

Genetic polymorphism and the link to stress-induced metabolic dysfunction

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Abstract

Background: The impact of stress on health is well-established and it continues to influence modern life. While some individuals may manage stress well, others may experience detrimental impacts on their physical and emotional health. As stress has been related to several illnesses, including obesity, diabetes, cardiovascular diseases, and more, there is growing concern about stress-induced metabolic dysfunction.

Main body: Here we review recent literature, elucidating the role of genetic polymorphisms in modulating an individual's reactivity to stress and susceptibility to stress-related metabolic disorders. This article discusses the genetic components, in particular the polymorphisms, that may predispose individuals toward metabolic dysregulation brought on by stress. Deoxyribonucleic acid (DNA) sequence differences that affect more than 1% of the population are known as genetic polymorphisms. Changes from genetic polymorphisms result in different gene expression, protein function, and other outcomes. Genetic polymorphisms in key stress-regulating genes can influence an individual's susceptibility to metabolic disturbances in response to chronic stress.

Conclusion: The hypothalamic pituitary adrenal (HPA) axis and related molecular pathways play a pivotal role in mediating the effects of stress on metabolism. Understanding the genetic basis of stress-induced metabolic dysfunction has implications for personalized medicine and preventive strategies. By identifying individuals with genetic susceptibility to metabolic disturbances, targeted interventions can be designed to mitigate the adverse effects of stress on metabolic health. Furthermore, lifestyle modifications, stress management techniques, and tailored dietary interventions may be employed to promote overall well-being and prevent stress-induced metabolic disorders.

Keywords: Stress-induced metabolic dysfunction, Genetic polymorphism, Hypothalamo-pituitary-adrenal axis, Metabolic syndrome

Background

Disruptions in the regular metabolic processes that turn food into inner strength and serve as foundation elements for cells and tissues are referred to as metabolic disorders. Obesity, insulin resistance, type 2 diabetes, and a few heart-related conditions have all been associated with this syndrome (1, 2). Metabolic dysfunction can result from the influence of habits, stress, nutrition, environment or heredity on metabolic pathways

and systems (3, 4). The influence of stress on metabolic systems, such as the breakdown of glucose, the breakdown of lipids, and energy balance (5) has been reported to disrupt metabolic processes, leading to disorders.

Stress is the body's normal reaction to psychological or environmental stressors that might be sudden or ongoing. While long-term stressors might endure for months or years, acute stresses are transient and disappear fast. In stress

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responses, the HPA axis produces the stress hormone known as cortisol, which as a consequence, can raise blood sugar levels and reduce insulin sensitivity, resulting in insulin resistance and diabetes. The "fight or flight" response, which raises blood pressure, the heart rate, and the body's glucose production, is brought on by the sympathetic nervous system (SNS) (5). According to Fardet and Feve, persistent SNS stimulation can cause insulin resistance, high blood pressure, and dyslipidemia (6). However, it has been demonstrated that hereditary variables also contribute to individual body sensitivity to metabolic disorders brought on by stress (3). Metabolic disorders like insulin resistance, dyslipidemia, and obesity are predicated on disorders of the body's energy homeostasis closely associated with the metabolic pathways that are under the control of the glucocorticoid receptor gene (NR3C1) for the control of stress (7). The Bcl polymorphism, which is a variation of this gene, has been linked to an increased risk of metabolic problems in response to stress. This study attempts to evaluate the genetic variation that predisposes people to metabolic disorders brought on by stress.

Main body

Hypothalamic Pituitary Adrenal Axis (HPA) Cycle Regulation

The HPA axis is responsible for regulating the body's stress response. It involves an intricate interplay between the hypothalamus, the pituitary gland, and the adrenal glands, which together control the release of cortisol or corticosterone, the hormone that helps the body cope with stress (8, 9). The control of the HPA axis has been linked

to several mechanisms (10, 11). The connection between the hypothalamus, pituitary gland, and adrenal gland is regulated by several endogenous signalling molecules that are released to activate one another (8, 9). Therefore, factors including hormones, neurotransmitters, and other signalling endogenous molecules play a role in how the HPA axis operates. The hypothalamus releases corticotropin-releasing hormone (CRH) in response to stressors, which in turn causes the pituitary gland to release adrenocorticotrophic hormone (ACTH). Cortisol is produced when ACTH stimulates the adrenal glands (10, 11). However, the released cortisol also has a significant impact. However, the released cortisol in turn actively regulates the HPA axis by reducing the CRH and ACTH, which inhibits cortisol synthesis. The HPA axis is involved in the control of additional hormones, including dehydroepiandrosterone (DHEA) and its sulfate form (DHEA-S), in addition to the pituitary driving cortisol release from the adrenal gland (12). DHEA is an androgen hormone produced by the adrenal glands and has been linked to the regulation of mood and cognition (12).

Hyperactivity of the HPA axis leading to increased cortisol levels and dysfunction in stress response has been linked to several mental health conditions (10, 11). Amidst the list of influences regulating the HPA axis is hereditary. Genetic coding of the glucocorticoid receptor which is involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis has been associated with the way individuals respond to stress and can determine the risk of physiological and psychological disorders that an individual may be susceptible to.

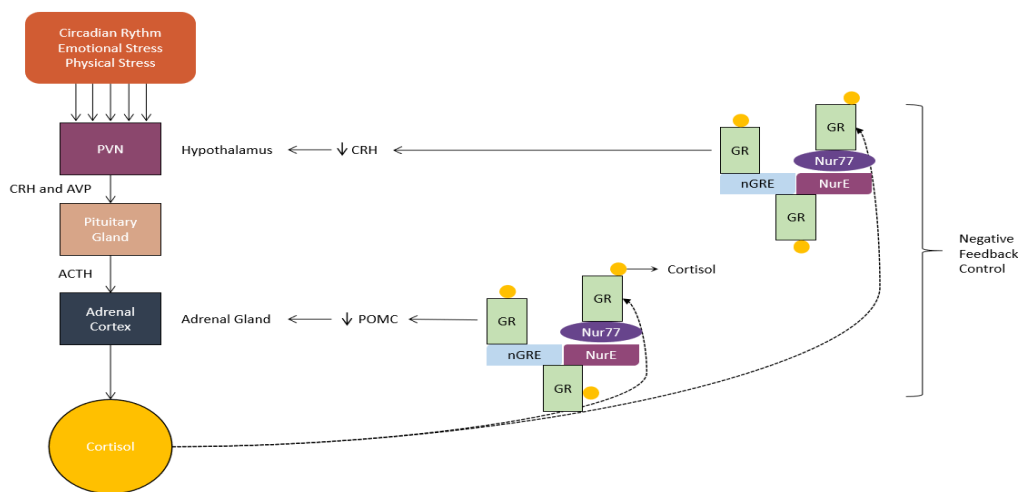


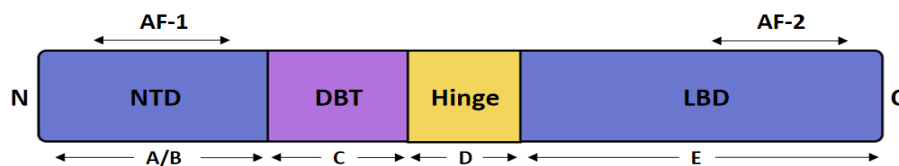
Figure 1: Hypothalamic-Pituitary-Adrenal axis

Steroid Receptors

Steroid receptors which include glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) are well represented in various tissues of the body as well as the HPA axis (13). The choice of the corticosteroid hormones they are bound to is directly related to the attraction and affinity for the corticosteroid hormones. This is the basis behind the binding of the MRs to the aldosterone as well as the binding of the GRs to the cortisol (13, 14). Many of the physiological events and processes in the body are directly influenced through numerous activations of GRs and MRs by cortisol and aldosterone, respectively, which in turn regulate physiological processes such as immune functions, stress responses, body metabolism etc. The differences in the sensitivities of the receptors to corticosteroids affect the actions in the biological system. There were reports that factors such as genetic polymorphism determine the sensitivity of these receptors to corticosteroids (13, 14). The differences in the glucocorticoids and the mineralocorticoids genes have been well studied particularly the genetic differences in their sensitivities to the corticosteroid hormones. Santen and co-investigators found that GR genes have a high affinity for corticosteroid dexamethasone meanwhile MR genes have a high affinity for aldosterone. Those findings further suggest that genetic polymorphisms influence the differences

that exist in GR and MR genes and their sensitivities to corticosteroids (14). Environmental factors have also been shown to influence corticosteroid sensitivity (9, 15). Exposure to chronic stress decreases the activity and sensitivity of the GR leading to the dysregulation of the HPA axis, with the manifestation of stress-associated disorders due to the imbalance in the HPA regulation of corticosteroid synthesis (9, 15). Furthermore, exposure to acute stress increased GR sensitivity in many studies, allowing for a rapid and effective stress response. When there is an imbalance in the corticosteroid regulation, there is an increase in GR sensitivity which is, primarily, a physiological response to the stress to restore homeostatic balance (8). The reverse is the case under chronic stress conditions in which a reduction in the GR activity and sensitivity to corticosteroid hormones is recorded due to epigenetic modification to the GR gene expression (16). One major example of epigenetic modification is DNA methylation. Therefore, epigenetic alterations have been implicated in the occurrences associated with stress-induced metabolic disorders (10). In general, the association of both genetic and environmental factors plays a crucial role in the regulation of the sensitivity of corticosteroids and stress responses (3).

A. Basic modular domain structure of steroid hormone receptors



B. Steroid hormone receptors with ligands

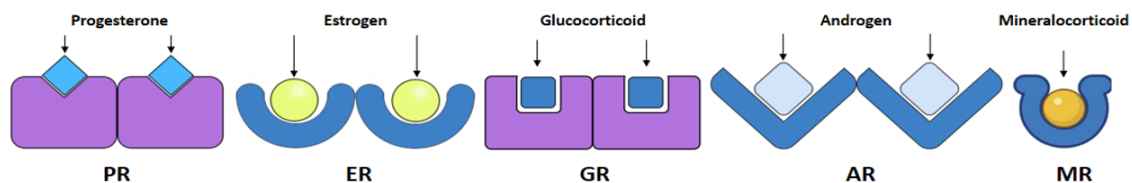


Figure 2: Structural representation of Steroid Hormone Receptors associated with ligands (17)

Glucocorticoid Receptor Variants

NR3C1 is the gene that codes for the glucocorticoid receptor and it is important in the regulation of the HPA axis. Disorders attributed to improper regulation of the HPA axis have led

researchers to examine the association between the NR3C1 gene and its different functions that are closely associated with stress-linked disorders. A variant of NR3C1, rs6198, was linked to reduced body cortisol levels which is a consequence of the

dysregulation of the HPA axis. Interestingly, the presence of the variant of rs6198 underscores a greater risk of development of obesity as a response to chronic stress (5). The subject of the association of the variants of glucocorticoid receptors and the metabolic disorders that are associated with chronic stress is rather complex as other factors determine the development of stress-induced metabolic disorder (18). The type of chronic stress and the duration of the stress play an important role in the development and the outcome of stress-induced metabolic disorders. Part of the findings of Fries and co-investigators includes the change in the cortisol reactivity of a variant of NR3C1 with acute and chronic stress. They further reported an increase in cortisol reactivity under acute stress while its reactivity was reduced under chronic stress (18).

The relationship between the genetic variants in NR3C1 and stress-induced metabolic dysfunction is a complex one but can be influenced by many other factors among which are sex, ethnicity and race (7). A study by Kokkinopoulou *et al.* reported that the association between NR3C1 genetic variants and insulin resistance was modified by sex (19). Pregnancy exposed to stress was reported to equally record epigenetic modification to the NR3C1 with the offerings showing an increased risk of developing metabolic disorder (20). In addition to genetic variants of NR3C1, other factors such as lifestyle habits, diet, exercise, and sleep duration may also contribute to stress-induced metabolic dysfunction (21). Further research will be required to unravel the mechanisms underlying this relationship and to identify potential therapeutic targets.

Epigenetic Modification in NR3C1

The alterations in the expressions of genes without altering the sequence of the DNA, known as epigenetic modifications, include DNA methylation, histone modifications, noncoding RNAs, and chromatin conformation (22). These modifications have significant impacts on the functions of the GR as the major regulator of stress responses (22, 23, 24). Epigenetic modifications that involve the addition of a methyl group to the cytosine nucleotide of a DNA sequence, resulting in the formation of 5-methylcytosine (5mC) are referred to as DNA methylation (25). Silencing of genes caused by DNA methylation has been linked with alteration in GR expression and stress response (24). Reduced GR expression and an increased risk of stress-related illnesses have been linked to hypermethylation of the GR gene's promoter region (26). According to a study by Vukojevic *et al.*, the GR gene's DNA methylation is linked to altered GR expression and a higher risk of developing post-traumatic stress disorder (PTSD) among genocide survivors (27). Other investigators have also linked the GR gene promoter's DNA methylation to altered GR expression and function in stress response (28). Reduced GR expression and diminished cortisol response to stress have been associated with an increase in methylation of the GR gene's promoter region (28). Additionally, the onset of stress-related diseases, such as depression, post-traumatic stress disorder (PTSD), and anxiety, has been linked to DNA methylation of the GR gene (29).

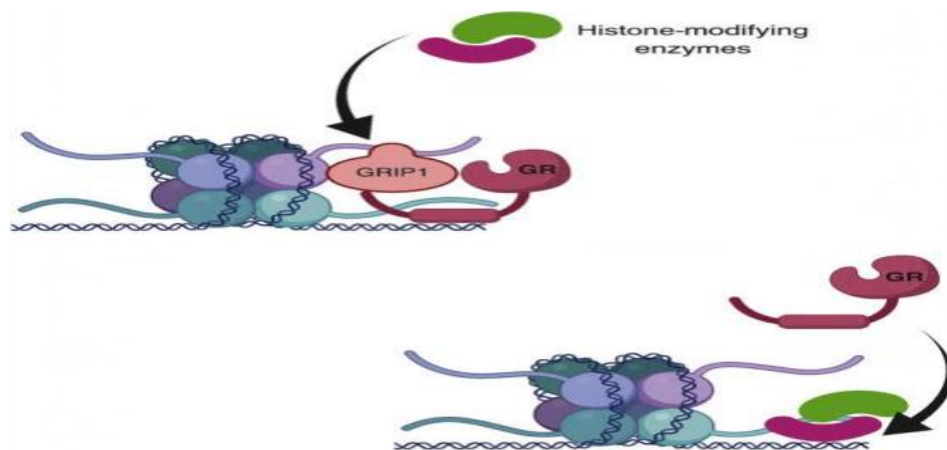


Figure 3: Post-Translational Modification of Histone-Modifying Enzymes (30)

Figure 3 shows how post-translational modification of histone-modifying enzymes acts as a switch for the activation or repression of target genes by glucocorticoids (30). Another kind of epigenetic alteration known as histone modification involves the post-translational altering of histone proteins, which control chromatin structure and gene expression (22). GR function can also be affected by histone changes (31). Histone acetylation is linked to higher levels of gene expression, whereas deacetylation is linked to lower levels of gene expression (31). According to research by Weaver *et al.* (2004), histone acetylation of the GR gene promoter region improved GR expression and function in response to stress (16). On the other hand, histone deacetylation of the GR gene promoter has been linked to decreased GR expression and reduced cortisol response to stress (24).

Methylation of histones can also either increase or decrease gene expression depending on the specific site and context of the modification. In addition, phosphorylation and ubiquitination of histones can impact chromatin structure and gene expression (24).

By binding to GR mRNA and altering its stability and translation, noncoding RNAs, such as microRNAs and long noncoding RNAs, can also influence GR function (22). According to Herceg, increasing expression of microRNA-124 has been linked to lower GR expression and an increased risk of depression. Changes in chromatin conformation, including alterations in the three-dimensional structure of chromatin also impact GR function (22). Furthermore, changes in the positioning of nucleosomes can either promote or inhibit GR binding to DNA and alter gene expression (22).

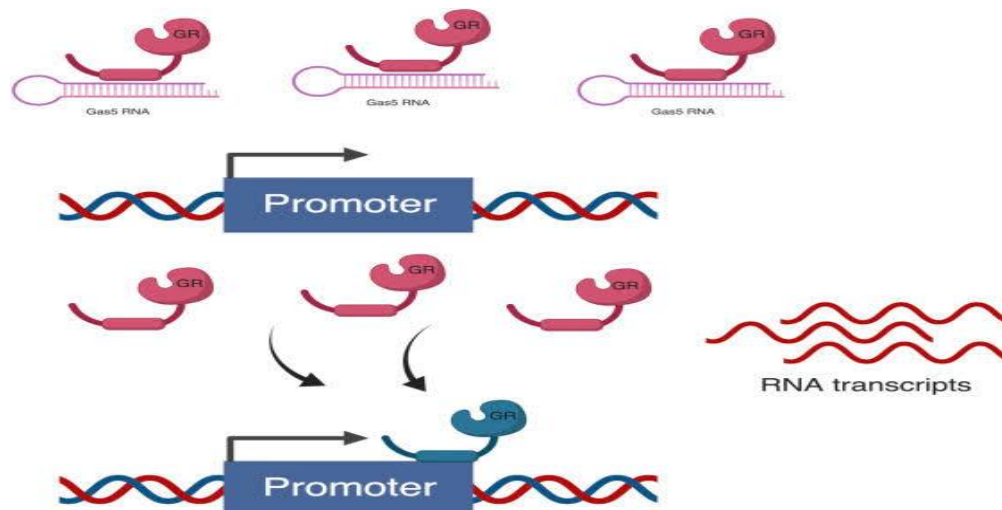


Figure 4: Noncoding RNA Gas5 Represses Glucocorticoid Receptor Induction of Target Genes (31)

Polymorphism in GR Gene Variant

ER22/23EK polymorphism and stress-induced metabolic dysfunction

The ER22/23EK polymorphism of the GR gene is a genetic variant that has been associated with altered GR sensitivity (32). This variant is located in the ligand-binding domain of the GR protein and has been shown to increase GR sensitivity to corticosteroids, leading to altered glucocorticoid signalling and physiological responses (32). ER22/23EK polymorphism is a genetic variant where the two contiguous codons 22 and 23 have modifications as a result of mutation (33). The development leads to the substitution of glutamic acid-arginine with glutamic acid-lysine. A study by Mora *et al.* reported that about 2.5% of people from their study were carriers of this polymorphism

(34). ER22/23EK polymorphism has been reported to show resistance to glucocorticoids. In humans, a study was conducted on elderly carriers of this variant of the GR gene indicated better insulin sensitivity and lower total and low-density lipoprotein cholesterol levels. In addition, Dutch elderly carriers showed lower C-reactive protein levels indicating benefit to the cardiovascular system (35, 36). According to van Rossum *et al.*, ER22/23EK polymorphism had only mild resistance to Glucocorticoid (35). Although there is a dearth of information in the literature on the effect of the genetic variant ER22/23EK on young people, Rossum *et al.*, reported evidence of ER22/23EK polymorphism linked resistant to Glucocorticoid in young subjects (35). This effect was said to be sex-

specific and is characterized by differences in muscle mass, strength and redistribution of fat and body composition (36).

Bcll polymorphism and Stress-Induced Metabolic Dysfunction

The Bcll polymorphism is a genetic variant in the glucocorticoid receptor gene (NR3C1) that has also been implicated in stress-induced metabolic dysfunction (37). The polymorphism of Bcll is located on intron B (38, 39). Bcll polymorphism alters the sensitivity of the glucocorticoid receptor to cortisol, the stress hormone, and has been associated with various metabolic disorders, including obesity, insulin resistance, and Type 2 diabetes (15).

A study conducted by Xiang and Marshall found that individuals with the GG genotype (homozygous for the G allele) of the Bcll polymorphism had a higher risk of developing metabolic syndrome in response to chronic stress compared to individuals with the CC genotype (homozygous for the C allele) (40). Individuals with homozygous carriers of the G allele are said to have decreased HPA axis responses to psychosocial stress (12).

Another study by Kumsta *et al.* examined the association between the Bcll polymorphism and cortisol reactivity to stress in women. The study found that women with the GG genotype had a blunted cortisol response to stress compared to women with the CC genotype, suggesting that the Bcll polymorphism may alter the HPA axis response to stress (41).

Bcll polymorphism is associated with a higher glucocorticoid sensitivity which consequentially leads to increased BMI and central obesity. It is also associated with metabolic issues such as an increase in blood pressure and insulin resistance (42, 43). Generally, individuals with Bcll polymorphism are more likely to have major depression (32).

N363S polymorphism and Stress-Induced Metabolic Dysfunction

N363S polymorphism is a genetic variant located on the human glucocorticoid receptor gene (NR3C1) and has been associated with altered sensitivity to stress-induced glucocorticoid production (44). The variant of GR, located in the

exon 2 is coding for a single nucleotide polymorphism (SNP) (41). Its ligand-binding domain and transcriptional activity are impacted by this polymorphism, which causes the amino acid asparagine to be changed to serine at position 363 of the glucocorticoid receptor protein (44, 45, 46).

N363S polymorphism and stress-induced metabolic dysfunction have been the subject of several investigations (46, 47, 48). It is significant to highlight that N363S has been connected to glucocorticoid hypersensitivity (49). According to studies, people with the N363S variation are more likely than people with the wild-type genotype to experience insulin resistance and excessive cortisol release when under stress (50). There were conflicting reports about N363S polymorphism, insulin resistance and diabetes mellitus. A study conducted among the Japanese and Spanish populations found no significant association between N363S polymorphism and insulin resistance, type 2 diabetes mellitus (51) and metabolic syndrome (32). Rosmond and Dobson *et al.*, reported an association between the N365S variant gene and waist-to-hip ratio among the male population and also BMI among the European population (48, 52). These conflicting results could be attributed to differences in study design, sample size, ethnic background, and environmental factors that could influence the relationship between N363S polymorphism and stress-induced metabolic dysfunction (32).

GR-9 β Polymorphism and Stress-induced Metabolic Dysfunction

Chronic stress-related metabolic disorders have been associated with the 9 β glucocorticoid receptor (GR) polymorphism (53). The 9 β GR is an alternative splicing isoform of the GR that is predominantly expressed in the liver and has been suggested to play a role in the regulation of glucose metabolism in the liver (53). A study by Castro-Vale *et al.* showed that 9 β glucocorticoid receptor polymorphism is associated with posttraumatic stress disorder (PTSD) due to low-level resistance to glucocorticoid (54). However, further investigation is required to independently confirm these findings and elucidate the underlying mechanisms.

Table 1: The Genetic Polymorphism Variants and their respective stress-induced effects

S/N	Genetic Polymorphism Variants	Action on GC sensitivity	Effects	References
1	BclI Polymorphism	Increase in glucocorticoid sensitivity	Has been linked with central obesity and BMI and metabolic syndrome such as insulin resistance and high blood pressure	(42, 43)
		Increase in glucocorticoid sensitivity	Cardiometabolic risk profile in patients with long-term remission of Cushing Syndrome	(55)
2	N363S Polymorphism	Increase in glucocorticoid sensitivity	Associated with higher BMI and increased LDL cholesterol in the elderly. Lead increased the transactivational capacity of GR <i>in vitro</i> and altered gene expression	(7, 56, 57)
3	ER22/23EK Polymorphism	Decrease in glucocorticoid action	Glucocorticoid resistance both <i>in vitro</i> and <i>in vivo</i> . Sex-specific changes in body composition. Male carriers have more muscle mass, increased muscle strength, and are taller and female carriers have smaller waist circumstances. It is linked to higher insulin sensitivity, CRP and LDL-cholesterol level	(7, 35, 36, 57)
4	GR-9 β Polymorphism		Has no effect on GR transactivation or decreases trans-repression activity of the GR and is associated with increased incidence of coronary heart disease	(45)

MC4R Gene Polymorphism and Stress-Induced Metabolic Dysfunction

The melanocortin 4 receptor (MC4R) gene, which is found on chromosome 18, encodes the MC4R, a G-protein-coupled receptor that is primarily expressed in the hypothalamus and other parts of the central nervous system. By balancing energy intake and expenditure, the (MC4R) gene is essential for controlling hunger. The MC4R is a desirable target for anti-obesity therapies because it reduces appetite and increases energy expenditure. The control of stress reactions is a previously unknown aspect of MC4R functionality, according to recent research (31). Recent research indicates that the development of the stress-induced MC4R gene is a dynamic process that occurs in response to different stressors. Chronic stressors like social isolation or eating a high-fat diet have been demonstrated to increase the expression of the MC4R in particular brain areas. This over-expression appears to be an adaptive strategy for reducing stress's harmful metabolic effects. In animal models, MC4R activation has also been associated with increased insulin sensitivity, suggesting a

potential function in preventing stress-related metabolic dysfunction (54).

An interesting approach to comprehending and managing the mechanisms underlying stress-induced metabolic dysfunction is to investigate MC4R gene variations and their relationship to stress response. There is proof that the MC4R gene variation and stress response interact physiologically. A few MC4R gene polymorphisms have been connected to changes in cortisol secretion patterns and stress sensitivity. The rs17782313 and rs489693 variants of the MC4R gene have been examined in relation to stress responses and their correlation with obesity and other metabolic illnesses. These variations have been linked to cortisol levels and metabolic effects brought on by stress. Under stressful circumstances, dysregulated cortisol release can intensify the metabolic effects, resulting in a feedback loop that promotes metabolic dysfunction (58). Variants in the MC4R gene have been associated with obesity in various populations (59). However, the role of MC4R gene variants in stress responses is not well understood.

There is some evidence suggesting an association between MC4R gene variants and stress responses. Acute emotional stress activates the MC4R gene, which in turn activates the hypothalamic-pituitary-adrenal (HPA) axis and increases the production and release of cortisol in the stress response (60). Another study found a positive interaction between MC4R variants and mental stress levels in relation to the risk of obesity in Korean adults (61). The study showed that individuals with MC4R minor alleles had higher body mass index (BMI) in the presence of high-stress levels, even after adjusting for confounding factors. This association was observed without any significant changes in energy and nutrient intake.

The minor allele (C allele) for the MC4R rs17782313 variant has been associated with depressed mood. Previous studies have also investigated the interaction between the MC4R gene variant and dominant dietary patterns on depression in obese and overweight women (62). Another study explored the impact of MC4R variants on overweight and obesity in children and adolescents participating in a lifestyle intervention. They observed higher diastolic blood pressure levels in males with MC4R risk alleles but reduced blood pressure levels in females with the same risk alleles (63). However, this study did not specifically focus on stress response.

There exist mutations in the MC4R gene that have been associated with sex-specific effects on the hypothalamic-pituitary-adrenal (HPA) axis tone, which is implicated in stress-associated cardiometabolic disease. However, the relationship between MC4R gene variants and stress regulation is still being investigated (64).

It is important to note that the available evidence on the role of MC4R gene variants in stress responses is limited and more research is needed to fully understand this association. Further studies should investigate the specific mechanisms through which MC4R gene variants may influence stress responses and their potential implications for obesity and related health outcomes.

LEPR Gene Variants and Stress Response: Unraveling the Link to Metabolic Dysfunction

Among the genetic actors of the intricate interplay between genetics, stress response, and metabolic dysfunction is the Leptin Receptor (LEPR) gene, a pivotal player not only in appetite regulation but also in the intricate connection of stress response and metabolic balance. The exploration of LEPR

gene variants and their association with stress response opens a fascinating avenue to understanding and addressing the mechanisms that contribute to stress-induced metabolic dysfunction. Found on chromosome 1, the LEPR gene encodes the Leptin Receptor, a transmembrane protein primarily expressed in the hypothalamus. An important hormone produced by adipocytes that helps to control hunger and expenditure of energy is leptin, the ligand for the LEPR receptor. The LEPR gene is essential for maintaining the complex equilibrium of energy homeostasis because it alters neural pathways in the central nervous system. According to Farooqi and Rahilly (2007), genetic polymorphisms within the LEPR gene have been connected to obesity, altered adiposity, and metabolic dysregulation (65). Emerging research has unveiled the intriguing connections between LEPR gene variants, stress response, and metabolic health. Specific polymorphisms within the LEPR gene have been associated with altered stress responsiveness and cortisol secretion patterns. LEPR gene variants, acting in synergy with the stress response pathways, may contribute to metabolic aberrations. Variants such as rs1137101 and rs8179183 have shown associations with stress-induced metabolic outcomes. These genetic twists can modulate the way individuals respond to stress, potentially amplifying the metabolic repercussions and contributing to the development of metabolic disorders (66).

The intricate interplay between LEPR gene variants, stress response, and metabolic pathways emphasizes the need for a comprehensive understanding of their roles in shaping metabolic health (67). Identifying individuals carrying specific LEPR polymorphisms can guide targeted strategies to mitigate stress-induced metabolic risks.

Conclusion

The diverse response to stress has always been linked to individual susceptibility, gender and environmental factors. However, more recent studies have made it clearer how genetic variation contributes to metabolic dysfunction driven by stress. A person's sensitivity to stress-induced metabolic dysfunction can be greatly influenced by genetic variation, according to recent studies. The interaction between genetic variants and environmental influences is complex. According to studies, genetic polymorphisms in several genes, including those that control the hypothalamus-

pituitary-adrenal (HPA) axis, might influence how the body responds to stress and increase the risk of metabolic dysfunction. The impacts of genetic susceptibility to metabolic dysfunctions linked to stress can also be exacerbated by environmental variables including chronic stress exposure and poor lifestyle choices. While genetics might increase an individual's risk, metabolic dysfunction is not determined by genetics, which is a crucial distinction to make. A healthier stress response can be facilitated by modifiable lifestyle factors like consistent exercise, a balanced diet, and stress management strategies. These factors may also contribute to reducing the impacts of genetic susceptibility. To completely comprehend the mechanisms underlying stress-induced metabolic dysfunction and how genetic polymorphisms and environmental factors interact to exacerbate this problem, more research is required. This knowledge may help guide public health initiatives meant to lessen the prevalence of this disorder in the general population as well as individualized interventions for people who have a genetic susceptibility to stress-induced metabolic malfunction.

List of Abbreviations

ACTH: Adrenocorticotropin Hormone
BMI: Body mass index
CC: Hemoglobin C from both parents
CRH: Corticotropin-releasing hormone
DHEA: Dehydroepiandrosterone
DNA: Deoxyribonucleic Acid
GR-9 β : 9 β glucocorticoid receptor
GRs: Glucocorticoid Receptors
HPA: Hypothalamic Pituitary Axis
LEPR: Leptin Receptor
MC4R: Melanocortin 4 Receptor
mRNA: messenger RNA
MRs: Mineralocorticoid Receptors
PTSD: Post Traumatic Stress Disorder
RNAs: Ribonucleic Acid
SNP: single nucleotide polymorphism
SNS: Sympathetic Nervous System

Declarations

Ethics approval and consent to participate

This review article does not need ethical approvals.

Consent for publication

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Availability of data and materials

The articles used in this study are available from the corresponding author upon reasonable request.

Competing interests

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Authors' contributions

MAM conceptualized the review article idea. AFO further provided insights that were considered. OPG provided support in the literature search and provided technical inputs. MAM prepared the draft manuscript. AFO participated in revising the manuscript for intellectual content. All the authors read and approved the final version of the manuscript.

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