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(REVIEW ARTICLE)

The Influence of MAOA Gene variants and hormonal regulation on aggression and psychiatric vulnerabilities

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Abstract

This review explores the connection between genetic factors and psychiatric disorders, emphasizing the role of the MAOA gene, cortisol, testosterone, and their interaction with environmental influences. Specifically, it investigates how the MAOA gene and hormone levels contribute to behavioral tendencies, such as aggression and impulsivity, by affecting the prefrontal cortex, amygdala, and limbic system. The study also considers how genetic predispositions are intensified by external stressors like trauma, highlighting the gene-environment interaction's significance in developing conditions like schizophrenia, bipolar disorder, and depression. Ultimately, the research aims to clarify the neurobiological mechanisms underlying these disorders, suggesting that integrating genetic and environmental factors could guide personalized treatments.

Keywords: Genetics; Psychiatric disorders; MAOA gene; Schizophrenia; Bipolar disorder; Depression

1. Introduction

The prefrontal cortex plays a crucial role in impulse control, decision-making, and emotional regulation. Individuals with the low-expression variant of the MAOA gene (MAOA-L) exhibit altered activity in this region, impacting their ability to manage emotions and control impulsive or aggressive responses. Reduced connectivity between the prefrontal cortex and the amygdala—an area involved in processing emotions and threat responses—limits the cortex's regulatory influence over the amygdala, leading to heightened aggression in response to stressors. This connectivity issue, compounded by low serotonin levels, can further hinder impulse control in those with the MAOA-L variant [1,2].

Central to this investigation is the influence of the MAOA gene on neurotransmitter regulation, particularly in areas of the brain involved in emotional control, such as the prefrontal cortex and amygdala. Prior studies suggest that the expression of MAOA can be affected by stress, especially during critical developmental periods like puberty, leading to changes in neurotransmitter levels that may predispose individuals to heightened aggression or impulsivity. This effect is particularly notable in individuals with a genetic predisposition who experience early trauma or chronic stress, underscoring the importance of gene-environment interaction [3,4].

Furthermore, this review examines how cortisol, often referred to as the "stress hormone," interacts with the MAOA gene to influence aggressive behavior. Variants of the MAOA gene modulate the hypothalamic-pituitary-adrenal (HPA) axis, affecting cortisol release during stressful situations. This modulation can result in varying stress responses, where individuals with certain MAOA genotypes experience higher cortisol peaks, potentially intensifying aggressive

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tendencies. The research also highlights testosterone's role in modulating behaviors, linking elevated levels of this hormone to impulsive and aggressive traits through its impact on specific neural circuits, including those associated with the limbic system [4,5].

The understanding of genetic factors in psychiatric disorders has evolved towards an integrative approach, which highlights the complex web of gene-environment interactions. In particular, the study of the MAOA gene has become a key point in deciphering how certain genetic predispositions, in combination with adverse environmental experiences, can influence human mental health and behavior [4,5].

1.1. How the 'Murderer Gene' Affects the Prefrontal Cortex

The MAOA gene (monoamine oxidase A) plays an important role in regulating key neurotransmitters such as serotonin, dopamine, and norepinephrine, which are essential for controlling emotions and impulses. This gene encodes the MAOA enzyme, which breaks down these neurotransmitters and thus influences the neurochemical balance in the brain. A variation in the MAOA gene, known as the low-expression variant (MAOA-L), has been associated with an increased predisposition to aggressive behaviors, especially when interacting with environmental factors such as stress or adverse childhood experiences [1].

The prefrontal cortex is crucial for impulse control, decision-making, and emotional regulation. People with the MAOA-L variant show altered activity in this region, affecting their ability to manage emotions and control impulsive or aggressive responses. Exposure to stressful situations during puberty, for example, can increase the expression of the MAOA gene in the prefrontal cortex, which has been associated with pathological aggressive behavior in adulthood [1,2].

Neuroimaging studies have shown that carriers of the MAOA-L variant have reduced functional connectivity between the prefrontal cortex and the amygdala, a region involved in emotional processing and threat response. This reduced connectivity limits the prefrontal cortex's ability to modulate amygdala activity, resulting in less regulation of negative emotions and increased aggressive responses to aversive stimuli [1,2].

Another factor contributing to aggression in MAOA-L carriers is the vulnerability of the serotonergic system. Acute tryptophan depletion, a precursor of serotonin, has been shown to further reduce connectivity between the amygdala and prefrontal cortex in individuals with the MAOA-L variant. This experimental method suggests that low serotonin availability exacerbates emotional reactivity in people with this genetic variation, further hindering impulse control and emotional regulation [1].

At the epigenetic level, it has been proposed that histone acetylation in the MAOA gene can facilitate its expression under stressful conditions, increasing the production of the MAOA enzyme and, consequently, increasing serotonin degradation in the prefrontal cortex. This reduction in serotonin levels may predispose individuals to impulsive and aggressive responses in stressful or threatening situations [1].

The MAOA gene, especially in its low-expression variant, appears to affect prefrontal cortex function in individuals predisposed to aggression. The combination of alterations in connectivity between the prefrontal cortex and the amygdala and low serotonin availability hinders emotional regulation and impulse control. These findings suggest that the interaction between genetics and the environment, especially under stressful conditions, may contribute to the development of aggressive behaviors in people with the MAOA-L variant [1,2].

1.2. Cortisol Related to the MAOA Gene

The interaction between the MAOA gene and cortisol in relation to aggressive behavior involves complex neurobiological mechanisms, especially in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. The MAOA gene encodes monoamine oxidase A, an enzyme that breaks down neurotransmitters such as serotonin, dopamine, and norepinephrine, all of which are implicated in mood and behavior. Variants in the MAOA gene, particularly the low-activity MAOA alleles (often referred to as MAOA-L), are associated with increased susceptibility to aggressive and impulsive behavior, especially under conditions of heightened stress or adversity. This genetic predisposition is observed primarily in males due to the gene's location on the X chromosome [3,4].

One primary mechanism through which MAOA influences aggression is via its modulation of cortisol, a hormone released in response to stress. Cortisol is central to the body's stress response and helps regulate emotional reactions. The HPA axis, which manages cortisol release, becomes activated under stress, and this response can be altered by genetic factors such as MAOA variations. Research indicates that individuals with the MAOA-L genotype tend to have an exaggerated cortisol response when exposed to stressors. For instance, in response to social stress tests, low-MAOA

carriers exhibit higher cortisol peaks compared to those with high-activity MAOA alleles (MAOA-H). This heightened response is thought to result from reduced monoamine degradation, leading to prolonged neurotransmitter presence and overstimulation of stress-related brain regions [4,5].

Studies have also shown that the interaction between MAOA-L and cortisol affects specific neural circuits, including regions involved in emotional processing and aggression, such as the amygdala and prefrontal cortex. Functional MRI research demonstrates that MAOA-L carriers show greater amygdala activation and altered connectivity between the amygdala and prefrontal areas during stress. This neural response pattern is associated with increased emotional reactivity, which can manifest as heightened aggression. Importantly, the combined effect of MAOA and cortisol on these neural regions may predispose individuals to aggressive behavior by decreasing their capacity to regulate emotions effectively under stress [5].

Moreover, environmental factors like childhood adversity can amplify this genetic effect. Studies report that individuals with the MAOA-L genotype who experience early trauma or chronic stress are particularly susceptible to aggressive and impulsive behaviors in adulthood. This gene-environment interaction highlights the role of MAOA and cortisol not only in acute stress responses but also in shaping long-term behavioral tendencies through the HPA axis and associated neural pathways [3,4].

1.3. Testosterone

Testosterone, a steroid hormone, exerts its effects by binding to the androgen receptor (AR), a nuclear receptor that functions as a transcription factor. This hormone-receptor complex then binds to specific DNA sequences, known as androgen response elements (AREs), to regulate the transcription of target genes. This mechanism is crucial for the development and maintenance of male sexual characteristics and various physiological functions [6].

The levels of circulating testosterone are highly heritable, and several genetic loci have been identified that influence these levels. A meta-analysis of genome-wide association studies (GWAS) identified significant loci associated with serum testosterone concentrations in men, including polymorphisms at the sex hormone-binding globulin (SHBG) locus and near the FAM9B gene on the X chromosome. These genetic variants can significantly affect testosterone levels and the risk of low testosterone. Additionally, specific single nucleotide polymorphisms (SNPs) associated with increased testosterone levels have been linked to muscle-related traits, such as muscle fiber size and strength, suggesting a genetic basis for the anabolic effects of testosterone [7,8].

Testosterone also has associations with temperament traits. Higher levels of testosterone have been linked to increased novelty seeking and reward dependence, suggesting that testosterone may influence certain behavioral traits and personality dimensions. This relationship is supported by findings that testosterone levels correlate with disinhibited personality traits, such as novelty seeking and impulsive sensation seeking, although these associations can be influenced by age and other hormonal factors [9,10].

1.4. Limbic system

An imbalance in neurotransmitter levels due to abnormal MAOA activity can lead to dysregulation in emotional processing, often resulting in anxiety, impulsivity, and aggression [11].

Variations in the MAOA gene, especially the MAOA-L variant, have been shown to increase emotional reactivity. Functional MRI studies indicate that carriers of the MAOA-L allele exhibit heightened activity in the amygdala, which is critical for processing fear and threat-related stimuli. This overactivation leads to stronger emotional responses, particularly in stressful or threatening situations. Moreover, These individuals often show reduced activation in the prefrontal cortex (PFC), the brain's region responsible for regulating impulses and controlling emotional outbursts. The imbalance between heightened limbic activity and impaired PFC control is thought to be a key factor in aggressive and impulsive behavior [11,12].

Multiple studies have explored the connection between MAOA activity and aggressive or criminal behavior. The MAOA-L variant is frequently associated with a predisposition to aggressive behavior, especially in individuals who have experienced early-life trauma. Research conducted on convicts and control groups has reinforced the idea that MAOA polymorphisms can serve as risk factors for violent behavior, though this is significantly modulated by the environment [12].

The review also indicates that MAOA activity influences neuroplasticity, particularly in stress-related brain regions like the hippocampus. In chronic stress conditions, high MAOA activity can lead to neurodegeneration in the hippocampus,

which plays a role in memory and learning. However, inhibitors of MAOA have been found to help reverse these negative effects, promoting neurogenesis and improving cognitive function. This opens up potential therapeutic avenues for treating stress-induced disorders, such as depression [11].

2. Neurobiological Mechanisms of the Relationship between MAOA Gene and Substance Use

The MAOA gene plays a role in substance use regulation, and various gender-related neuromodulatory mechanisms have been identified for this central genetic resource. The main reason for this is that the etiology of substance use disorder occurs through complex interactions between environmental and genetic factors [13].

However, an unbiased micromolecular association analysis of MAO expression and nicotine intake in mammalian models demonstrated that transmembrane protein 151A is strongly correlated with the number of ribosomes and nicotine consumption in reward-related cortical and striated areas in a sex-specific manner, and this could be a potential alternative to MAOA in the MAOA linkage area [14].

The catecholaminergic hypothesis emphasizes the role of neurotransmitter activity in the CNS reward system in determining vulnerability to substance use and substance use-related disorders such as substance use disorder, alcohol dependence, and drug reward, and epigenetic regulation. Animal studies have shown that the MAOA gene plays a role in regulating ethanol consumption and substance use disorder. Adult male MAOA knockout mice show high ethanol intake [13].

In addition, resistance to lithium chloride-induced conditioned taste avoidance, reduced 5-HT content in the lateral septum, and increased exploratory motor activity have been observed [14,15].

3. Conclusion

The research concludes that while genetic factors, including specific gene variants such as MAOA, significantly influence the risk of psychiatric disorders, they do not act in isolation. Environmental factors, like stress and childhood trauma, play a crucial role in modulating genetic risk, particularly in the context of behavioral and emotional regulation. This gene-environment interaction, especially regarding hormones like cortisol and testosterone, provides insight into the complexity of psychiatric illnesses.

Understanding these interactions highlights both the challenge and the opportunity in addressing psychiatric conditions. The findings underscore the need to move beyond a purely genetic or purely environmental perspective and adopt a holistic approach that considers the dynamic interplay between these influences. The complexity of gene-environment interactions also suggests that psychiatric disorders may not follow a single pathway but rather arise from multiple factors that interact in unique ways for each individual.

Future research should aim to explore these pathways in more detail, potentially identifying biomarkers or genetic profiles that predict responses to environmental factors, such as stressors or social support. Further studies are essential to develop personalized therapeutic approaches that integrate both genetic and environmental considerations, paving the way for interventions that are more effective and tailored to the individual needs of patients with psychiatric disorders. Ultimately, such approaches hold promise for improving mental health outcomes by aligning treatment strategies with each patient's unique genetic and environmental background.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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