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REVIEW

Physiological Responses to Psychosocial Stress

Exploring the complex relationship between psychosocial stress and the gut microbiome: implications for inflammation and immune modulation

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Abstract

There is growing interest in understanding the complex relationship between psychosocial stress and the human gastrointestinal microbiome (GIM). This review explores the potential physiological pathways connecting these two and how they contribute to a proinflammatory environment that can lead to the development and progression of the disease. Exposure to psychosocial stress triggers the activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary axis (HPA), leading to various physiological responses essential for survival and coping with the stressor. However, chronic stress in susceptible individuals could cause sustained activation of HPA and SNS, leading to immune dysregulation consisting of redistribution of natural killer (NK) cells in the bloodstream, decreased function of T and B cells, and elevation of proinflammatory cytokines such as interleukin-1, interleukin-6, tumor necrotic factor-α, interferon-gamma. It also leads to disruption of the GIM composition and increased intestinal barrier permeability, contributing to GIM dysbiosis. The GIM dysbiosis and elevated cytokines can lead to reciprocal effects and further stimulate the HPA and SNS, creating a positive feedback loop that results in a proinflammatory state underlying the pathogenesis and progression of stress-associated cardiovascular, gastrointestinal, autoimmune, and psychiatric disorders. Understanding these relationships is critical for developing new strategies for managing stress-related health disorders.

gastrointestinal microbiome; immune modulation; inflammation; microbiota-gut-brain axis; psychosocial stress

INTRODUCTION

If actual or perceived environmental demands surpass an individual's capacity to cope, this results in stress (1). The internal or external environmental demands that produce stress are called stressors. Stress can cause acute or lasting effects on physiological processes that can lead to the development or progression of disease (1). However, a brief exposure to a stressor may benefit most people as it can improve physiological functions and endurance. We refer to this kind of stress as eustress (1, 2). The response to eustress is adaptive, aiming to overcome threats or challenges, and is mediated via complex interactions between neuroendocrine and immune mechanisms. Thus, it enhances metabolic, immunological, cardiovascular, and cognitive performance, ultimately improving survival (3). However, when stress continues for a prolonged period (chronic stress), it becomes maladaptive and negatively affects physiological mechanisms. This type of stress is distress (2). In susceptible individuals, it could have long-term implications at the organ system, cellular, and molecular level and is associated with disease development and progression (4). The stress response is subjective as an individual's previous experiences with stressors, genetics, sleep, diet, and resilience influence how they react to stress (5). Coping mechanisms, self-awareness, optimism, social support, education, heredity, previous experience, and sleep habits determine an individual's physiological and psychological resilience (5) (Fig. 1).

Depending on the type of stressor, stress can be physiological or psychological. Physiological stress occurs due to pain, heat, cold, hypoglycemia, exercise, hemorrhage, illness, injury, sleep deprivation, and nutritional deficiencies. On the other hand, psychological and social stressors like job strain, divorce, loss of a loved one, caregiving for a chronically ill loved one, racial discrimination, low social status, unemployment, perceived dangers, anxieties, and social isolation cause psychosocial stress. Psychosocial stress is present in 36.55% of individuals globally (6). Around 22.6% of working-age adults in the United States have been reported to have psychosocial stress in 2017–2018 (7).

Studies have shown that stress affects neural, endocrine, and immune mechanisms to trigger an inflammatory response, which underlies the pathogenesis of most stress-associated diseases (8, 9). More recently, researchers have

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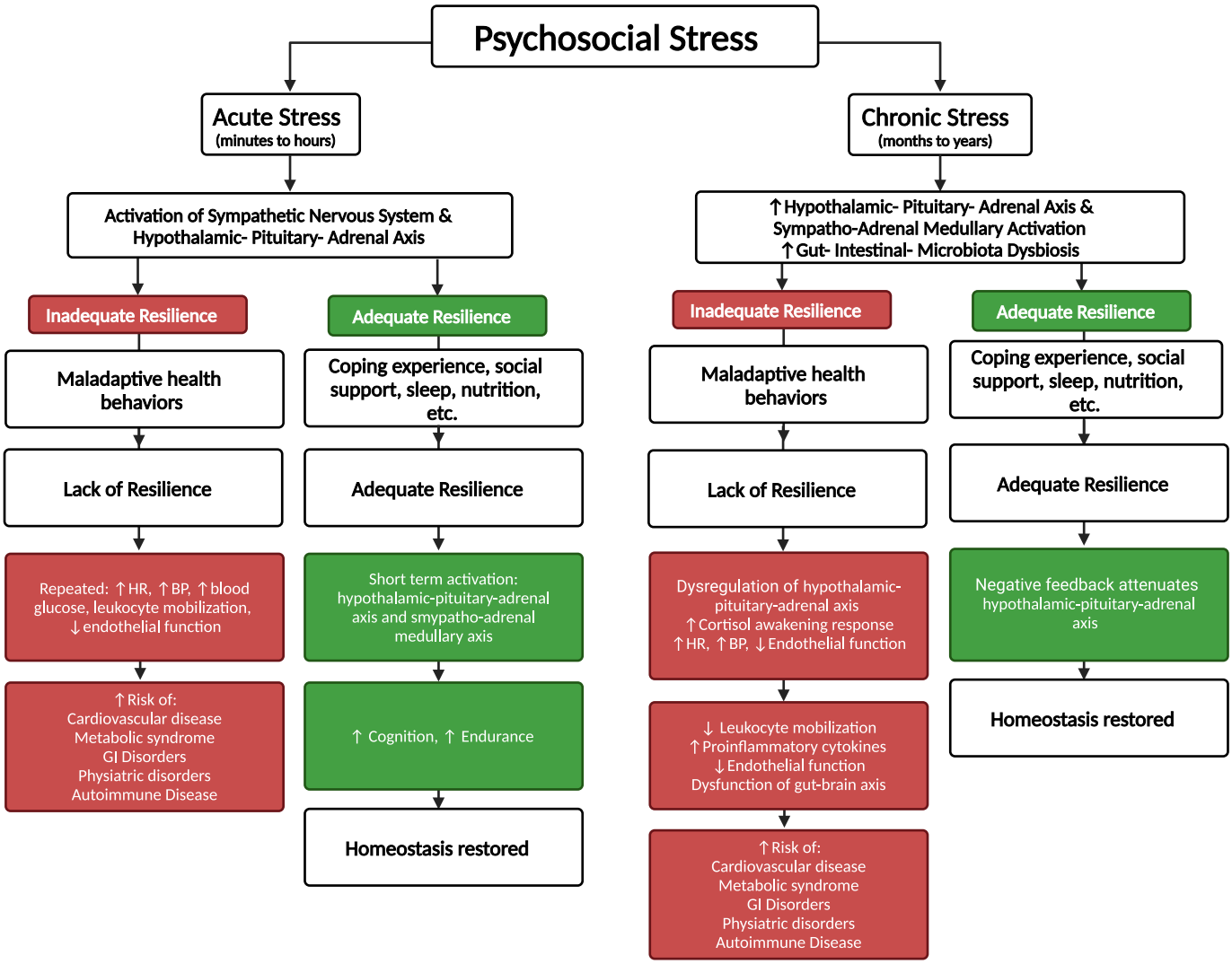

Figure 1. The responses to psychosocial stress. Stress activates the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, where inadequate resilience leads to maladaptive behaviors and increased risk of cardiovascular, metabolic, gastrointestinal, psychiatric, and autoimmune diseases. In contrast, adequate resilience, supported by coping mechanisms and social support, restores homeostasis. Chronic stress also activates the HPA axis and causes gut microbiota dysbiosis, with inadequate resilience leading to prolonged dysregulation and similar health risks, whereas adequate resilience through effective coping strategies restores homeostasis. Both types of stress highlight the importance of resilience and adaptive behaviors in mitigating adverse health outcomes. BP, blood pressure; GI, gastrointestinal; HR, heart rate. This figure was created by BioRender.

also uncovered its impact on the gastrointestinal microbiome (GIM) and how stress affects GIM and contributes to the development of a number of diseases (10).

The gastrointestinal microbiome (GIM) encompasses all microorganisms, their structural elements, metabolites, and the environment in which they live in the gastrointestinal tract (11). On the other hand, microbiota includes only the living microorganisms residing in a particular environment; e.g., gut microbiota refers to microorganisms residing in the gut (12). The human gut microbiota is composed of *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria*, and *Verrucomicrobia,* but the predominant bacterial phyla are Actinobacteria, Firmicutes, Bacteroidetes, and Proteobacteria. In addition, there are various viruses, fungi, phages, archaea (13), and some pathogenic bacteria like *Campylobacter jejuni, Vibrio cholera*, and *Salmonella enteric* (14). The composition of the GIM varies along the length of the gastrointestinal tract. Age, how an individual was delivered at birth (vaginal vs. caesarian delivery), diet, medication, gastrointestinal (GI) infection, and the use of antibiotics also affect its composition (15). GIM plays an integral role in the digestion of nutrients, synthesis of vitamins and amino acids, development of the host immune system, drug metabolism, maintenance of the structural integrity of the gastrointestinal barrier, and bolstering innate immunity in the host. It also helps prevent the proliferation of harmful microbes in the gut (16, 17). Disruption of normal GIM is found to be associated with diseases like cardiovascular disease (CVD), obesity, diabetes, colon cancer, inflammatory bowel disease (IBD), etc. (16, 18). Studies have shown an association of these diseases with stress, too. Recently, exposure to stress has also been found to impact the composition of GIM (19, 20), which increases vulnerability to enteric infection and produces an excess of

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inflammatory mediators that underlie these diseases (21). Though different studies have separately found an association between stress and diseases and between GIM disruption and diseases, it is not clear whether the role of stress in causing disease is mediated through the disruption of GIM. The details of the mechanism correlating stress to the disruption of GIM and its health consequences are still being researched and are ambiguous. This review will explore the potential relationship between psychosocial stress and the GIM and attempt to explain the potential physiological pathways linking stress and GIM, leading to a proinflammatory state that underlies most stress-associated diseases.

PHYSIOLOGICAL PATHWAYS UNDERLYING PSYCHOSOCIAL STRESS RESPONSE AND THEIR IMPACT ON GIM

Stress response begins as an adaptive mechanism to prepare for potential challenges from internal or external stressors (1). However, if the exposure to a stressor is prolonged (chronic stress) or recurrent (acute repetitive stress), the stress response becomes inappropriate and maladaptive, which may lead to cardiovascular, gastrointestinal, autoimmune, and psychiatric disorders like depression, anxiety, and cognitive decline (21, 22). Although intriguing, the stress-disease relationship is a complex puzzle that we are still deciphering. Recent studies have revealed complex neuroendocrine and immune mechanisms' interactions with GIM that eventually produce proinflammatory states responsible for disease development and progression.

Stress-Induced Activation of the Sympathetic Nervous System

The sympathetic nervous system (SNS) is one of the two divisions of the autonomic nervous system. Its main role is to inhibit the parasympathetic nervous system and alter the body's physiology to respond to actual or perceived threats (23). In certain stress-related diseases, the sympathetic nervous system (SNS) remains continuously activated without being counteracted by the parasympathetic system (24). On acute exposure to a stressor, the prefrontal cortex receives and integrates various neurosensory signals and communicates this information via the uncinate fasciculus to the amygdala, the center associated with the stress response, which further passes on this information to the hypothalamus via the stria terminalis (25). When stimulated, the dorsomedial hypothalamus (DMH) activates the sympathetic nervous system by sending excitatory signals to the brain stem, specifically to the rostral medullary raphe region (rMR) and the rostral ventrolateral medulla (RVLM). These regions contain sympathetic premotor neurons that project to the spinal cord and synapse with preganglionic sympathetic neurons (25). The preganglionic sympathetic neurons release acetylcholine, which binds to nicotinic receptors on chromaffin cells in the adrenal medulla. This stimulates the release of catecholamines [epinephrine (Epi) and norepinephrine (NE)] into the bloodstream (26). The catecholamines act on various adrenergic receptors throughout the body, facilitating the "fight-or-flight" response like increased heart rate, blood pressure, enhanced glucose mobilization, lipolysis, and thermoregulatory responses to stress (27, 28). Thus, the hypothalamus is mainly responsible for altering the body's autonomic signaling and putting us into a sympathetic, controlled state. Acute stress triggers time-limited behavioral and physiological changes. Behavioral changes include increased arousal, alertness, cognition, and analgesia (29, 30). The physiological responses include increased heart rate, blood pressure, vascular tone, respiratory rate, and intermediate metabolism (gluconeogenesis and lipolysis) (31). These changes redirect vital substrates like oxygen and nutrients to central nervous system (CNS) and stress-responding organs while energy-consuming functions (e.g., digestion, reproduction, growth, and immunity) are temporally suppressed. In summary, the acute stress response involves the activation of the sympatho-adrenal-medullary (SAM) axis. This coordinated response involves the hypothalamus, brainstem, and adrenal medulla, releasing catecholamines and the classic "fight-or-flight" response (Fig. 2).

During chronic psychosocial stress, SNS overactivity is sustained through central and peripheral pathways. Centrally, chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus (31). The elevated CRH stimulates noradrenergic centers in the brainstem and spinal cord, including locus coeruleus, which further projects to sympathetic preganglionic neurons in the spinal cord and parasympathetic preganglionic neurons in the brainstem and the spinal cord (32). This leads to increased sympathetic activity and reduced parasympathetic activity. Increased SNS activity has positive feedback on the hypothalamus and stimulates the release of CRH by the hypothalamus, creating a positive bidirectional feedback loop (32). Also, increased CRH will act on the anterior pituitary and release adrenocorticotropic hormone (ACTH), which acts on the adrenal cortex to release glucocorticoids and on the adrenal medulla to release catecholamines (epinephrine and norepinephrine) (1). The adrenal medulla mainly secretes epinephrine and norepinephrine to a small extent only. Chronic stress also leads to the activation of the locus coeruleus norepinephrine (LC-NE) system. Locus coeruleus is a small brainstem nucleus that is the primary source of norepinephrine (NE). Stimulation of the LC-NE system leads to the release of NE, which further stimulates the HPA axis and enhances CRH release (33). Elevated glucocorticoids from HPA axis stimulation potentiate the effect of SNS activation by increasing the transcription and expression of α-1B adrenergic receptors. This upregulation enhances the sensitivity of target tissues to catecholamines, thereby amplifying the effects of SNS activation (34). Also, a sustained increase in glucocorticoids during chronic stress will lead to desensitization of glucocorticoid receptors (GRs), leading to a decrease in negative feedback, which eventually leads to sustained activity of the HPA axis and SNS activation (35).

The chronically increased catecholamines and cortisol levels result in physiological consequences such as sustained vasoconstriction, increased heart rate, blood pressure, cardiac output, gluconeogenesis, lipolysis, increased blood glucose, endothelial dysfunction, insulin resistance, eventually leading to hypertension, dyslipidemia, increased risk of cardiovascular events like myocardial infarction and stroke (36–39). The sustained increase in catecholamines activates

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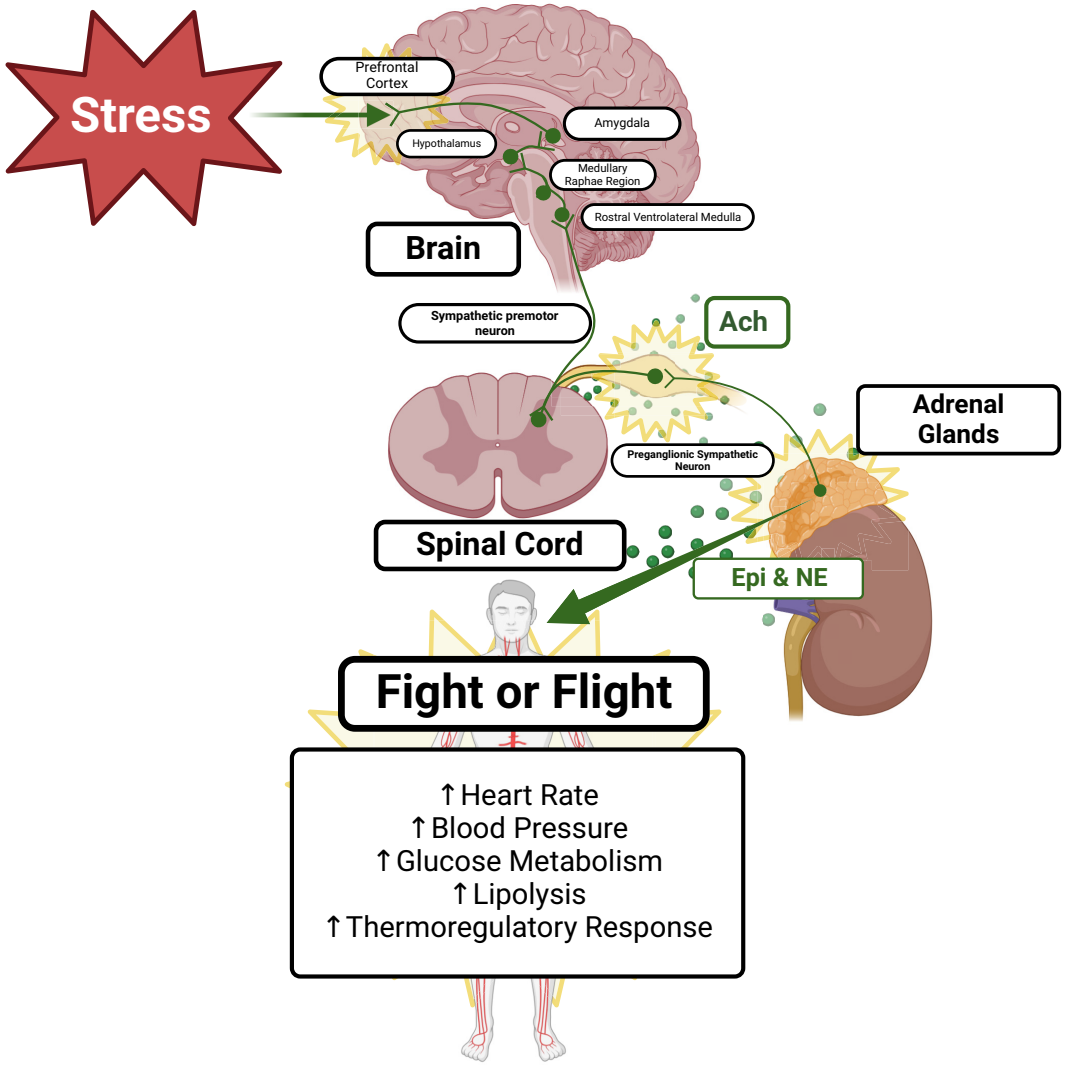

Figure 2. The acute sympathetic stress response begins when a stressor activates the prefrontal cortex in the brain, which then signals via the uncinate fasciculus to the amygdala and the stria terminals to the hypothalamus. This activation cascade continues to the medullary raphe region and the rostral ventrolateral medulla, which then sends signals to the spinal cord. In the spinal cord, sympathetic premotor neurons are activated, releasing acetylcholine (Ach) by preganglionic sympathetic neurons. This release stimulates enterochromaffin cells in the adrenal medulla to secrete epinephrine (Epi) and norepinephrine (NE) into the bloodstream. The surge of these hormones increased heart rate, elevated blood pressure, enhanced glucose metabolism, increased lipolysis, and an improved thermoregulatory response. These changes prepare the body to handle the immediate stressor by enhancing physical and mental performance. This figure was created by BioRender.

β2-adrenergic receptors in immune cells and modulates their activity (40). Increased catecholamines also cause a redistribution of immune cells, such as natural killer (NK) cells, into the peripheral blood, suppress T cells and B cells function, and impair their ability to respond to infections effectively (40). In addition, an increase in epinephrine and norepinephrine and a decrease in acetylcholine (Ach) during chronic stress leads to an increased release of proinflammatory cytokines like interleukin-6 (IL-6) from immune cells. Under normal circumstances, Ach has been reported to inhibit the release of tumor necrotic factor-α (TNF-α) and proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and interleukin-18 (IL-18). In chronic stress, a decrease in parasympathetic activity and, thus, a decrease in Ach can lead to an increase in TNF-α, IL-1, and IL-6 (41).

The connections between the prefrontal cortex and the amygdala offer insight into how psychosocial stress can activate the SNS and cause an inflammatory state. Under normal circumstances, the prefrontal cortex dampens or heightens the amygdala's response to stress. The prefrontal cortex blocks the signal from the amygdala to the hypothalamus when a threat ends or is judged by higher processing as nonthreatening. This results in the cessation of SNS activation. However, with chronic psychosocial stress, the prefrontal cortex does not suppress the amygdala, which increases the amygdala's reactivity to stressful stimuli (42). As a result, the SNS and HPA axis are chronically activated.

The SNS has connections to the enteric nervous system (ENS) within the gastrointestinal (GI) tract. The ENS controls mucosal function, gastrointestinal barrier and permeability, mucosal immune system, and motility. The physiologic

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consequence of these connections is that when SNS signaling predominates, the ENS is dampened, and thus, digestion is slowed. This slowing of fecal transit in the GI tract has consequences on the microbiota within the GI system, demonstrating increased heterogeneity of the gut microbiome in those with slower fecal transit. It was also shown that species and genus-specific differences occur in those with slower transit time (43). In particular, *Bacteroides* species significantly decreased in those with GI dysmotility. Other studies have reported decreased *Lactobacillus* and *Bifidobacterium* in individuals exposed to chronic stress and a relative increase in potentially pathogenic bacteria, such as those from the Proteobacteria phylum (20). Stress-induced sympathetic stimulation also decreases gastric acid secretion, affecting gut microbiota (44). Sustained catecholamine increase also disrupts tight junctions in the gut epithelium, increasing intestinal permeability. Due to this, bacteria and their products can leave the GI lumen and enter the blood, which triggers an inflammatory response involving mast cells, neutrophils, and monocytes, further contributing to gut inflammation and systemic immune dysregulation. These changes can be collectively called dysbiosis (45). Dysbiosis of the gut microbiome correlates with many pathologies underlying the GI tract, such as obesity, inflammatory bowel disease, and irritable bowel syndrome (46). It has also been shown that changes to the gut microbiota can impact the gut's motility via interactions with ENS (47) (Fig. 3). Other researchers have demonstrated that ENS signaling communicates reciprocally with the SNS. Activation of the ENS was associated with reciprocal parallel firing in the SNS neurons (32). This connection between these two branches of the autonomic nervous system allows us to understand the interplay regarding the role of psychosocial stress.

Stress-Induced Hypothalamic-Pituitary-Adrenal Axis Activation

The hypothalamic-pituitary-adrenal (HPA) axis is highly critical for regulating the body's homeostatic processes. It leads to the secretion of glucocorticoids, which, under normal conditions, have anti-inflammatory, antiallergic, and immunesuppressive roles, such as inhibiting antigen presentation, apoptosis, and the expression of major histocompatibility complex class II and antibodies (3, 48, 49). Glucocorticoids regulate proinflammatory genes encoding cytokines, chemokines, and inflammatory enzymes associated with the repression of nuclear factor-κB (NF-κB) transcription. It also regulates metabolism, promotes gluconeogenesis, stores carbohydrates as glycogen, and produces ATP (48–50). The tightly regulated glucocorticoid levels underscore the HPA axis's pivotal role in maintaining the body's equilibrium. The secretion of cortisol, the main glucocorticoid in humans, follows a circadian rhythm. Its levels are highest when rising in the morning and peak around 30–45 min after awakening. This morning rise is called cortisol awakening response (CAR). After that, the cortisol levels steadily decline, reaching the lowest level during sleep. This synchronization of circadian rhythm is dependent on environmental cues, and this process is called entrainment. The suprachiasmatic nucleus (SCN) receives environmental cues like a light-dark cycle. When it is dark, the SCN sends this information to the PVN to inhibit the release of CRH and arginine vasopressin (AVP) during the inactive phase of the circadian rhythm. This is responsible for very low ACTH and glucocorticoids at night (48, 50). This diurnal rhythm is critical for the normal functioning of target tissues.

When an individual experiences stress, signals from the prefrontal cortex, amygdala, and hippocampus project to the hypothalamus's PVN cells. A discrete population of CRH neurons located in the dorsomedial parvocellular division of the PVN is mainly responsible for the stress response. These neurons project to the median eminence and release CRH and AVP (48, 51). The CRH binds to corticotropin-releasing hormone receptor-1 (CRH-R1) of the anterior pituitary and stimulates the pro-opiomelanocortin (POMC) gene transcription encoding adrenocorticotropic hormone (ACTH), leading to ACTH production and release from the anterior pituitary gland. AVP released from the hypothalamus acts on arginine vasopressin 1B (AVP1B) receptors to activate protein kinase C, which complements the actions of CRH. AVP is a potent synergistic factor to CRH for ACTH release (52). The ACTH acts on melanocortin 2 receptors in zona fasciculata cells of the adrenal cortex to release glucocorticoids, mainly cortisol, in humans (Fig. 3).

Under normal physiological conditions, CRH/AVP/ACTH secretion is tightly regulated and controlled by the circadian rhythm. Elevated glucocorticoids suppress ACTH and CRH secretion via a negative feedback loop at the anterior pituitary gland, PVN, and hippocampus level, thus preventing further increases in glucocorticoids.

When an individual is exposed to acute stress, the HPA axis is activated, leading to an abrupt increase in ACTH within minutes, which acts on the adrenal glands to release cortisol. The peak cortisol levels occur within 15–20 min of stressor exposure (49). This burst in cortisol is helpful as it plays a role in metabolism; it increases blood glucose via glycogenolysis, thus increasing glucose availability to the brain and muscles, increasing protein and fat mobilization, and is anti-inflammatory. The negative feedback mechanism effectively terminates the response after the stressor subsides. However, in susceptible individuals having inadequate resilience, there can be an abnormal release of cortisol after exposure to acute stress. The degree to which an individual's cortisol levels are affected in response to acute stress is critical, as studies have found that exaggerated and blunted cortisol response to stress can lead to an increased risk of diseases (53–55). In a study by Hamer and Steptoe (54) using the Whitehall II cohort, it was found that individuals with increased cortisol reactivity to acute stress had a 59% increase in the odds of developing hypertension for each standard deviation change in cortisol responsivity to a stressor. Studies also found that individuals with heightened cortisol reactivity to stress have increased progression of coronary artery calcification (55, 56), cellular aging, and shortened telomeres length compared with individuals eliciting normal cortisol increase (57). Though the increased cortisol response to acute stress has been studied in much detail, there are a few studies that reported an association between weak cortisol reactivity to acute stress and obesity and the future risk of developing depression and anxiety (58) and adverse health outcomes (59). Blunted cortisol reactivity to acute stress has been found in individuals who had

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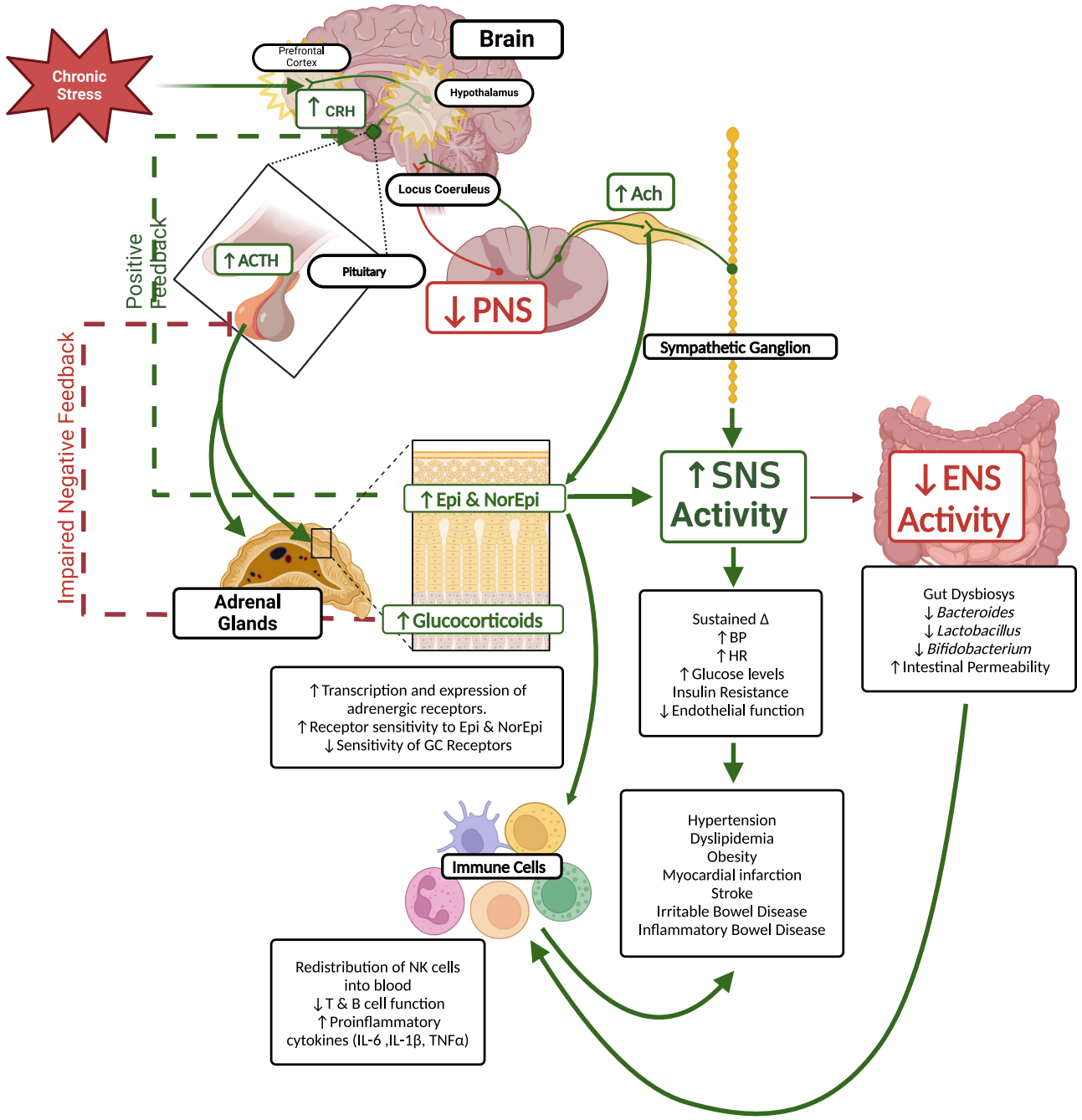

Figure 3. The physiological response to chronic stress, highlighting interactions between the brain, endocrine, and immune systems. Chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH promotes the release of glucocorticoids (cortisol) and catecholamines (epinephrine and norepinephrine) from the adrenal glands. This results in heightened transcription and expression of adrenergic receptors, increased sensitivity to epinephrine and norepinephrine, and decreased sensitivity of glucocorticoid receptors. The elevated levels of glucocorticoids and catecholamines enhance sympathetic nervous system (SNS) activity while reducing parasympathetic nervous system (PNS) activity. This sympathetic activation sustains increased blood pressure (BP) and heart rate (HR), raises glucose levels, induces insulin resistance, and impairs endothelial function, contributing to hypertension, dyslipidemia, obesity, myocardial infarction, stroke, irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD). Furthermore, chronic stress leads to a redistribution of natural killer (NK) cells into the bloodstream, a reduction in T and B cell function, and increased production of proinflammatory cytokines. In addition, chronic stress disrupts the enteric nervous system (ENS) activity, causing gut dysbiosis characterized by decreased levels of *Bacteroides*, *Lactobacillus*, and *Bifidobacterium* and increased intestinal permeability, further contributing to gastrointestinal disorders. This figure was created by BioRender.

previously made a suicide attempt (60) and in caregivers of individuals with autism spectrum disorder (61). Also, a meta-analysis of studies on early-life adversities found strong evidence of an association between early-life adversity and a blunted cortisol response to social stress (62). Though the current understanding of blunted cortisol response in acute stress and underlying pathways is not robust, these studies suggest a nonlinear inverted-U relationship between stress-

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induced cortisol levels and the risk of disease development (63) and underscore the importance of tightly controlled cortisol levels by negative feedback mechanisms.

In chronic stress, this negative feedback loop is dysregulated. Individuals susceptible to the adverse effects of stress tend to experience excessive activation of the HPA axis (3). The persistent activation of CRH-secreting neurons in the PVN of the hypothalamus leads to continuous secretion of ACTH from the pituitary gland, which stimulates the adrenal cortex to produce elevated cortisol levels (3). Cortisol acts on two types of receptors: mineralocorticoid (type-I) and glucocorticoid (type-II) receptors. Both types of receptors are involved in negative feedback mechanisms. However, cortisol has a 5–10 times higher affinity for the mineralocorticoid receptors (MRs) than glucocorticoid receptors (GRs). Due to its binding affinity for MRs, the cortisol levels in the blood are maintained relatively low under normal physiological conditions. Under situations like stress where the cortisol concentration is elevated, cortisol binds to the GRs (present throughout the brain and peripheral tissues) with lower affinity. During stress, the binding of cortisol to GRs in the brain, especially in the hippocampus, amygdala, basal ganglia, and lateral septum, activates the GRs (3); it increases synaptic plasticity, which is responsible for stress-induced behavioral changes, including the effect on decision-making, risk assessment, and attention (64).

Under physiological conditions, binding cortisol to GR receptors on the anterior pituitary also leads to negative feedback. This finely tuned negative feedback control mechanism keeps the secretion of ACTH and, thus, cortisol levels within a relatively narrow range. This mechanism is of utmost importance in maintaining homeostasis, as excessive or insufficient exposure to cortisol can adversely affect health and overall well-being (65). Stress-induced high cortisol levels can lead to desensitization of glucocorticoid receptors (3). This impairs the normal inhibition of CRH and ACTH release, perpetuating the overproduction of these hormones and sustaining high cortisol levels that affect almost every system in the body, including the immune, cardiovascular, reproductive, respiratory, and GI systems (65). Chronic stress also causes markedly increased production of AVP, which plays a role in the chronic drive of the HPA axis. Elevated cortisol levels produce detrimental cardiovascular, metabolic, immune, and psychiatric effects (65). They promote visceral adiposity, insulin resistance, dyslipidemia, and hypertension, contributing to metabolic syndrome (66). Elevated cortisol levels are associated with cognitive decline, anxiety, depression, and other mood disorders (66). Moreover, prolonged HPA axis activation leads to glucocorticoid resistance, resulting in elevated levels of proinflammatory cytokines such as IL-6 and TNF-α, which can exacerbate inflammatory diseases and contribute to atherosclerosis, endothelial damage, and other cardiovascular diseases (33). Increased cortisol levels are also known to profoundly affect the gut microbiota and the microbiota gut-brain (MGB) axis.

Cortisol can affect gut microbiota in several ways, including gut transit time, intestinal permeability, nutrients, and the overall composition of the biome (67–70). It affects immune cells, epithelial cells, smooth muscle, the Cajal cells, and enterochromaffin cells (67). Gut motility can be modulated by different neurotransmitters like GABA, serotonin, melatonin, histamine, and acetylcholine and metabolites from microbiota such as nitric oxide and hydrogen sulfide (67). Another significant effect of cortisol on the gut is increased paracellular permeability. Cortisol must bind to the glucocorticoid receptors, which are ligand-activated transcription factors. The glucocorticoid receptor binds to the occluding promoter site, decreasing its transcription in the GI tract (71). It has also been shown to cause reduced transcription of claudin 5 (67, 71). This allows for increased paracellular permeability by the gut microbiota, which increases inflammation and activates the immune response (67, 71). This also enables microbial products to get into circulation, potentially gaining access to the CNS. Chronically increased cortisol levels have been shown to change the composition of the gut microbiome by having bacterial overgrowth and reduction in diversity due to changes in nutrient availability, motility, and permeability (67, 69, 70). The changes in gut microbiota diversity can change the peptides produced by enteroendocrine cells. A neuropeptide called galanin can activate the PVN cells of the hypothalamus to produce CRH (70). This allows for a potential positive feedback loop between the HPA and MGB axes.

Stress-Induced Proinflammatory Cytokine Elevation

Stress responses in the body produce a proinflammatory background (72). In the context of human evolution, this inflammatory induction by stress is logical, as stress usually accompanies situations that necessitate inflammation to resolve. This mechanism can be classical, as in the case of infection or physical harm, where endogenous signals are released to recruit inflammatory cells (73). However, more contemporary studies have now mapped a pathway for psychosocial stress to induce a proinflammatory background. When a person undergoes chronic psychosocial stress, the HPA will have been chronically activated. In normal physiology, this results in the suppression of proinflammatory cytokines via inhibition of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB). This inhibition also results in the downregulation of glucocorticoid receptors, which respond to our stress hormones. This downregulation demonstrates that in times of chronic stress, our body becomes resistant to glucocorticoids, resulting in a lack of inhibition of immunity and leading to a proinflammatory background. This inflammation is associated with increases in cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrotic factor-alpha (TNF-α), and interferon-gamma (IFN-γ) (74).

The impact of this cytokine signaling on the body can be observed within the GI system. In chronic stress, the gut's inflammatory background mimics the aforementioned changes. This increases the recruitment and activation of neutrophils, macrophages, and microglia (75). This change in resident leukocyte profile has multiple consequences but also impacts our gut microbiota. The resident leukocytes of our GI tract maintain our immune tolerance to native flora and prevent immune responses resulting in inflammation. The microbiota, if in dysbiosis, can induce worsening of the proinflammatory background (76). In the setting of chronic psychosocial stress, there is a weakening of the GI lumen barrier due to persistent inflammation

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(77). This then allows the proinflammatory leukocytes to encounter antigens to respond to and induce worsening of inflammation and lead to further dysbiosis of the gut microbiota as resident immune cells target native flora (78).

The current physiological model that can be understood from this is as follows. A person undergoes chronic psychosocial stress, leading to chronic activation of the HPA. This chronic activation of the HPA leads to eventual glucocorticoid resistance in target cells, preventing normal NF-κB inhibition by the HPA. This lack of inhibition then leads to the induction of proinflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-γ. These cytokines illicit their impact on their targets, recruiting and activating more inflammatory immune cells and dysregulating the gut lumen barrier. These proinflammatory cells now having access to native flora antigens respond and target them leading to further inflammation in the GI tract and dysbiosis of the GI microbiota. This dysbiosis in the microbiota leads to GI tract dysfunction and thus recruits more proinflammatory signals.

DISRUPTION OF THE GASTROINTESTINAL MICROBIOME

Stress-Induced Microbiome Dysbiosis

Any change in GIM's composition, distribution, or metabolism is called dysbiosis. It involves a decrease in the diversity of bacteria, the growth of proinflammatory or harmful bacteria, a decrease in beneficial bacteria, and a change in bacterial activity. Dysbiosis, like stress response, is also affected by host-specific factors, namely, their genetic makeup, diet, lifestyle, health status, use of food additives, and antibiotics (79). Host-derived factors like gastric acid, bile, and antimicrobial molecules (defensins, lysozymes, and antibacterial lectins) also affect the composition and function of GIM (79).

Studies have found stress-associated decreases in *Lactobacilli* in humans (80) and decreases in *Lactobacilli* and *Bifidobacterium* in animals (81, 82). Although lactobacillus has been found to have a role in immunomodulation, Bifidobacterium is suggested to have anxiolytic and antidepressive effects when given as a probiotic (83, 84). Patients suffering from inflammatory bowel disease (IBD) are found to have a reduced number of *Faecalibacterium prausnitzii*. It is suggested that the relative decrease of *F. prausnitzii* could be responsible for the inability to limit colonic inflammation in IBD (85, 86). Another study reported a stress-induced increase in Proteobacteria (87).

Stress affects microbiota and increases the intestinal tract's permeability (79) leading to movement of bacteria and bacterial products from the gut into the bloodstream. This can cause local and systemic inflammation, possibly causing disease (19), such as inflammatory bowel disease (IBD), obesity, allergic disorders, Type 1 diabetes mellitus, autism, and colorectal cancer in both human and animal studies (88). Stress is also found to cause GIM dysbiosis.

Stress-Induced Intestinal Barrier Dysfunction

The permeability of gastrointestinal mucosa is tightly regulated by tight junctions that hinder water and other hydrophilic substances from crossing the cell layer. The mucus layer above the epithelium contains intestinal bacteria and their byproducts. Under physiological conditions, this mucous prevents bacteria adhesion to the cell surface of the intestines (89, 90). The naturally occurring microbiota of the digestive tract is critical in maintaining healthy levels of essential vitamins and nutrients, such as vitamin K or folate. It helps boost the immune system against pathogenetic microbiota. At the correct balance, or eubiosis of bacteria, the microbiome and its byproducts play a protective function in the body. However, if there is a drastic change in the commensal bacteria, also known as dysbiosis, new pathogenic bacterial growth can occur and trigger proinflammatory reactions with harmful effects throughout the body, including the brain (89).

Several studies have shown that eubiosis can help mitigate physiological and psychological stress in the body. In particular, increased levels of the *Bifidobacterium* and *Lactobacillus* genus have been shown to have anxiolytic or stress-relieving effects on the body. Both genera have been shown to interact with the vagus nerve to decrease anxiety and decrease depressive symptoms in mice and humans (91, 92). This increased presence of the *Lactobacillus* genus has been shown to decrease corticosterone levels and urinary-free cortisol levels, attenuate proinflammatory cytokines, such as TNF-α and IL-6, and increase T-regulatory cells and anti-inflammatory cytokines, such as IL-10 (91). The increased levels of the *Bifidobacterium* genus have been correlated with increased tryptophan levels, a hormone essential for serotonin production. Many gut microbes like *Lactobacillus*, *Parabacteroides*, *Eubacterium*, and *Bifidobacterium* synthesize γ-aminobutyric acid (GABA) as well. However, GABA produced by the gut microbiome may act locally on the enteric nervous system or the vagus nerve as it cannot cross the blood-brain barrier and enter the brain (93). Besides serotonin and GABA, the gut microbiota also produces dopamine, which plays crucial roles in mood regulation and stress response. However, these hormones are unlikely to reach the brain from the gastrointestinal system. Furthermore, bacterial byproducts such as fructo-oligosaccharide, galacto-oligosaccharide, polydextrose, lactoferrin, and short-chain fatty acids (SCFA) not only release neuropeptides from the enteroendocrine cell (91), they are more likely to alter brain activity and initiate immune signaling (92). These bacterial byproducts can affect the brain through G-protein-coupled receptors, histone deacetylases, and the production of cytokines.

However, when the body's normal gut biome and dysbiosis occur, this has damaging effects on the intestines, such as disrupting the intercellular junction, increasing the intestine's permeability to pathogens, such as *Enterobacteriaceae* and *Escherichia-Shigella*, and lipopolysaccharides (LPS) (94). Dysbiosis can occur with antibiotic use, physiological stress, and diet (92). Increased psychological stress increases the cortisol produced by adrenal glands, which increases the permeability of the intestinal mucosa by disrupting the cell's tight junctions, introducing pathogens and LPS. In addition, the physiological and psychological stress decreases the homeostatic biodiversity of the intestines, allowing for the proliferation of pathogenic bacteria. Together, this triggers a proinflammatory response through Toll-like receptor 4, Th-17 cells, G-CSF, IL-6, IFN-γ, TNF-α, and C-reactive protein, which can alter serotonin and glutamate neurotransmitters. Furthermore, inflammatory cytokines can downregulate

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genes that help promote the tight junctions of the digestive epithelium (90, 92, 94).

Multiple studies have shown that dysbiosis in early childhood impacts brain development. For example, early maternal separation in mouse models leads to dysbiosis and behavior changes in young mice. In addition, depression and anxiety are often comorbid with inflammatory bowel disease, a disease marked by the disruption of the intestinal mucosa, and studies have shown that they both share similar proinflammatory markers, as previously mentioned (92). Furthermore, a meta-analysis conducted by Nikolova et al. (95) identified certain microbiome balance changes in psychiatric disorders, including psychosis, schizophrenia, anxiety, and major depressive disorder. For example, the genus *Eggerthella*, which depletes short-chain fatty acids, is elevated in each of these disorders. In contrast, *Faecalibacterium*, *Coprococcus*, and *Lactobacillus*, which increase the production of short-chain fatty acids, were decreased in each of these disorders. It has been observed that in many stress-related psychiatric disorders like depression and anxiety, the underlying inflammation is partly contributed by GIM dysbiosis. With the loss of intestinal integrity, there occurs increased intestinal permeability of lipopolysaccharides (LPS), which eventually triggers systemic inflammation by producing proinflammatory cytokines, such as IL-6 and TNF-α, and increased macrophage reactivity (45).

Probiotics can be useful in reversing or mitigating dysbiosis. A meta-analysis conducted in 2020 found 23 studies that showed that patients who were administered probiotics had a statistically significant reduction in depressive symptoms (96). Other studies have shown that probiotics and soluble fibers can help restore eubiosis and decrease proinflammatory responses (97). For example, administration of *Bifidobacteria* can help stabilize the proteins that make up tight junctions, sealing the intestinal cell layer from pathogens and increase the production of IgA antibodies, which help maintain the digestive system's immunity (89).

Bidirectional Communication between the Gut Microbiome and the Brain

The human gastrointestinal (GI) tract is inhabited by a highly diverse microbial community with ~2,000 identified species (98, 99). Numerous studies in the past few years have described the prominent role of the gut microbiome in almost all facets of health and disease (100). The gut microbiota direct multiple processes via exchanges with other organs to support homeostasis. Recent studies have uncovered the bidirectional exchange between the gut microbiome and the central nervous system (CNS). This is described as the "microbiota-gut-brain axis" (101, 102). Although the mechanism of the gut-brain interaction is not fully defined, at least five pathways of communication between the gut microbiota and the central nervous system have been described, including the enteric nervous system (ENS), the neuroendocrine system, the immune system, the circulatory system, and the vagus nerve (102–104). The gut microbiota also produces fermentation metabolites that act on the CNS. Multiple reports describe the production of several important neurotransmitters such as γ-aminobutyric acid (GABA) (93), serotonin (105–107), and dopamine by the gut microbiome (108). Moreover, the gut microbiome is responsible for the metabolism of tryptophan, controlling its bioavailability for pathways involved in neurotransmitter production, such as gut integrity (109, 110).

Increasing evidence supports the gut microbiome's function in modulating psycho-social stress. Preclinical studies have made evident the elaborate contribution of the gut microbiota in controlling depression (19, 20, 22–24), social behavior (27, 28, 32, 33), physical performance, and motivation (34, 36, 37). In addition, Buffington et al. (111) have shown in a mouse model of autism spectrum disorder that the gut microbiome regulates social behavior but not the animal's motor activity (26). Interestingly, treating the mutant mice with *Limosilactobacillus reuteri* rescued the lack of sociability phenotype as did the microbe-produced metabolite tetrahydrobiopterin (BH4) (20). BH4 has been shown to improve the socio-behavioral symptoms of patients with autism spectrum disorder (ASD) (37). In addition, it was also shown that fecal transplants from patients with autism spectrum disorder (ASD) led to behavioral symptoms in mice (27). The gut microbiota influences mice's behavior, including anxiety (24).

Psychosocial stressors are frequently associated with the onset of depression (38). Numerous studies have demonstrated drastic changes in the gut microbiome composition as a result of psychosocial stresses such as depression. A decrease in the richness and diversity of the gut microbiota was observed in a study of a rat model of depression (39). In addition, *Bacteroidetes* and *Proteobacteria* were found to be enriched in patients with severe depression disorders, whereas *Firmicutes* was lowered (40). In humans, it was also shown that the richness and diversity of the gut microbiota were significantly reduced in patients suffering from depression (39). Moreover, fecal transplants from the depressed patients into microbiota-depleted rodents induced anxiety-like behaviors and anhedonia, tell-tale phenotypes associated with depression in the recipient animals. A significant increase in the ratio of kynurenine/tryptophan was also observed in the recipient animals, indicating a disruption in the metabolism of tryptophan, a key player in depression (39). These data support a bidirectional regulatory control of the gut microbiota-brain axis in depression.

In another study using inescapable electric stress as a learned helplessness model to mimic of stress-related disorders in rats, the data showed that the gut microbiota was altered at the order, family, and genus level, with the numbers of bacteria of the genera *Lactobacillus*, *Clostridium* cluster III, and *Anaerofustis* being significantly higher in the susceptible rats compared with the control and resilient rats (41). Furthermore, the concentration of the short-chain fatty acids, such as acetic acid and propionic acid, was lower in the feces of susceptible rats, in contrast to the higher level of lactic acid in these rats when compared with the control and resilient rats (41) indicating that abnormal composition of the gut microbiota may contribute to predisposition to learned helplessness in rats exposed to inescapable electric shock (41). The authors did not perform a fecal transplantation experiment using material from the resilient animals to determine whether the susceptible animals could be rescued behaviorally and biochemically. In addition, rats with antibiotic-induced dysbiosis displayed severe depression symptoms accompanied

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by a decline in *Firmicutes* and *Bacteroidetes* and a rise in Proteobacteria and Cyanobacteria phyla. Likewise, lower serotonin, altered expression in the dopamine precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), higher noradrenaline, and tryptophan plasma levels, which are all physiological markers of depression, were observed in these rats (112).

Patients with spinal cord injury (SCI) often suffer from depression and anxiety. In a recent study of the relationship between the gut microbiome and mood disorders, it was found that treatment of rats with cervical contusion SCI with a fecal transplant blocked the spinal cord injury-induced dysbiosis and the occurrence of anxiety-related behavior. This study establishes the association between an incomplete unilateral cervical spinal cord injury, affective disorders, and intestinal dysbiosis. It suggests that they can both be prevented by fecal transplant therapy (113).

Probiotics have also been proposed to be involved in stress resilience by lowering corticosterone release, anxiety, and depression symptoms in rats and humans (83, 114). In a double-blind and placebo study using *Lactobacillus plantarum* P8 taken orally, a significant decrease in the plasma IFN-γ and TNF-α levels was observed, along with heightened memory and cognitive functions in the patient group (114). Interestingly, there was no difference in cortisol levels between the two groups, indicating that the probiotic treatment affected the inflammatory response (114).

Considering all these studies, it would be fitting to conclude that stress can impact the activity of gut functions that influence gut microbiota composition. In turn, gut microbes can also affect stressor-induced HPA axis activity and behavioral responses. This indicates a positive feedback loop, where stress exposure alters gut microbiota composition, leading to microbial dysbiosis. The dysbiotic microbial populations then modify the stressor-induced neuroendocrine activity and behavioral responses, suggesting bidirectional communication between GIM and the neuroendocrine stress response (Fig. 4).

BIDIRECTIONAL RELATIONSHIP BETWEEN STRESS AND IMMUNE FUNCTION

Stress Hormones and Immune Modulation

Stress hormones, particularly cortisol, have a significant impact on the immune system, influencing both the production of cytokines and the distribution of immune cells. Cortisol, released by the adrenal cortex in response to acute stress, has immunosuppressive and anti-inflammatory effects (115, 116). Cortisol can inhibit the production of proinflammatory cytokines such as IL-1, IL-6, and TNF-α, which are crucial in the body's response to infection and injury (116, 117). This suppression of cytokine production can reduce inflammation and tissue damage but may also impair the body's ability to fight infections and heal wounds. In addition, cortisol can promote the production of anti-inflammatory cytokines, like IL-10, further dampening the immune response (116, 117).

However, during chronic stress, the sustained increase in cortisol will lead to glucocorticoid resistance that results in decreased sensitivity to the anti-inflammatory effects of glucocorticoids, particularly monocytes and macrophages, becoming less responsive to cortisol's regulatory effects. As a result, the usual suppression of proinflammatory cytokines by cortisol is impaired, leading to an unchecked inflammatory response, thus producing a proinflammatory state (118). In addition, chronically elevated cortisol enhances the immune-stimulating effects of proinflammatory cytokines, like interferon-υ (IFN-υ) (119). Also, there occurs enhanced activation of nuclear factor-kappa B (NF-κB), a key transcription factor that promotes the expression of proinflammatory genes. This is exacerbated by the reduced sensitivity to glucocorticoids, which normally inhibit NF-κB activity (120, 121). Thus, cortisol plays an adaptive role in stress. In acute response to stress, cortisol shows an anti-inflammatory effect, suppresses early proinflammatory responses, and primes immune cells for an augmented response to a subsequent immune challenge but when the levels of cortisol are chronically elevated, it leads to cortisol resistance, decreased anti-inflammatory response, and elevation of proinflammatory cytokines like interferon upsilon (119) and activation of nuclear factor-kappa B (NF-κB). The distribution of immune cells is also affected by cortisol. During stress, cortisol can induce the redistribution of immune cells from the bloodstream to other body compartments, such as the bone marrow and spleen (116, 117). This process, known as lymphocyte trafficking, decreases the number of circulating lymphocytes, including T cells, B cells, and natural killer (NK) cells, thereby weakening the body's immediate immune response. Moreover, cortisol can inhibit the activation and proliferation of these cells, further compromising the immune system's effectiveness. Chronic stress, characterized by prolonged cortisol exposure, can lead to sustained immune suppression, increasing the risk of infections and slowing the healing process (116, 117). Also, chronic stress leads to mobilization of monocytes from the bone marrow into circulation, where they exhibit a proinflammatory phenotype (122). Stress augments the recruitment of these monocytes to the brain and induces a neuroinflammatory state that may produce psychiatric disorders associated with stress (122).

Chronic stress-associated changes in gut microbiota diversity also alter the peptides produced by enteroendocrine cells. Stress-induced neuropeptide galanin production continuously stimulates the hypothalamus to produce CRH (70), thus creating a positive feedback loop between the HPA and MGB axes. Continual activation of the HPA due to this loop results in glucocorticoid resistance in target cells, disrupting normal NF-κB inhibition by the HPA. Consequently, proinflammatory cytokines like IL-1, IL-6, TNF-α, and IFN-γ are induced. These cytokines then affect their targets by recruiting and activating additional inflammatory immune cells, causing disruption of the gut lumen barrier. As a result, proinflammatory cells gain access to native flora antigens and cause inflammation in the GI tract and dysbiosis. This dysbiosis causes dysfunction in the GI tract, triggering more proinflammatory signals and perpetuating the cycle of inflammation. Thus, the interaction between stress hormones and immune cells plays a crucial role in modulating the immune response, with significant implications for health and disease.

Immune Activation and Feedback to HPA Axis

The immune system and the HPA axis are interconnected, with immune responses capable of stimulating the HPA axis.

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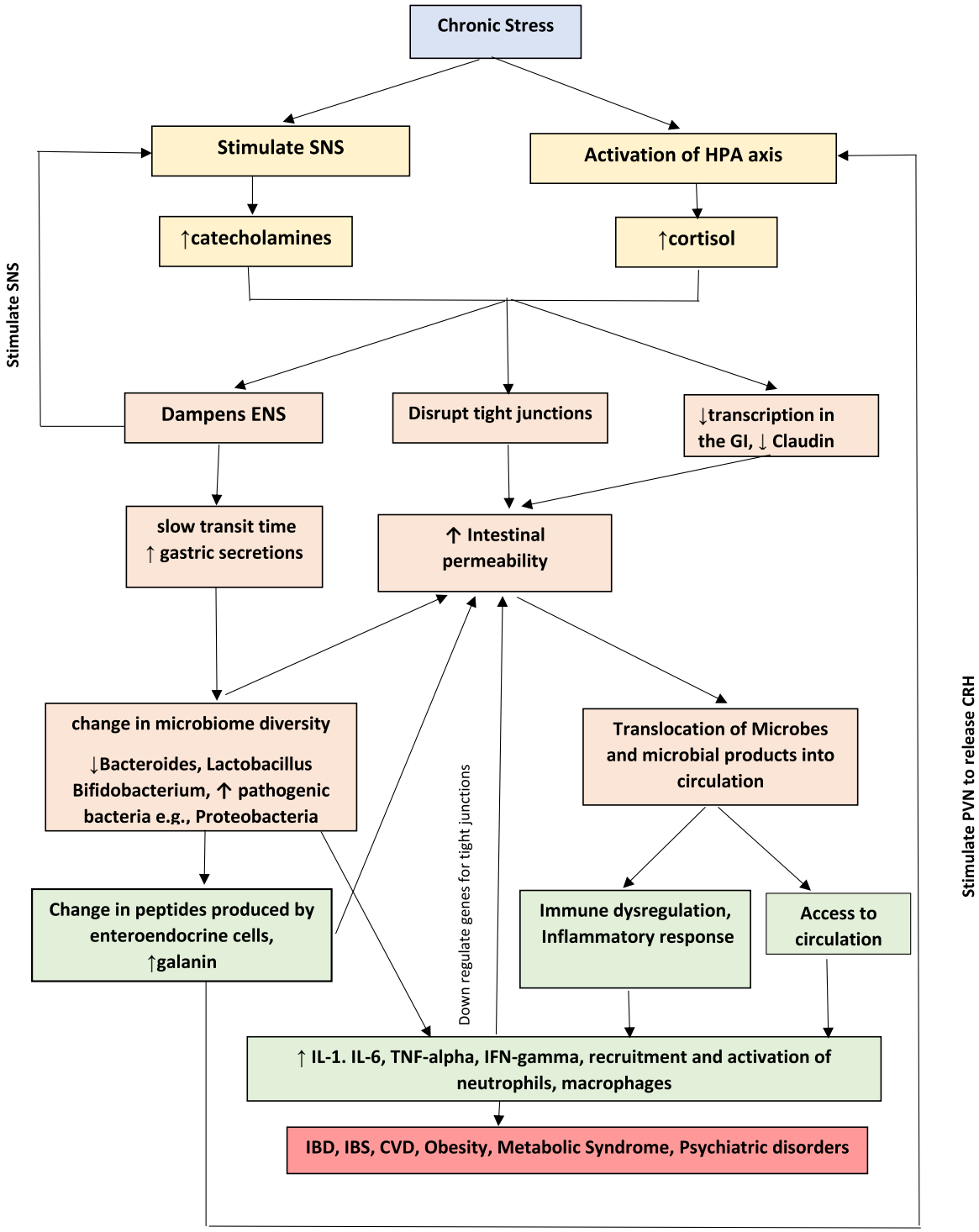

Figure 4. The physiological response to chronic stress, highlighting interactions between the gut microbiome and immune systems. Chronic stress activates the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal axis, increasing catecholamines and cortisol. Increased catecholamine and cortisol increase fecal transit time, intestinal permeability, and the overall composition of the microbiome. Increased catecholamine and cortisol secretion causes a redistribution of immune cells, such as natural killer, T cells, and B cells function, and impairs their ability to respond to infections effectively. Increased catecholamines affect microbiome diversity, causing a decrease in *Bacteroides* species, *Lactobacillus*, *Bifidobacterium*, etc. Change in the microbiome causes an increase in TNF-α and proinflammatory cytokines such as IL-1, IL-6, and IL-18. These inflammatory cytokines disrupt tight junctions in the gut epithelium, increasing intestinal permeability and translocating microbes and their products into circulation. Cortisol also increases gut permeability. This triggers an inflammatory response involving mast cells, neutrophils, and monocytes and the release of proinflammatory cytokines. This further contributes to gut inflammation and systemic immune dysregulation. Changes in the microbiome can change the peptides produced by enteroendocrine cells, e.g., there can be increased production of galanin, which can activate hypothalamic paraventricular nucleus (PVN) for more cortisol secretion, thus establishing a positive feedback loop. This all sets a proinflammatory state that underlies the pathogenesis of numerous cardiovascular disease (CVD), gastrointestinal, autoimmune, and psychiatric disorders. TNF-α, tumor necrotic factor-α.

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When an infection or injury occurs, immune cells release proinflammatory cytokines. These cytokines can influence the brain, particularly the hypothalamus, a crucial regulator of the HPA axis (123, 124). The hypothalamus responds to these signals by secreting CRH, which then acts on the pituitary gland, prompting it to release ACTH (123). ACTH travels through the bloodstream to the adrenal glands, stimulating the production and release of cortisol (123). This hormone helps modulate the immune response by reducing inflammation and promoting the resolution of the immune challenge (124).

However, this interaction between the immune system and the HPA axis can create a positive feedback loop that exacerbates the effects of stress. When cortisol is released in response to immune activation, it primarily suppresses further cytokine production and inflammation (123, 124). However, if the initial immune response is strong or if the stressor persists, cortisol resistance occurs and it continuously stimulates the HPA axis. In addition, sustained cortisol will elevate levels of proinflammatory cytokines (119). Chronic exposure to cortisol can have detrimental effects, such as impaired immune function, increased susceptibility to infections, and disruption of normal physiological processes, including metabolism and cardiovascular function (123, 124).

The potential for a positive feedback loop lies in the fact that chronic stress and prolonged cortisol exposure can further dysregulate the immune system. High cortisol levels can lead to glucocorticoid resistance in immune cells, diminishing their responsiveness to the hormone's anti-inflammatory effects (123, 124). Consequently, the immune system may continue to produce proinflammatory cytokines, maintaining the stimulation of the HPA axis. This ongoing cycle can result in chronic inflammation and stress, contributing to the development of various stress-related disorders, including autoimmune diseases, depression, and metabolic syndrome. Understanding this interplay between the immune response and the HPA axis is crucial for developing interventions that can break this cycle and mitigate the adverse health effects of chronic stress.

Chronic psychosocial stress leads to pronounced changes in gene expression, mainly downregulation of genes involved in type 2 immunity (*Il33, Il13ra, retnla*) and antimicrobial peptides (*ang4, Itln1, lyz2*). Elevated glucocorticoids drive the generation of an inflammatory subset of enteric glia that promotes monocyte- and TNF-mediated inflammation (125). Chronic stress also alters the gut microbiota composition, leading to an increase in proinflammatory bacteria and a decrease in beneficial bacteria. This dysbiosis can trigger immune responses and increase intestinal permeability (94, 118, 126) resulting in the translocation of bacteria and endotoxins that further triggers local and systemic inflammation (10, 126). This creates an environment conducive to stress-related gastrointestinal and systemic disorders. A recent study demonstrated this connection in mice subjected to chronic restraint stress, which made them more susceptible to dextran sulfate sodium (DSS)-induced colitis (124). These mice exhibited elevated leukocyte levels and activation of IL-6/STAT3 signaling, though stress-induced colitis persisted even in IL-6 knockout mice. Notably, the gut microbiota of stressed mice showed a higher abundance of proinflammatory operational taxonomic units (OTUs) such as *Helicobacter*, *Peptostreptococcaceae*, *Streptococcus*, and *Enterococcus faecalis* (124). Furthermore, fecal microbiota transfers from stressed to control mice induced DSS colitis in the latter group, highlighting the role of stress-altered microbiota in driving inflammation and immune dysfunction. These findings underscore the intricate link between stress, immune regulation, and gut microbiota composition, emphasizing how chronic stress contributes to gastrointestinal disease through immune-mediated mechanisms.

CLINICAL IMPLICATIONS AND POTENTIAL INTERVENTIONS

Stress-Related Gastrointestinal Disorders

Over the past several years, researchers have investigated the interplay between dysbiosis of the gut microbiome and several different disease processes. Much of the focus has been on irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), which have served as the primary disease model of the gut-brain axis. IBS is a chronic syndrome marked by abdominal pain and altered bowel habits. Several studies have found that a risk factor for IBS is early life stress and trauma, and this syndrome is highly comorbid with anxiety and depression (91, 92). Microbiome dysbiosis-induced inflammation is a main underlying factor in the pathogenesis of inflammatory bowel disease (IBD) and psychiatric disorders. Many researchers have explained how stress-related changes in the gut microbiota and intestinal permeability can affect the HPA axis and immune mechanisms that are implicated in the pathogenesis of IBD and psychiatric disorders (45, 127).

It has been found that patients with depression and IBS have similar increases in proinflammatory cytokines, including IL-6, TNF-α, and C-reactive protein, and patients with both IBS and depression have been shown to have increased adrenal-pituitary axis activity (126). Furthermore, it has been postulated that the visceral pain associated with IBS is modulated by the gut microbiome (128). This hypersensitization to visceral pain has been recreated in several experiments by introducing physiological and psychological stress in animal models and humans, administering antibiotics that induce dysbiosis, and transplantation fecal matter from patients with IBS into animal model (129). IBD, which includes Crohn's disease and ulcerative colitis, is a chronic, episodic disease marked by repeated inflammation of the intestinal tract (130). IBD has been increasing worldwide with an estimated prevalence of 0.3%–0.5% in the global population (131). Changes to the intestinal permeability and alternations to the intestinal microbiome play a key role in the development and the relapsing and remitting course of these diseases. Studies have shown that patients with IBD have increased intestinal permeability before symptoms of their disease begin, and the severity of the disease has been correlated to increased tight junction protein abnormalities (19, 89).

Several studies have identified an increased in the *Proteobacteria* and *Bifidobacteria* genera and a decrease in the *Firmicutes* genus in patients with IBD (89, 97). Other studies have shown a reduction in the *Adlercreutzia* genus,

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which has been shown to have anti-inflammatory properties, and an increase in the *Colidextribacter* genus, which has been shown to increase intestinal permeability (89). A common feature of IBD is dysbiosis, leading to an imbalance between beneficial and damaging bacteria taxa, which contributes to injury and impairment of the microbial barrier. A previous study has shown a significant decrease in *Bifidobacterium longum* in patients with ulcerative colitis. Similarly, in patients with Crohn's disease and ulcerative colitis, the concentration of *Eubacterium rectale*, *F. prausnitzii*, *Roseburia intestinalis*, and other beneficial was drastically reduced, whereas harmful bacteria such as *Bacteroides fragilis* flourished (132). In addition, *Ruminococcus torques* was found to be more abundant in CD and UC at the start of the disease (132, 133).

Other diseases that have a similar increase in *Proteobacteria* and *Bifidobacteria* with a decrease in *Firmicutes* bacteria include type 2 diabetes mellites and depression (89, 92). In addition, both type 2 diabetes and nonalcoholic fatty liver disease have been shown to have concurrent increases in intestinal permeability. Specifically in nonalcoholic fatty liver disease, it has been proposed that the increase in intestinal permeability allows for increased LPS into the portal vein, and pathogenic bacteria, such as *E. coli*. Both LPS and *E. coli* are known to increase reactive oxygen species production, which would exacerbate liver disease (89).

Previous studies have shown that autophagy plays an important role in intestinal dysbiosis. Autophagy is a cellular process by which cytoplasmic molecules are digested and recycled by the lysosome. Autophagy has a role in the control of gut microbiota composition, and dysfunctional autophagy has been linked with intestinal dysbiosis (134, 135). A number of IBD-related genes, including autophagy-related 16 like 1 (ATG16L), are associated with the low abundance of bacteria of the genus *Roseburia* in the gut of affected patients (136). Tsuboi et al. (134) identified the autophagy-related gene, atg7, as a major player in IBD. They have reported that Atg7 conditional knockout mice developed severe colitis with increased invasion of bacteria into the epithelium of the colon These mice also displayed dysbiosis, with an increase in *Clostridium leptum*, *Eubacterium cylindroides*, and *Bacteroides fragilis* compared with the control group (134) Furthermore, there was a sharp decrease in the production of antimicrobial and antiparasitic peptides in the conditional knockout mice, accompanied by a decrease in colonic mucins, which normally function as a barrier against bacterial invasion. Taken together, these data indicate that in mice, autophagy in the colonic epithelial cells prevents colitis by conserving the normal gut microflora and sustaining mucus production (134).

Although further studies need to be conducted, intestinal permeability and dysbiosis have been implicated in other for other disease processes as well. For example, recent patients with myocardial infarction were found to have increased levels of LPS, germ-free mice were found to have decreased atherosclerosis, and dysbiosis was found in both multiple sclerosis patients and patients with systemic lupus erythematosus (89, 130).

Therapeutic Strategies

Studies have reported that dietary and pre- and probiotic changes, when used as therapy, can mitigate stress-induced changes, including reversing GIM dysbiosis. Most of these studies have used *Bifidobacterium*, *Lactobacillus*, and *Lactococcus* as probiotics and found beneficial effects in reversing stress-associated pathological processes (137). *Lactobacillus* promotes a parasympathetic effect, and *Bifidobacterium* decreases morning cortisol levels, usually elevated in stress. Probiotics also reduce visceral pain and bloating in patients with IBS (138) and increase IL-10, which attenuates the proinflammatory immune responses in the body (139, 140). Both prebiotics and probiotics have been shown to improve intestinal cell junctions, decrease permeability, maintain barrier integrity (135, 136), reduce stress-induced inflammatory responses, and increase resilience to stress-related behavioral abnormalities (10). Furthermore, a large cross-sectional study showed that just increasing fermented foods in one's diet can help decrease levels of social anxiety (74). Sugar and saturated fat-rich diets increase intestinal permeability, cause chronic intestinal inflammation, and change the microbiome (89, 91). In contrast, a Mediterranean diet containing high fiber and polyphenols improves gut microbial diversity, the intestinal barrier, and prevents inflammation (10). Fecal microbiota transplantation (FMT) is another novel intervention being studied for restoring gut microbiota balance and reducing systemic inflammation. It was found to help treat *Clostridium difficile* infection and IBD, but more trials are required for its wider use, long-term efficacy, and safety profile (141).

CONCLUSIONS

Summary of Key Findings

This review emphasizes the complex and bidirectional link between psychosocial stress and the human GIM, highlighting its importance in understanding stress-related health disorders. The research implies that psychosocial stress triggers a series of physiological changes by activating the HPA axis and the sympathetic nervous. These physiological changes include the production of proinflammatory cytokines and disrupted GIM, which may cause a positive feedback loop, further activating HPA axis and GIM dysbiosis and eventually establishing a proinflammatory state. These changes explain the role of stress and GIM dysbiosis in many gastrointestinal, autoimmune, cardiovascular, and psychiatric disorders. The complex interplay of stress hormones, inflammatory processes, and microbiome suggests a dynamic and reciprocal relationship with important implications for adverse health outcomes. This review improves our scientific understanding of this directional relationship and highlights areas of knowledge gap that need more research.

Future Directions

A lot has been discovered about the role of stress in altering microbiota, which then impacts the function of the gut-intestinal barrier and immunological responses and causes systemic inflammation. However, how these modifications lead to particular disease development is still unclear. The correlation between stress, GIM dysbiosis, and systemic inflammation (116, 134) is being extensively studied, but there is a dearth of research on causal connections. Understanding these disease-causing mechanisms in detail will help in the

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development of therapeutic approaches targeting the gut-brain axis. Also, there is a need for vigorous clinical trials to assess the long-term efficacy and safety of therapies like probiotics and prebiotics that have shown potential in preclinical research (142). Currently, the research is limited by confounding factors such as diet and medicine (143, 144). In conclusion, more research is needed to establish the causal relationship between stress, gut microbiota dysbiosis, and disease, assess therapeutic approaches' long-term safety and efficacy, and investigate the possibility of integrated treatments that target the gut-brain axis.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

K.M. conceived and designed research; K.M. and N.H. prepared figures; K.M., R.C., K.A., K.C., D.C.G.M., and J.C. drafted manuscript; K.M. edited and revised manuscript; K.M., N.H., D.C.G.M., and J.C. approved final version of manuscript.

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