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Gut microbiome-derived metabolites and epigenetic modulation as potential countermeasures to acute stress

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Abstract

Acute stress induces widespread physiological and biochemical changes, significantly altering gut microbial composition and function. Herein, we explore how stress-driven shifts in the gut microbiome may impact metabolic pathways involved in neurotransmission, inflammation, and gut-brain communication. The role of microbiome-derived metabolites in shaping the host stress response is discussed. Evidence suggests that acute stress disrupts microbial balance, leading to alterations in metabolite production that may influence stress-related physiological processes. These include changes in compounds that regulate gut barrier integrity, immune responses, and neural signalling. Stress also affects pathways linked to neurotransmitter synthesis and metabolism, leading to shifts that may contribute to mood disturbances and cognitive changes. Additionally, acute stress may induce epigenetic modifications that influence gene expression in stress-regulatory pathways, further shaping the host's physiological adaptation. Understanding these complex interactions may help identify biomarkers of stress responses and inform strategies for microbiome-based therapeutic interventions. It is anticipated that gut microbiome and/or their derived metabolites as probiotics or prebiotics may serve as potential modulators of acute stress responses by acting on the gut microbiome-brain axis pathway. We discuss these changes in response to acute stress with an eye to comprehend gut-brain axis and the associated molecular mechanisms by which the gut microbiota communicates with the brain, affecting stress responses.

1 Gut Microbiome and acute stress

In this review, we aim to understand the relationship between the gut microbiome and acute stress, as well as discussing epigenetic modifications. While progress has been made in exploring how acute stress influences gut microbial composition and overall health, several important gaps remain, such as clarifying the long-term effects of acute stress on health, integrating responses across multiple systems, examining the impact of modern stressors and lifestyle factors, and considering the psychosocial aspects of stress. Addressing these gaps will deepen understanding of how acute stress affects both health and disease, ultimately paving the way for improved interventions and therapeutic



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strategies. In this regard, it is well recognized that gut microbiome (primarily gut bacteria) plays a major role in the physiology of its host [1–5]. One way the gut microbiome exerts its effects, is via production of metabolites, termed short-chain fatty acids (SCFAs): such as butyrate, acetate, propionate [6, 7], likely accompanied with epigenetic changes [8, 9]. Of note, many of these compounds, including SCFAs, are not strictly microbial metabolites and can be acquired through diet [10]. Under normal conditions, the major SCFAs metabolites such as butyrate, acetate, propionate etc. exhibit anti-inflammatory effects, maintain intestinal barrier integrity, modulate immune responses and brain function [11, 12]. Notably, butyrate can enhance catecholamine synthesis in the host through epigenetic mechanisms and can also activate the hypothalamic-pituitary-adrenal (HPA) axis [13, 14]. Furthermore, the influence of the gut microbiota on host stress physiology has been recognized for decades. Previous studies from the 1960s demonstrated that the microbiota could modulate a range of biochemical compounds, from biogenic amines to SCFAs, highlighting its pivotal role in regulating stress-related pathways [15]. Hence, modulation of gut microbiome and/or metabolites may provide an opportunity to impact and/or reverse host physiology, psychology, physical, molecular and structural alternations. A complete understanding of the gut microbiome composition and associated metabolites in response to specific environmental, physiological and pathological conditions can identify countermeasure(s) to neutralize abnormalities. It is anticipated that gut microbiome and/or their derived metabolites as probiotics or prebiotics can serve as potential modulators of acute stress responses by acting on the gut microbiome-brain axis pathway [16]. Here, we explore how acute stress induces changes that will enhance the understanding of the gut-brain axis and the molecular mechanisms through which gut microbiota communicate with the brain, influencing stress responses.

Acute stress can reduce populations of bacteria such as *Lactobacilli* and *Bifidobacteria*, while promoting the growth of *Clostridium* [7, 17, 18]. Nonetheless, the stratification of bacteria into ‘beneficial’ versus ‘harmful’ categories is not appropriate, as many strains of *Clostridium spp.* are commensal in the gut. Instead, the focus should be on how stress can initiate pathogenicity, enhance virulence, or cause functional shifts in gut microbial species [19, 20]. However, longitudinal studies are needed to determine specific changes in gut microbial and/or their derived metabolites before, during, and after acute stress to identify potential biomarkers linked to acute stress with the intention to reverse gut microbial dysbiosis. Many studies focus on the general effects of stress on gut microbiota or the role of gut microbiota in health and disease, but a detailed, longitudinal investigation of acute stress’s effect on microbiota composition and metabolites across different time points is still needed. In this regard, several lines of evidence suggest that acute stress impacts production of short-chain fatty acids, neurotransmitters, etc. by gut bacteria [7]. For simplicity, changes in major bioactives under acute stress are described (see Tables 1, 2).

2 Major bioactive bacterial metabolites under acute stress

Butyrate is produced by *Lactobacillus*, *Faecalibacterium*, *Ruminococcus* species. Under acute stress, butyrate levels are reduced, associated with increased inflammation, increased gut permeability, brain function and mood changes [21]. Acute stress has also been shown to reduce tryptophan levels in the gut, leading to lower serotonin levels [22]. Tryptophan is produced by *Bacteroides*, *Clostridium*, and *Enterococcus* species and used

Table 1 Metabolites dysregulated under acute stress

Metabolites	Produced by	Levels under stress
Butyrate	Bacteroides, Firmicutes (e.g., <i>Lactobacillus</i> , <i>Faecalibacterium</i>), <i>Ruminococcus</i> species	Reduced
Lactate	<i>Lactobacillus</i> , <i>Bifidobacterium</i> species, and precursor for other SCFAs like butyrate	Increased
Tryptophan	produced by <i>Bacteroides</i> , <i>Clostridium</i> , and <i>Enterococcus</i> species and used as a precursor to serotonin (5-HT)	Reduced
Pyridoxine (vitamin B6)	produced by <i>Lactobacillus</i> and <i>Bifidobacterium</i> species	Reduced
Catecholamines	produced by <i>Escherichia</i> , <i>Bacillus</i> , and <i>Proteus</i> species	Increased
Histamine	produced by <i>Lactobacillus</i> and <i>Bifidobacterium</i> species	Increased

as a precursor to serotonin (5-HT), which plays a key role in mood regulation [23]. Gut bacteria can convert tryptophan into various metabolites, including indoles and kynurenine, which impact serotonin levels. As indole exhibit anti-inflammatory properties and affect gut barrier integrity and immune responses, its reduced levels impair gut barrier and increase inflammation [24]. Nonetheless, there are many indole compounds some of which negatively affect the host. For example, indoxyl sulfate is associated with acute anxiety, thus reflective of the complex nature of indoles on host health in relation to stress [25]. Changes in serotonin affects gut motility (diarrhea or constipation) and mood disturbances (anxiety and depression) [26, 27]. A study demonstrated that microbiota influences the gastrointestinal serotonergic response to acute stress in a sex- and region-dependent manner [28]. Male-specific post-stress increases in colonic serotonin were absent in germ-free mice but were restored following colonization. In the frontal cortex, the absence of the microbiome altered basal serotonin levels, its main metabolite 5-hydroxyindoleacetic acid, and prevented stress-induced changes in serotonin turnover [28].

Pyridoxine (vitamin B6): produced by *Lactobacillus* and *Bifidobacterium* species is also reduced under acute stress. Pyridoxine is important for the synthesis of neurotransmitters like serotonin, dopamine, and gamma-aminobutyric acid (GABA) leading to increased anxiety [29]. GABA is a neurotransmitter inhibitor that is produced by selected gut bacteria, *Lactobacillus* and *Bifidobacterium* species, involved in reducing neural excitability and promoting relaxation [30, 31]. Lactate is produced by *Lactobacillus*, *Bifidobacterium* species, is increased during acute stress and may play a role in maintaining gut-brain axis by impacting neurotransmission. A study revealed that plasma lactate levels rose during acute psychosocial stress in humans [32]. Catecholamines: produced by *Escherichia*, *Bacillus*, and *Proteus* species are increased during acute stress [33], and responsible for increased heart rate, blood pressure, mental alertness, adrenaline release for extra energy [34]. Recently, studies have demonstrated that acute stress causes microbiota-linked increases in intestinal concentrations of catecholamines (dopamine, norepinephrine), serotonin, as well as histamine. A study focused on a novel model to study the relationship between the avian microbiome and microbial endocrinology-based host-microbe interactions and demonstrated that cold stress triggers catecholaminergic and serotonergic responses in the chicken gut, leading to functional shifts in the microbiome [35, 36].

Table 2 Key genes that undergo methylation changes during acute stress

Gene	Mechanism	Methylation
Glucocorticoid Receptor (<i>NR3C1</i>)	binds cortisol and mediate its effects by regulating metabolic, immune, and anti-inflammatory pathways.	Acute stress can cause hypermethylation of the <i>NR3C1</i> promoter region, reducing the expression of glucocorticoid receptors
<i>FKBP5</i> (FK506 Binding Protein 5)	regulates glucocorticoid receptor, and modulate the receptor's sensitivity to cortisol	Acute stress, hypomethylation of the <i>FKBP5</i> gene has been observed leading to increased expression of <i>FKBP5</i> and reducing the efficiency of glucocorticoid receptor signaling, prolonging the stress response and increasing cortisol levels
Brain-Derived Neurotrophic Factor (<i>BDNF</i>)	Important for neuronal plasticity, synaptic regulation, and stress resilience, particularly in brain regions such as the hippocampus and prefrontal cortex	Acute stress is associated with hypermethylation of the <i>BDNF</i> promoter, leading to reduced <i>BDNF</i> expression that impairs neuroplasticity and increase vulnerability to stress-related disorders
Serotonin Transporter (<i>SLC6A4</i>)	Regulates the reuptake of serotonin from the synaptic cleft	Acute stress increase methylation of the <i>SLC6A4</i> promoter region, leading to decreased serotonin transporter expression that can disrupt serotonin signaling, contributing to altered stress reactivity and mood regulation.
Oxytocin Receptor (<i>OXTR</i>)	Important for social bonding, stress regulation, and emotional behavior by attenuating stress responses by reducing cortisol levels.	Acute stress has been associated with increased methylation of the <i>OXTR</i> gene, which can reduce oxytocin receptor expression that impairs the buffering effects of oxytocin on the stress response
Corticotropin-Releasing Hormone (<i>CRH</i>)	Released by the hypothalamus that triggers the secretion of adrenocorticotrophic hormone (ACTH), initiating the HPA axis stress response.	Acute stress can lead to hypermethylation of the <i>CRH</i> gene promoter in certain brain regions, altering <i>CRH</i> expression and modifying the strength of the stress response
IL6 (Interleukin-6)	Pro-inflammatory cytokine that plays a major role in the immune response and inflammation, particularly during stress-induced activation of the immune system.	Acute stress can result in hypomethylation of the IL6 promoter, leading to increased IL-6 expression and heightened inflammatory responses contributing to prolonged inflammation following stress.
Tumor Necrosis Factor-alpha (TNF- α).	Involved in the regulation of immune responses and inflammation, especially under conditions of stress.	Acute stress has been shown to hypomethylate the TNF gene, enhancing TNF- α expression and promoting inflammatory signaling
GABA Receptor (<i>GABRA1</i>)	Inhibitory neurotransmitter receptor in the brain, playing a role in calming neural activity and reducing stress-induced excitation.	Acute stress can cause hypermethylation of the <i>GABRA1</i> gene, reducing the expression of GABA receptors and potentially leading to an overactive stress response and anxiety
Reelin (<i>RELN</i>)	Involved in synaptic plasticity and neuronal migration, and it has been linked to stress-related changes in brain function.	Acute stress increases methylation of the <i>RELN</i> promoter, resulting in decreased Reelin expression, which may contribute to alterations in brain structure and function associated with stress.
Monoamine Oxidase A (<i>MAOA</i>).	Enzyme breaks down neurotransmitters like dopamine, norepinephrine, and serotonin, helping to regulate their levels during stress.	Acute stress has been associated with changes in the methylation of the <i>MAOA</i> gene. Increased methylation typically reduces <i>MAOA</i> expression, which can lead to elevated neurotransmitter levels and heightened stress reactivity

Table 2 (continued)

Gene	Mechanism	Methylation
<i>COMT</i> (Catechol-O-Methyltransferase)	Enzyme degrades catecholamines, such as dopamine, norepinephrine, and epinephrine, which are elevated during acute stress.	Acute stress can increase methylation of the <i>COMT</i> gene, reducing its activity and slowing down the degradation of catecholamines, thereby prolonging their action during acute stress.
<i>NGF</i> (Nerve Growth Factor)	Important for the growth, maintenance, and survival of neurones, and plays a role in stress-induced neuroplasticity.	Acute stress has been shown to alter the methylation status of the <i>NGF</i> gene, typically leading to hypermethylation, which reduces <i>NGF</i> expression and may impair neuronal resilience.

Histamine is produced by *Lactobacillus* and *Bifidobacterium* species are increased during acute stress leading to increased inflammation and gut motility such as diarrhea and abdominal pain [37]. Furthermore, dopamine, norepinephrine, and epinephrine precursors may be increased, which are important for the stress response [38, 39]. Acute stress shifts tryptophan metabolism toward the kynurenine pathway, leading to elevated levels of kynurenine, kynurenic acid, and quinolinic acid [40], producing metabolites like quinolinic acid, with neuroactive properties, influencing mood and cognitive function during stress [41, 42].

Given the primary role of gut bacteria in host metabolism, species belonging to *Lactobacillus*, *Bifidobacterium*, *Clostridium*, and *Bacteroides* modify bile acids (produced by the liver) into secondary bile acids that affect lipid metabolism and immune responses [43]. However, modulation of gut bacteria under acute stress affects bile acid metabolism resulting in gut permeability and inflammation [44]. These findings suggest that acute stress over prolonged periods can increase gut permeability, that results in LPS, a component of the outer membrane of gram-negative bacteria (such as *Escherichia coli* and *Bacteroides*), to spread hematogenously and trigger systemic inflammation that contribute to anxiety and depression, nonetheless while acute stress can affect intestinal permeability, the extent to which these changes influence bacterial translocation, whether of bacteria or lipopolysaccharides LPS, remains unclear. Moreover, no definitive link has been established between altered permeability and host health outcomes [45–47].

Despite a plethora of studies, there is incomplete understanding of variability due to genetics, age, sex, ethnicity, and environmental factors that affect response to acute stress. For example, gender differences affect acute stress responses, particularly in hormone release (cortisol versus catecholamines), but the underlying molecular mechanisms require further investigations [48,49]. Similarly, how age-related differences affect neuroendocrine and cardiovascular responses to acute stress, or variations in the NR3C1 gene coding for the glucocorticoid receptor (genetic component of stress response) as well as a complete range of genetic polymorphisms that influence stress sensitivity remains incompletely understood [48,49].

Overall, acute stress modulates gut microbiota and alters the production of major metabolites such as SCFAs, neurotransmitters (e.g., serotonin and GABA), histamine, indoles, and LPS (an outer component of gram-negative bacteria). These changes can influence gut permeability, immune responses, and communication with the brain, affecting mental health through the gut-brain axis. Further research is needed to understand how modulation of gut microbial metabolite production affects responses during acute stress and to identify the underlying molecular mechanisms. While therapies such

as dietary interventions or prebiotics/probiotics may help support gut health [50], there is currently limited evidence that stabilizing the gut barrier directly counteracts the negative health impacts of acute stress-induced inflammation [51, 52].

3 Epigenetic modulation under acute stress

The gut microbiome exerts its effects by producing metabolites likely accompanied with epigenetic changes [53]. DNA methylation is an epigenetic modification where a methyl group is added to cytosine bases in the DNA, typically at CpG islands. This modification often leads to the silencing or downregulation of gene expression [54]. Dietary interventions, including probiotic supplementation, have been explored for their broad effects on microbiota composition and immune system function. Probiotics may help restore intestinal dysbiosis and alleviate clinical symptoms by increasing SCFA levels in the gut [55]. While the exact mechanisms through which these dietary factors exert their effects remain unclear, SCFA metabolites like butyrate also serve as histone deacetylase inhibitors (HDACi), influencing the epigenome by inducing changes in chromatin structure [55]. Some of the key genes that undergo methylation changes during acute stress are discussed. Glucocorticoid Receptor (*NR3C1*) is important for binding cortisol and mediating its effects on stress responses. It regulates metabolic, immune, and anti-inflammatory pathways. Acute stress can cause hypermethylation of the *NR3C1* promoter region, reducing the expression of glucocorticoid receptors. This results in altered sensitivity to cortisol and impaired feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis [56]. *FKBP5* (FK506 Binding Protein 5) plays a role in stress adaptation by regulating glucocorticoid receptor, and modulating the receptor's sensitivity to cortisol. During acute stress, hypomethylation of the *FKBP5* gene has been observed leading to increased expression of *FKBP5* and reducing the efficiency of glucocorticoid receptor signaling, prolonging the stress response and increasing cortisol levels [57].

Brain-Derived Neurotrophic Factor (*BDNF*) is important for neuronal plasticity, synaptic regulation, and stress resilience, particularly in brain regions such as the hippocampus and prefrontal cortex. Acute stress is associated with hypermethylation of the *BDNF* promoter, leading to reduced *BDNF* expression that impairs neuroplasticity and increase vulnerability to stress-related disorders [58]. Serotonin Transporter (*SLC6A4*) regulates the reuptake of serotonin from the synaptic cleft. Methylation: Acute stress increase methylation of the *SLC6A4* promoter region, leading to decreased serotonin transporter expression that can disrupt serotonin signaling, contributing to altered stress reactivity and mood regulation [59]. Oxytocin Receptor (*OXTR*) is important for social bonding, stress regulation, and emotional behavior by attenuating stress responses by reducing cortisol levels. Acute stress has been associated with increased methylation of the *OXTR* gene, which can reduce oxytocin receptor expression that impairs the buffering effects of oxytocin on the stress response [60]. Corticotropin-Releasing Hormone (CRH) is released by the hypothalamus that triggers the secretion of adrenocorticotrophic hormone (ACTH), initiating the HPA axis stress response. Acute stress can lead to hypermethylation of the *CRH* gene promoter in certain brain regions, altering CRH expression and modifying the strength of the stress response [61].

IL6 (Interleukin-6) is a pro-inflammatory cytokine that plays a major role in the immune response and inflammation, particularly during stress-induced activation of the immune system. Acute stress can result in hypomethylation of the IL6 promoter, leading

to increased IL-6 expression and heightened inflammatory responses contributing to prolonged inflammation following stress [42]. Tumor Necrosis Factor- α (TNF- α) is involved in the regulation of immune responses and inflammation, especially under conditions of stress. Acute stress has been shown to hypomethylate the TNF gene, enhancing TNF- α expression and promoting inflammatory signaling [62]. GABA Receptor (GABRA1) is a major inhibitory neurotransmitter receptor in the brain, playing a role in calming neural activity and reducing stress-induced excitation. Acute stress can cause hypermethylation of the *GABRA1* gene, reducing the expression of GABA receptors and potentially leading to an overactive stress response and anxiety [63].

Reelin (*RELN*) is involved in synaptic plasticity and neuronal migration, and it has been linked to stress-related changes in brain function. Acute stress increases methylation of the *RELN* promoter, resulting in decreased Reelin expression, which may contribute to alterations in brain structure and function associated with stress [64]. Monoamine Oxidase A (*MAOA*) enzyme breaks down neurotransmitters like dopamine, norepinephrine, and serotonin, helping to regulate their levels during stress. Acute stress has been associated with changes in the methylation of the *MAOA* gene. Increased methylation typically reduces *MAOA* expression, which can lead to elevated neurotransmitter levels and heightened stress reactivity [65]. *COMT* (Catechol-O-Methyltransferase) enzyme degrades catecholamines, such as dopamine, norepinephrine, and epinephrine, which are elevated during acute stress. Acute stress can increase methylation of the *COMT* gene, reducing its activity and slowing down the degradation of catecholamines, thereby prolonging their action during acute stress [66]. *NGF* (Nerve Growth Factor) is important for the growth, maintenance, and survival of neurones, and plays a role in stress-induced neuroplasticity. Acute stress has been shown to alter the methylation status of the *NGF* gene, typically leading to hypermethylation, which reduces *NGF* expression and may impair neuronal resilience [67].

The methylation of genes during acute stress can have profound effects on the regulation of the HPA axis, neurotransmission, immune function, and inflammation. Methylation changes are often gene- and context-specific, leading to either suppression or overactivation of key pathways involved in stress adaptation. A complete understanding of the molecular mechanisms using physiologically relevant species will reveal potential targets in the rationale development of therapeutic interventions. In this regard, while animal models (e.g., rodents) are widely used to understand acute stress, although fully translating stress models to humans presents challenges [68, 69], such research has yielded significant benefits. In fact, much of the literature supporting this review is based on animal models and their relevance to human health. Nonetheless, the physiological responses to stress vary between species, especially in the hypothalamic-pituitary-adrenal (HPA) axis dynamics [70]. Additionally, acute stressors used in animal models may not be applicable to the complexity of stresses faced by humans, such as psychological stress combined with physiological challenges [71]. Despite these shortcomings, rodent models are useful in determining underlying molecular mechanisms and real-time monitoring of the long-term consequences of acute stress such as cardiovascular disease, anxiety disorders, dysregulation of the HPA axis, hypertension, metabolic syndrome, etc [72, 73]. In addition to physiological stresses, animal models are of value in determining the psychological and social context including factors such as perceived control, social support, and resilience [74, 75].

Overall, the study of gut microbiome and acute stress has advanced significantly, but several research gaps remain including individual variability, improving the translational value of animal models, clarifying the long-term health impacts of acute stress, integrating multisystem responses, exploring modern stressors and lifestyle influences, and examining the psychosocial context of stress. Addressing these gaps will provide a more comprehensive understanding of how acute stress affects health and disease, allowing for better interventions and treatments. Given the strong interplay between gut microbiota and stress physiology, microbiome-targeted therapies represent a promising avenue for mitigating the adverse effects of acute stress. While probiotics, prebiotics, and postbiotics have shown potential in restoring microbial balance and supporting stress resilience, such as a recent study which established that the ingestion of a probiotic composition containing selected strains by BALB/c mice for 2 weeks led to a reduction in depressive-like behavior in the forced swimming test, with effects similar to those of fluoxetine [76]; and another study which investigated the effects of *Lactobacillus farciminis* on the hypothalamic-pituitary-adrenal (HPA) axis stress response, intestinal permeability, and endotoxemia in female rats subjected to partial restraint stress, finding that *L. farciminis* prevented stress-induced hyperpermeability, endotoxemia, and neuroinflammation by reducing circulating LPS levels and protecting the intestinal barrier [77]. Further research is needed to elucidate their mechanisms of action, identify optimal formulations, and assess long-term efficacy. Future studies should focus on personalized microbiome interventions, integrating multi-omics approaches to develop precision-based strategies for stress management. Expanding clinical trials will be crucial in validating the effectiveness of these therapies and translating findings into evidence-based interventions for stress-related disorders.

Author contributions

RS and NAK conceptualized the study amid critical discussions with SKM and DL. RS and NAK reviewed and prepared the first draft of the manuscript. SKM and DL corrected the manuscript. All authors approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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