neuropsychiatric function to gastrointestinal and immune regulation.	[1-3, 59-64].
5-HT4 (HTR4)	Gs , Gi, Go , Gq, G13, ↑ cAMP (via Gs), Ca^{2+}, β -arrestin/ERK, Ras-Raf/ERK	CNS (cortex, limbic system: olfactory bulbs, striatum, ventral pallidum, septum, hippocampus and amygdala; GABAergic, glutamatergic, and cholinergic neurons), PNS, gastrointestinal tract, heart, adrenal glands, bladder, lungs, genitals	It is implicated in the regulation of appetite, specifically inducing hypophagia. The receptor also modulates learning, memory, mood, and motor skills. In the cardiovascular system, it contributes to increased cardiac contractility, exhibiting an inotropic effect. In the realm of neurotransmission, 5-HT4 facilitates the release of several key neurotransmitters, including acetylcholine, GABA, and dopamine. Intriguingly, like the 5-HT3 receptor, it is localized on the mitochondrial membrane and has a role in regulating mitochondrial function. A noteworthy aspect of 5-HT4 receptor biology is its age-dependent expression, which tends to decline with advancing age. Additionally, under normal conditions, the receptor interacts with the p11 protein (S100A10), further diversifying its functional implications.	It is implicated in the etiology and clinical manifestations of depression, serving as a pivotal regulator in the homeostasis of various neurotransmitter systems. This regulatory role positions the receptor as a potential key player in neurodegenerative and neuropsychiatric disorders, including Alzheimer's disease, Huntington's disease, Parkinson's disease, and major depressive disorder. Polymorphisms in the HTR4 gene have been identified as potential contributors to bipolar disorder, adding another layer of complexity to the receptor's involvement in mental health. Furthermore, the receptor is associated with metabolic disorders, specifically obesity, suggesting a far-reaching impact on both neurological and metabolic homeostasis.	[1-3, 64-68].
5-HT5A* (HTR5A)	Gi, Go, Gs, ↓ cAMP (via Gi/o)	It is primarily localized in the CNS, notably in regions such as the limbic cortex, the nuclei of the raphe reticular formation, and the spinal cord. Additionally, the receptor is found in genital tissues.	Despite its implication in a range of physiological and cognitive functions, including motor activity, cognition, memory, acoustic startle response, pain modulation, learning, and food intake, the receptor remains one of the least studied in the 5-HT family. Interestingly, knockout models of this receptor in transgenic mice have not exhibited significant observable changes. This might indicate a degree of functional redundancy with other receptors or compensatory mechanisms that mitigate the loss of this particular receptor.	Exhibits a dual role in mental health, contributing to antidepressant effects but also implicated in hallucinations, psychosis, and schizophrenia. The compound valeric acid serves as an agonist for this receptor, adding another layer of complexity to its pharmacological profile. Moreover, there is tentative evidence to suggest a possible association with breast tumor pathogenesis.	[1-5, 69-74]
5-HT5B (HTR5B)	Pseudogene in humans	-	-	-	-

Receptor (Gene)	Cell Transduction Factors	Localization	Function	Pathology	Literature
5-HT6 (HTR6)	Gs , Gq , ↑ cAMP , mTOR , Cdk 5, GTPases - Rho , Ras - Raf / ERK , Src and Fyn kinases , MAPK - JNK	In the CNS, 5-HT6 is localized primarily to GABA interneurons, and 5-HT6 is also present on glutamatergic pyramidal neurons in the prefrontal cortex and hippocampus .	Cognition, learning, memory, mood, appetite (hyperphagia). Reduces the release of dopamine, norepinephrine, reduces glutamatergic and cholinergic neurotransmission, but enhances GABAergic signal transmission. In embryogenesis, it modulates key processes in the development of the nervous system, from neuronal migration to the formation of brain circuits.	Manifests a complex role in various neuropsychiatric conditions, including anxiety, depression, schizophrenia, and epilepsy. Notably, there is a diminished expression of this receptor in the cortical regions of Alzheimer's disease patients, further complicating its role in cognitive function. Studies using 5-HT6 knockout mice have demonstrated cognitive impairment along with abnormal anxiety levels, reinforcing the receptor's critical involvement in both cognition and emotional regulation. Beyond the nervous system, emerging evidence suggests that 5-HT6 may also influence the immune microenvironment within tumor tissues.	[1-3, 75-80].
5-HT7* (HTR7)	Gs , G12, ↑ cAMP, Cdk5, Ca^{2+}, Rho GTPase , Ras-Raf/ERK, PI3K/AKT/ mTOR	CNS (cortex, thalamus, hypothalamus, hippocampus, cerebellar Purkinje neurons, spinal cord), PNS, blood vessels, gastrointestinal tract, genitals. T lymphocytes.	Plays a crucial role in various physiological functions, including the modulation of immune responses, specifically through the production of IL-10 by T cells. Additionally, it has vasoregulatory effects, evidenced by its capacity to reduce vascular resistance in internal organs and skeletal muscles. Its ability to promote venous vasodilation further underscores its vascular functions. Interestingly, the receptor forms heterodimers with the 5-HT1A receptor, implicating a likely coordinated modulation of serotonin signaling. On a cellular level, 5-HT7 is involved in neurogenesis and influences synaptic plasticity by increasing the expression of NMDA receptors through the cAMP/PKA signaling pathway. These diverse roles indicate that the 5-HT7 receptor is integral to both immune modulation and neural plasticity, making it a subject of interest for further research in both immunological and neurological disorders.	It is implicated in anxiety disorders and appears to be activated in neuropathic pain, a condition that often coexists with depression. Experimental studies have shown that the receptor's interaction with the S100B protein induces depressive-like behavior, further implicating it in mood disorders. Beyond its role in the central nervous system, the receptor also appears to facilitate tumorigenesis, as its activation has been shown to promote the growth of tumor cells. Additionally, the receptor's ability to activate the TRPA1 ion channel suggests a role in the somatosensory system, specifically in inducing itching sensations.	[1-3, 81-87].

Note. * - possibility of functioning as an autoreceptor when localized on the presynaptic membrane. The main types of G -proteins that mediate the function of the receptor are highlighted in bold , 5-HT is 5-hydroxytryptamine (serotonin), GABA – gamma-aminobutyric acid, R – receptor, cAMP – cyclic adenosine monophosphate, cAMP – cyclic guanosine monophosphate, PI 3 K – phosphoinositol 3-kinase, PLC – phospholipase C , IP 3 – inositol 3-phosphate, PKC – protein kinase C, CNS - central nervous system, PNS - peripheral nervous system, GIT - gastrointestinal tract, ACTH - adrenocorticotropic hormone, S100 - calcium-binding proteins (belong to the DAMP category), MAPK - mitogen-activated protein kinases (ERK , JNK), Cdk 5 **-cyclin** - dependent _ kinase 5.

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