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Review article

Exploring the influence of stress on aggressive behavior and sexual function: Role of neuromodulator pathways and epigenetics

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ABSTRACT

Stress is a complex and multifaceted phenomenon that can significantly influence both aggressive behavior and sexual function. This review explores the intricate relationship between stress, neuromodulator pathways, and epigenetics, shedding light on the various mechanisms that underlie these connections. While the role of stress in both aggression and sexual behavior is well-documented, the mechanisms through which it exerts its effects are multifarious and not yet fully understood. The review begins by delving into the potential influence of stress on the Hypothalamic-Pituitary-Adrenal (HPA) axis, glucocorticoids, and the neuromodulators involved in the stress response. The intricate interplay between these systems, which encompasses the regulation of stress hormones, is central to understanding how stress may contribute to aggressive behavior and sexual function. Several neuromodulator pathways are implicated in both stress and behavior regulation. We explore the roles of norepinephrine, serotonin, oxytocin, and androgens in mediating the effects of stress on aggression and sexual function. It is important to distinguish between general sexual behavior, sexual motivation, and the distinct category of "sexual aggression" as separate constructs, each necessitating specific examination. Additionally, epigenetic mechanisms emerge as crucial factors that link stress to changes in gene expression patterns and, subsequently, to behavior. We then discuss how epigenetic modifications can occur in response to stress exposure, altering the regulation of genes associated with stress, aggression, and sexual function. While numerous studies support the association between epigenetic changes and stress-induced behavior, more research is necessary to establish definitive links. Throughout this exploration, it becomes increasingly clear that the relationship between stress, neuromodulator pathways, and epigenetics is intricate and multifaceted. The review emphasizes the need for further research, particularly in the context of human studies, to provide clinical significance and to validate the existing findings from animal models. By better understanding how stress influences aggressive behavior and sexual function through neuromodulator pathways and epigenetic modifications, this research aims to contribute to the development of innovative protocols of precision medicine and more effective strategies for managing the consequences of stress on human behavior. This may also pave way for further research into risk factors and

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underlying mechanisms that may associate stress with sexual aggression which finds application not only in neuroscience, but also law, ethics, and the humanities in general.

1. Introduction

Sexual aggression is a complex and pervasive issue with profound consequences for individuals and society. It encompasses a range of behaviors that involve the use of force, coercion, or manipulation to engage in non-consensual sexual behaviors [1]. The causes of sexual aggression are multifaceted, with both psychological and biological factors playing a role. Among these factors, stress and the interplay of neuromodulator pathways and epigenetic modifications have emerged as critical areas of investigation [2] (see Fig. 3).

Stress, as a physiological and psychological response to challenging or threatening situations, has been implicated in various forms of aggression, including sexual aggression [3]. Stress can activate the body's neuroendocrine system, triggering a cascade of events that culminate in the release of stress hormones such as cortisol [4]. This hormonal response affects multiple physiological systems, including the brain, and can profoundly influence behavior [5]. Understanding the intricate interplay between stress and sexual aggression is essential for unraveling the underlying mechanisms and developing effective interventions.

Neuromodulator pathways, such as the hypothalamic-pituitary-adrenal (HPA) axis, serotonergic system, and androgen system, play crucial roles in regulating stress responses and modulating aggression. These pathways involve intricate networks of neurotransmitters, receptors, and signaling molecules that orchestrate the physiological and behavioral responses to stress. Dysregulation or alterations in these pathways can have profound effects on an individual's propensity for aggressive behavior, including sexual aggression.

Epigenetic modifications, which involve changes in gene expression without altering the underlying DNA sequence, have recently gained attention as potential mechanisms linking stress, neuromodulator pathways, and sexual aggression [2]. Epigenetic modifications can be influenced by various environmental factors, including stress, and can persist over time, shaping an individual's biological and behavioral responses. Understanding the epigenetic underpinnings of stress and sexual aggression can shed light on the long-term consequences of traumatic experiences and provide insights into potential targets for intervention and prevention strategies.

The primary focus of this article is to discuss the biological mechanisms underlying stress, aggressive behavior, and sexual behavior, exploring the intricate relationship between stress, neuromodulator pathways, epigenetic modifications and their involvement in aggressive behavior and sexual behavior. The discussion of these mechanisms in relation to "sexual aggression" is based on the premise that these systems play roles in both aggressive and sexual behaviors but may not be directly linked to sexual aggression. Synthesizing findings from animal and human studies, we will examine the role of the HPA axis, serotonergic system, and androgen system in mediating stress and sexual behavior and possibly sexual aggression, as well as the emerging evidence on epigenetic modifications as molecular mechanisms linking these phenomena. This article focuses on the neural circuits and molecular mechanisms of behavior neuroscience and is not limited to psychological definition and theory.

By gaining a deeper understanding of the physiological and molecular processes involved in stress and sexual behavior, we can develop more targeted and effective approaches to address these issues related with sexual aggression. Such knowledge can inform the development of preventive measures, therapeutic interventions, and legal policies aimed at reducing sexual aggression and its impact on individuals and society. Ultimately, the integration of neurobiological and epigenetic perspectives can contribute to a comprehensive understanding of stress and sexual aggression, paving the way for a more informed and compassionate approach to prevention and intervention strategies.

1.1. Sexual aggression defined

Sexual aggression refers to a pattern of sexually coercive or non-consensual behavior in which one individual attempts to engage in sexual activity with another person without their freely given consent [6]. It involves actions or behaviors aimed at forcing, pressuring, or intimidating another person into engaging in sexual acts against their will. Sexual aggression can manifest in various forms in both animal models and humans. In animal models, sexual aggression refers to behaviors in which one animal, typically males, engages in aggressive or coercive actions aimed at mating or engaging in sexual activity with another animal, usually a female, without her consent. These behaviors are observed in various species, particularly mammals like rodents and primates.

Sexual aggression in animal models includes forced copulation, pursuit and harassment, interference with female choice, and mate guarding. In forced copulation male animals forcibly mate with females, even if the female initially resists or attempts to avoid mating. This involves physically subduing the female and engaging in copulation against her will. In pursuit and harassment males relentlessly pursue and harass females, making it difficult for them to escape or engage in normal activities. This involves persistent following, nuzzling, or attempts at mounting. Interference with female choice occurs when male animals interfere with the mating choices of females by physically preventing them from approaching or mating with other males. This often includes aggressive competition to monopolize access to receptive females. Lastly, mate guarding can be observed when some males exhibit aggressive behaviors to prevent rival males from approaching or mating with females they have selected as their mates. This is often seen in species with territorial or monogamous mating systems [7].

Sexual aggression in humans can manifest as verbal harassment including sexually explicit comments, catcalling, or making unwanted sexual advances. It can also manifest physically through unwelcome and unconsented touching, fondling, or groping and most aggressively as sexual assault and rape (forced sexual intercourse without the consent of the victim). In other instances, it occurs as

coercion, which involves psychological manipulation or the use of threats to pressure one into committing sexual acts against their will [8].

Sexual behavior is a complex phenomenon that encompasses various aspects, including general sexual behavior, sexual motivation, and sexual aggression, each of which constitutes distinct constructs that warrant individualized examination [9]. General sexual behavior pertains to consensual and normative sexual interactions between individuals, reflecting the natural expression of sexual desires and emotional connections [10]. On the other hand, sexual motivation encompasses the psychological and physiological processes that drive individuals toward engaging in sexual activities, focusing on factors like desire, arousal, and incentive salience [11]. Lastly, sexual aggression, involves non-consensual, coercive, or violent sexual behaviors that are harmful, and infringe on the autonomy and well-being of others [6]. Understanding the distinctions between these constructs is vital, as they involve diverse motivations, underlying mechanisms, and implications, necessitating targeted investigation to comprehensively address their features within the realm of human sexual behavior.

Sexual and aggressive behaviors serve adaptive functions in both animals and humans, rooted in evolutionary imperatives for survival, reproduction, and the establishment of social hierarchies. These behaviors, ranging from courtship rituals and mate selection to territorial defense and resource competition, have evolved to address biological and environmental challenges, ensuring gene transfer and species survival [12,13]. While influenced by cultural and social factors in humans, these behaviors remain aligned with the fundamental goals of reproduction and survival. Aggressive behaviors, including territorial aggression in animals and self-defense or competition in humans, are crucial for securing resources, protecting families, and enhancing social status, contributing to the survival of individuals and groups [14,15].

However, sexual aggression, characterized by unwanted sexual advances or harm, stands apart as a distinctly maladaptive behavior that violates consent and disrupts well-being. Unlike adaptive sexual and aggressive behaviors, sexual aggression undermines social structures and can inflict significant physical and psychological harm, necessitating a clear distinction between these behaviors [16]. Recognizing the adaptive origins of sexual and aggressive behaviors while acknowledging the detrimental impact of sexual aggression provides insight into the complex interplay of genetics, environment, and social dynamics that underpin these behaviors.

Sexual aggression is a complex behavioral phenotype that can emerge from stress exposure, affecting individual psychology, social interactions, and ultimately behavior. Stress influences neurobiological pathways related to aggression and sexual behavior, leading to heightened anxiety, impulsivity, and emotional dysregulation, which may increase the propensity for aggressive or coercive sexual behaviors. This is compounded by the disruption of normal social interactions and relationships, making sexual aggression a maladaptive response to stress [17,18]. Furthermore, stress impacts sexual behavior through complex neurochemical and receptor-based mechanisms, with cortisol release via glucocorticoid receptors and the noradrenergic system, particularly the locus coeruleus-norepinephrine system, enhancing sexual motivation and potentially aggressive behaviors. This is contrasted by the serotonergic system, which may decrease sexual motivation and aggression, indicating a nuanced role of neurotransmitters in stress-induced sexual aggression [19]. Sexual aggression, distinguished by the absence of freely given consent, constitutes a serious violation of personal boundaries, often recognized as a criminal offense across various jurisdictions. The multifaceted nature of sexual aggression, driven by individual, social, and biological factors, underscores the importance of understanding its underpinnings for addressing this issue effectively.

1.2. The hypothalamic-pituitary-adrenal axis and sexual aggression

The hypothalamic-pituitary-adrenal (HPA) axis is a central player in the body's response to stress, orchestrating the release of key neurochemicals and hormones. While the HPA axis has been associated with both aggressive behavior and sexual behavior, understanding its direct involvement in "sexual aggression" is an intricate task. The relationship between the HPA axis and sexual aggression remains a complex and evolving subject.

A neurochemical of particular interest is corticotropin-releasing hormone (CRH), a significant player in the stress response (Fig. 1). CRH is released from the hypothalamus in response to stress, thereby regulating the HPA axis. It binds to CRH receptors in the anterior pituitary gland, instigating the release of adrenocorticotropic hormone (ACTH) [20]. ACTH, in turn, prompts the adrenal glands to secrete cortisol, a hormone associated with heightened sexual motivation and aggression in animal studies [21,22]. Cortisol further binds to glucocorticoid receptors dispersed throughout various brain regions, including the amygdala and prefrontal cortex, where it

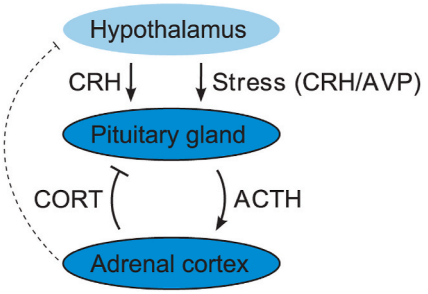

Fig. 1. Diagram showing the HPA axis and feedback control [24].

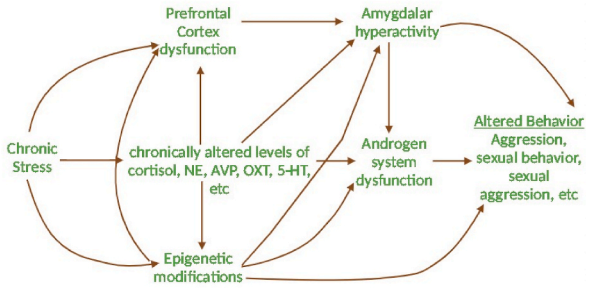

Fig. 2. This diagram illustrates the intricate interplay between chronic stress, neuromodulator neurotransmitters (e.g., cortisol, serotonin, norepinephrine, and arginine vasopressin), epigenetic modifications, and aggressive behavior. Three key brain areas are highlighted: the prefrontal cortex, amygdala, and the androgen system. Chronic stress activates the HPA axis, leading to increased cortisol release and potential epigenetic changes. These epigenetic modifications can influence the expression of genes in the androgen system and other relevant pathways. The prefrontal cortex and amygdala play pivotal roles in regulating emotional responses and aggression. Understanding these connections is vital for comprehending the neural basis of stress-induced aggression and provides insights for future research and interventions.

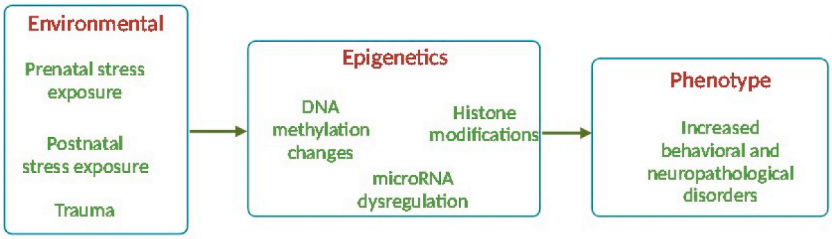

Fig. 3. This diagram illustrates the intricate connection between environmental factors (prenatal stress, postnatal stress, and trauma) and epigenetic mechanisms, including DNA methylation changes, histone modifications, and microRNA dysregulation. These epigenetic modifications, in turn, can impact neurobehavioral phenotypes, such as increased aggression, sexual aggressive behavior, and various psychiatric conditions. Understanding this complex relationship sheds light on how environmental experiences can leave a lasting imprint on gene regulation and behavior, offering insights for both research and potential interventions in the field of mental health and behavior.

can influence neuronal excitability and potentially impact aggressive behavior [23] (see Fig. 2).

Studies have shown that exposure to stress can alter the activity of the HPA axis, leading to dysregulation of cortisol secretion [25]. For instance, chronic exposure to stress can result in hyperactivity of the HPA axis, leading to elevated cortisol levels. On the other hand, acute stress can result in reduced HPA axis activity, leading to decreased cortisol levels [26]. While acute stress-induced cortisol release can sometimes enhance sexual motivation as part of a "fight or flight" response, the effects of chronic or prolonged cortisol exposure may have different outcomes. Chronic stress and cortisol elevation can negatively impact overall health, potentially impairing fertility, and reproductive functions. The effects of cortisol on sexual motivation are nuanced, influenced by the duration and context of cortisol exposure. Studies have shown that exposure to stress can increase the likelihood of engaging in sexual aggression [27]. For instance, stressors such as relationship problems, financial difficulties, and job stress have been linked to increased sexual aggression in both men and women [28,29].

The HPA axis has been implicated in the relationship between stress and sexual aggression. Research has shown that cortisol levels are elevated in individuals who engage in sexual aggression compared to those who do not [30]. Additionally, studies have shown that stress can alter the activity of brain regions involved in sexual aggression such as the amygdala and the prefrontal cortex (PFC) [31,32]. The amygdala is a region of the brain that is involved in the processing of emotional information, including fear and aggression. Studies have shown that the amygdala is activated during exposure to sexual stimuli in individuals who engage in sexual aggression [33,34].

The role of the HPA axis in sexual aggression is further underscored by findings indicating elevated cortisol levels in individuals who engage in sexual aggression compared to those who do not [30]. Moreover, stress has been found to modulate the activity of brain regions involved in sexual aggression, particularly the amygdala and prefrontal cortex (PFC) [31,32]. The amygdala, known for its involvement in processing emotional information like fear and aggression, exhibits heightened activity during exposure to sexual stimuli in individuals engaged in sexual aggression [33,34]. Elevated cortisol levels, on the other hand, have been associated with reduced PFC activation [35,36].

Eckhardt et., 2017 investigated the role of acute stressors, particularly those related to relationship conflicts, in the perpetration of sexual aggression [29]. They found that stressors in relationships were associated with increased sexual aggression in both men and women. This link is influenced by individual stress levels and their ability to regulate their emotions and engage in effective problem-solving. When high individual stress combines with poor interaction styles and problem-solving skills, the risk of intimate partner aggression increases.

A clinical study, conducted by Dennis et al., 2012, examined the psychological and behavioral factors in individuals who have committed sexual offenses [37]. The study delved into the experiences of stress and its role in sexual offending behaviors, providing valuable clinical insights into this complex relationship. Additionally, Efrati et al., 2019 explored the differences between sex offenders and sexual aggressors (SAs) in Compulsive Sexual Behavior Disorder (CSBD) and its underlying processes like maladaptive schemas, impulsivity, and sensation seeking [38]. The findings indicate that CSBD is present among sex offenders but affects only a small proportion of them. SAs showed significantly higher levels of the processes associated with CSBD, such as maladaptive schemas, impulsivity, and sensation seeking, which can explain the differences in CSBD prevalence between the two groups. Maladaptive schemas, especially in sexual contexts, appear to play a significant role in CSBD, highlighting the importance of addressing these cognitive patterns in both sex offenders and SAs.

A functional magnetic resonance imaging (fMRI) study also explored the neural correlates of stress-induced sexual arousal and aggressive behavior. Their findings indicated that stress can activate brain regions associated with sexual arousal and aggression, such as the amygdala and prefrontal cortex [39]. These studies collectively provide insights into the complex relationship between stress, the HPA axis, sexual behavior, and sexual aggression in humans. They highlight the multifaceted nature of this connection, involving psychological, clinical, neurobiological, and genetic factors. While more research is needed to fully understand the intricacies of this relationship, these studies contribute to our understanding of how stress can influence sexual aggression in human populations.

Concurrently, the prefrontal cortex (PFC), responsible for regulating behavior, is implicated in inhibiting impulsive behaviors, including sexual aggression [40–42]. Chronic stress exposure, however, can disrupt PFC activity regulation, potentially diminishing the inhibition of impulsive behaviors such as sexual aggression [43,44]. While the HPA axis is associated with both aggressive and sexual behaviors, establishing its direct involvement in "sexual aggression" is a nuanced endeavor. It is essential to recognize that these associations remain complex and multifaceted, necessitating further in-depth exploration and understanding.

1.3. The locus coeruleus-norepinephrine system and implications on sexual behavior

The activation of the locus coeruleus-norepinephrine (LC-NE) system in response to stress has garnered attention as a potential mechanism contributing to sexual aggression. The LC-NE system is instrumental in regulating arousal, attention, and aggressive behaviors [45]. However, it is crucial to approach the connection between this system and "sexual aggression" with the recognition that the precise involvement is multifaceted and remains a topic of ongoing investigation.

Stress triggers the activation of the LC, a small nucleus located in the brainstem that contains noradrenergic neurons. These neurons release norepinephrine (NE) throughout the brain, influencing various brain regions involved in emotional and behavioral responses, including aggression [46]. NE acts on different adrenergic receptors, primarily the α1, α2, and β receptors, which are widely distributed throughout the brain [47].

One proposed mechanism suggests that the activation of the LC-NE system due to stress leads to increased NE release in specific brain regions associated with sexual aggression, such as the amygdala, hypothalamus, and prefrontal cortex [48]. NE, via its interaction with α1 adrenergic receptors, can heighten arousal and contribute to behaviors linked to aggression [49]. Animal studies have demonstrated that the administration of α1 adrenergic receptor agonists can elevate aggressive behavior [50]. Conversely, the role of NE interaction with α2 adrenergic receptors in sexual aggression remains a subject of exploration. Activation of α2 adrenergic receptors may potentially reduce NE release and attenuate aggressive behavior [51]. However, it is vital to acknowledge that the specific effects of α2 adrenergic receptors in the context of sexual aggression are not yet comprehensively understood and may be influenced by various factors, including context and individual differences.

Significantly, NE also modulates the activity of other neurotransmitter systems, such as the serotonergic and dopaminergic systems, further contributing to the complex regulation of sexual aggression [52]. NE's interaction with serotonin receptors, like the 5-HT1A and 5-HT2A receptors in brain regions including the prefrontal cortex and amygdala, can influence aggressive behavior [53]. Additionally, NE can interact with dopamine receptors in the mesolimbic pathway, involved in reward and motivation, potentially affecting sexual motivation and behavior [54,55].

In human studies, the LC-NE system has also been implicated in the regulation of aggression and sexual behavior. Functional magnetic resonance imaging (fMRI) investigations have demonstrated LC-NE system activation in response to stimuli involving both aggression and sexuality [56,57]. Recent studies have further delved into the potential role of the LC-NE system in the development of sexual aggression. Individuals with higher aggression levels and a history of sexual aggression have exhibited increased LC-NE system activation in response to sexual stimuli [58–60]. These findings hint at the LC-NE system's possible involvement in the development of sexual aggression in certain individuals. Furthermore, research has explored the LC-NE system in relation to post-traumatic stress disorder (PTSD) and sexual dysfunction in women who have experienced sexual trauma [61,62]. These studies have observed that women with both PTSD and sexual dysfunction had lower cerebrospinal fluid NE levels compared to women with only PTSD, or healthy controls, suggesting the LC-NE system's potential role in the development of both PTSD and sexual dysfunction in the context of sexual trauma.

An imaging study utilized functional magnetic resonance imaging (fMRI) to identify neural correlates associated with stress-induced sexual aggression. Participants exposed to stressors underwent fMRI scans, allowing the observation of brain regions activated during stress-related sexual aggression [63]. The fMRI scans revealed altered activity in the amygdala, a brain region associated with emotional processing and regulation. Under stress, there was increased amygdala activation in response to sexually aggressive stimuli. The prefrontal cortex, involved in decision-making and impulse control, exhibited reduced activity during stress-induced sexual aggression, suggesting a potential impairment in inhibitory control. The striatum, associated with reward and motivation, showed increased activation in response to sexual aggression cues under stress. This heightened activity may indicate increased

motivation for aggressive behavior. The hypothalamus, a key structure in the endocrine system, demonstrated altered activity. Hormonal changes associated with stress, such as increased cortisol levels, may influence sexual aggression. The heightened striatal activation may imply increased motivation for sexual aggression under stress, suggesting that stress may enhance the reward value of aggressive behavior.

Besteher et al., 2017 explored the structural brain changes related to stress-induced aggression using a voxel-based morphometry (VBM) approach [64]. The study revealed a significant reduction in grey matter volume in the amygdala of individuals exhibiting stress-induced aggression. Similarly, the hippocampus, responsible for memory and stress regulation, displayed reduced grey matter volume in individuals prone to stress-induced aggression. This finding suggests a potential connection between memory processes, stress, and aggressive behaviors. Grey matter volume changes were observed in the frontal cortex, a region associated with decision-making and impulse control. These alterations may contribute to difficulties in controlling aggressive impulses when under stress. The reduction in amygdala grey matter volume suggests that structural changes in this region are associated with stress-induced sexual aggression [63]. This finding aligns with previous research emphasizing the role of the amygdala in emotional regulation and the expression of aggressive behaviors. It implies that structural alterations may contribute to heightened emotional responses in such individuals. Hippocampal atrophy hints at a potential link between memory processes and aggression under stress [63,64]. It implies that alterations in this region may influence how individuals process and respond to stressful situations, contributing to aggressive behaviors. Grey matter volume changes in the frontal cortex suggest structural alterations in brain regions responsible for impulse control and decision-making. This may result in difficulties inhibiting aggressive behaviors, particularly under stressful conditions.

However, it is crucial to emphasize the limitations and complexities surrounding the hypothesis of stress-induced LC-NE system activation as a facilitator of sexual aggression. The specific role of the LC-NE system in sexual aggression, including the intricate neurochemical and receptor interactions involved, requires further investigation and comprehensive understanding. Stress-induced activation of the LC-NE system is a proposed mechanism for the facilitation of sexual aggression. The release of NE in various brain regions, coupled with its interaction with adrenergic receptors, contributes to the modulation of arousal, attention, and aggressive behaviors. While human studies have offered insights into the link between the LC-NE system and sexual aggression, understanding the specific mediators and interactions within this system remains an evolving challenge. Further research is imperative to gain a nuanced understanding of the LC-NE system's contributions, in conjunction with other neurotransmitter systems, in the context of stress-induced sexual aggression and to pave the way for targeted interventions for individuals grappling with aggression or sexual dysfunction linked to LC-NE system dysregulation.

1.4. The Hypothalamic-Neurohypophyseal System and its implications in stress-induced sexual behavior

Scientific inquiry into the direct involvement of the Hypothalamic-Neurohypophyseal System (HNS), characterized by the release of oxytocin and vasopressin, in stress-induced sexual aggression is a subject that has not garnered extensive attention within the scientific literature. While the HNS is recognized for its role in modulating various social behaviors, including sexual behavior, establishing its precise contribution to stress-induced sexual aggression remains an ongoing and evolving area of research [65].

The HNS assumes a pivotal position in governing both physiological and behavioral responses to stress. Comprising the paraventricular nucleus (PVN) of the hypothalamus and the neurohypophysis, which encompasses the posterior pituitary gland, the HNS encompasses two key sets of neurons: corticotrophin-releasing hormone (CRH) neurons and oxytocin neurons. CRH neurons release CRH, activating the hypothalamic-pituitary-adrenal (HPA) axis and leading to the release of glucocorticoids. Conversely, oxytocin neurons release oxytocin, a neurohormone recognized for its anxiolytic effects and its role in social bonding and affiliative behaviors [66]. The intricate interplay between these two neurohormones is pivotal in modulating physiological and behavioral responses to stress, including those related to sexual aggression.

The effects of oxytocin and vasopressin on sexual aggression are mediated by their actions on specific receptors in various brain regions. The distribution of these receptors varies across brain regions, with the amygdala, prefrontal cortex, and hypothalamus showing the highest levels of expression. The amygdala has been implicated in the regulation of emotional and social behaviors and is known to play a critical role in the expression of sexual aggression [67]. Oxytocin has been shown to modulate the activity of the amygdala, leading to a reduction in anxiety and fear responses and an increase in social approach behavior [68,69]. Similarly, vasopressin has been shown to modulate the activity of the prefrontal cortex and hypothalamus, leading to an increase in social bonding and aggression behaviors [31,70,71]. Animal studies have provided evidence for the role of the HNS in modulating sexual behavior in response to stress. In male rats, acute restraint stress increased the activity of CRH neurons in the PVN and resulted in increased sexual behavior, while chronic restraint stress decreased sexual behavior [72]. In female rats, exposure to predator odor decreased sexual receptivity and was associated with increased CRH expression in the PVN [73]. In male rats, the administration of OT attenuated the effects of stress on sexual behavior [74].

Human studies have also provided evidence for the involvement of the HNS in regulating sexual behavior in response to stress. In healthy men, a laboratory-induced stressor (public speaking task) was associated with increased levels of plasma OT and increased sexual arousal to visual sexual stimuli [75–77]. In contrast, in men with sexual dysfunctions, exposure to a laboratory-induced stressor (Trier Social Stress Test) was associated with decreased levels of plasma oxytocin and decreased sexual arousal to visual sexual stimuli [78].

A study investigating the relationship between traumatic stress, HNS function, and sexual aggression in combat veterans, revealed that combat veterans with a history of traumatic stress, particularly those diagnosed with PTSD, exhibited impaired HNS function. Specifically, they had altered oxytocin and vasopressin levels, which are associated with HNS function. The study found a positive correlation between HNS function impairment and the propensity for sexual aggression among combat veterans with traumatic stress.

Veterans with compromised HNS function were more likely to engage in sexually aggressive behaviors [79]. The findings suggested that traumatic stress could lead to HNS dysregulation, impacting social and sexual behaviors. This study sheds light on the connection between traumatic stress, HNS function impairment, and sexual aggression in combat veterans. The research highlights the importance of considering neurobiological factors in understanding and addressing sexual aggression within this population. Another study explored the relationship between PTSD, HNS system dysregulation, and sexual behavior in men. The study found that men diagnosed with PTSD exhibited HNS dysregulation. Specifically, there were alterations in oxytocin and vasopressin levels, both of which are associated with the HNS [36]. The research indicated that HNS dysregulation was linked to sexual behavior in men with PTSD. Men with compromised HNS function reported lower sexual desire and arousal compared to controls, and men without PTSD. The findings suggest that the relationship between PTSD and changes in sexual behavior might be mediated by the effects of stress on the HNS. HNS dysregulation may contribute to reduced sexual functioning in individuals with PTSD.

Examining the relationship between stress, sexual behavior, and aggression among college students, Hales and Gannon., 2019 found a significant association between high levels of stress and changes in sexual behavior [1]. College students experiencing elevated stress reported a decrease in sexual desire and frequency of sexual activity. Elevated stress levels were also linked to increased aggression among college students. Those under higher stress reported more frequent aggressive behaviors in various aspects of their lives, a finding corroborated by the study of [80]. The research identified gender differences in the impact of stress. Female college students were more likely to report decreased sexual desire under stress, while male students were more likely to report increased aggression. The study raises questions about the underlying mechanisms connecting stress, sexual behavior, and aggression in college students. Does increased stress directly lead to changes in sexual behavior and aggression, or are these factors simply correlated with stress? How do these short-term changes in behavior, driven by stress, affect the long-term well-being and relationships of college students? Investigating the potential long-term consequences is important for comprehensive understanding.

A study by Ruesink and Georgiadis, 2017 delved into the neurobiological underpinnings of sexual aggression in response to stress [81]. It employed advanced neuroimaging techniques to investigate changes in brain connectivity within the HNS regions and their connection to sexual aggression. The study revealed that stress induces altered connectivity within the HNS regions. This altered connectivity suggests that stress can disrupt the neural circuits involved in regulating social and sexual behaviors. The study identified specific neural substrates within the HNS system that are associated with sexual aggression. These findings emphasized the critical role of these brain regions in modulating aggressive sexual behaviors in response to stress. The study established a correlation between the observed changes in HNS connectivity and behavioral measures of sexual aggression. This correlation strengthens the link between neural connectivity and aggressive sexual behaviors driven by stress. The findings suggest that the neural circuitry within the HNS system is a key player in the manifestation of sexual aggression under stressful conditions. It also highlights the potential of altered brain connectivity as a biomarker for assessing an individual's susceptibility to sexual aggression when exposed to stressors. This could have clinical implications for risk assessment and prevention.

A study by Iovino et al., 2019 employed neuroimaging techniques to investigate the neural activity in the HNS system during stress-induced sexual aggression in men [82]. The study identified the involvement of neural circuitry connecting the hypothalamus, amygdala, and related brain regions in orchestrating stress-induced sexual aggression. These findings underscore the complexity of the brain's response to stressors. The study reaffirms the importance of the HNS system in regulating sexual aggression under conditions of stress. Understanding the neural basis of these behaviors can aid in designing targeted interventions for individuals at risk. It also highlighted the potential of neuroimaging as a diagnostic tool to assess an individual's susceptibility to stress-induced sexual aggression. Integrating neuroimaging with traditional clinical assessments may improve risk evaluation and intervention strategies.

The HNS is a critical neuroendocrine system involved in regulating the physiological and behavioral responses to stress, including sexual behavior. The interplay between CRH and oxytocin is crucial in modulating these responses, and the dysregulation of this balance may lead to sexual aggression. Animal and human studies have provided evidence for the involvement of the HNS in regulating sexual behavior in response to stress, and recent research has focused on the role of epigenetic modifications in the regulation of the HNS. Further research is needed to fully understand the complex interactions between the HNS, stress, and sexual behavior and the potential therapeutic targets for the treatment of sexual aggression.

1.5. The serotonergic system and sexual aggression

The role of the serotonergic system in stress-induced sexual aggression has been investigated through both animal and human studies, providing valuable insights into the complex mechanisms involved. While the understanding of this relationship is still evolving, there is evidence to suggest that stress can modulate the serotonergic system, leading to alterations in sexual aggression-related behaviors.

Animal studies have provided valuable insights into the effects of stress on the serotonergic system and its relationship with sexual aggression. For example, research conducted on rodents has shown that exposure to chronic stress can lead to decreased serotonin levels in various brain regions, including the prefrontal cortex, amygdala, and hypothalamus [83,84]. These changes in serotonin levels have been associated with increased aggressive behavior, including sexual aggression, in these animals. Additionally, animal studies have revealed that stress can alter the expression and function of serotonin receptors, such as the 5-HT1A and 5-HT2C receptors, which are known to be involved in the regulation of aggression [85,86]. The activation or inhibition of these receptors in response to stress can influence the expression of sexual aggression. Human studies have also contributed to our understanding of the relationship between stress, the serotonergic system, and sexual aggression. For instance, research examining individuals with a history of exposure to chronic stress or trauma has shown alterations in serotonin function. Studies using neuroimaging techniques have revealed reduced serotonin transporter binding, suggesting lower serotonin availability in certain brain regions, such as the

amygdala and prefrontal cortex, in individuals with a history of stress or trauma [87,88]. Furthermore, genetic studies have explored the associations between variations in genes related to serotonin synthesis, transport, and receptor function and aggressive behavior. Variations in genes such as TPH2, SLC6A4, and HTR2A have been implicated in the susceptibility to aggressive behavior, including sexual aggression, under conditions of stress [89,90].

Neurochemicals, such as serotonin, play a crucial role in the modulation of sexual aggression. Serotonin acts on various receptor subtypes, including 5-HT1A, 5-HT1B, and 5-HT2C receptors, among others. The activation of these receptors can have different effects on aggression. For example, activation of 5-HT1A receptors has been associated with inhibitory effects on aggression, while activation of 5-HT2C receptors may have excitatory effects [91,92]. The balance between these receptor subtypes and the availability of serotonin in specific brain regions can influence the expression of sexual aggression in response to stress.

A study to investigate the relationship between the serotonergic system, and sexual aggression in a group of individuals with a history of sexual aggression, found that individuals who reported higher stress levels were more likely to exhibit impulsive sexual behavior and a higher propensity for sexual aggression. Moreover, those with serotonin receptor gene polymorphisms associated with reduced serotonin function were more likely to engage in sexually aggressive behaviors when exposed to stress. The findings suggest that serotonergic system dysfunction, combined with high stress levels, may increase the risk of sexual aggression in some individuals [93]. Murrough et al., 2011 examined a clinical population with high stress levels and various patterns of sexual behaviors [88]. The study showed that individuals with elevated stress and sexual aggression tendencies exhibited lower serotonin transporter binding in key brain regions, leading to reduced serotonin availability. This reduction in serotonin function was associated with heightened aggression and impulsivity in sexual behavior. The findings highlight the importance of considering serotonergic dysfunction in the context of high stress when assessing and treating sexual aggression. Another clinical study investigated the role of serotonergic genetic variations in the context of stress and sexual aggression. The study revealed that individuals with serotonin transporter-linked promoter region (5-HTTLPR) polymorphisms associated with reduced serotonin activity were more likely to engage in sexual aggression, particularly when facing high levels of stress. These individuals exhibited decreased impulse control and heightened aggressive sexual behaviors.

A study aimed to investigate the association between the serotonin transporter gene (5-HTT) polymorphism and different facets of aggression in females, found that individuals with the low-activity 5-HTT polymorphism (SS) exhibited increased scores on the Indirect Hostility scale, indicating a greater tendency toward indirect forms of aggression. These individuals also showed decreased scores on the Negativism scale, suggesting reduced negative emotional expression and interpersonal hostility. In contrast, those with the LL genotype displayed contrasting patterns, emphasizing the role of 5-HTT polymorphism in modulating various facets of aggression [94]. Butovskaya et al., 2018 investigated the association between serotonergic gene polymorphisms (5-HTTLPR, rs6295 in 5HTR1A, and rs6311 in 5HTR2A) and aggression across three different populations: two traditional populations (Hadza and Datoga populations, from the Mangola region of Northern Tanzania) and one industrial population (Russian, university students) [95]. For the Hadza sample, the study revealed a significant effect of the 5HTR2A polymorphism on total aggression. In the Datoga population, the interaction effect between 5-HTTLPR and 5HTR1A was significant, indicating that the combination of these two polymorphisms was associated with aggression. The study extended previous findings by demonstrating the role of the rs6311 polymorphism in the 5HTR2A gene in aggression in healthy adult men and women from the samples. G-allele carriers were rated higher on total aggression, suggesting an association between this gene variant and aggressive behavior.

The HPA axis and the serotonergic system are both involved in the response to stress and have been implicated in the modulation of sexual aggression. Stress-induced activation of the HPA axis may increase sexual aggression through its effects on cortisol levels and the serotonergic system. Low levels of serotonin have been associated with increased sexual aggression, and the interaction between the HPA axis and the serotonergic system in the modulation of sexual aggression has also been investigated [96,97]. Genetic factors may also interact with the HPA axis and the serotonergic system to modulate sexual aggression.

The relationship between stress, the serotonergic system, and sexual aggression is complex and multifaceted. The effects of stress on the serotonergic system and subsequent sexual aggression can be influenced by various factors, including individual differences, genetic predispositions, and environmental contexts. Additionally, the interplay between other neurochemical systems, such as the dopaminergic and noradrenergic systems, further adds to the complexity of this relationship. The role of the serotonergic system in stress-induced sexual aggression is a topic of ongoing research and debate. Studies examining the effects of serotonergic manipulations on aggression have yielded inconsistent findings, and the effects may vary depending on factors such as individual differences, context, and the specific serotonergic receptor subtypes involved. While there is evidence suggesting the involvement of the serotonergic system in aggression, the exact mechanisms and the specific neurochemicals and receptors involved are not yet fully understood. The link between the serotonergic system with sexual behavior and sexual aggression is not clear and is poorly established. Therefore, it is important to approach this discussion with caution, acknowledging the complexities and limitations of the current understanding. Further research is needed to fully understand the complex interplay between these systems in the modulation of sexual aggression.

1.6. The androgen system and sexual aggression

The impact of stress on the physiology of the androgen system and its role in the development of sexual aggression has been investigated through animal and human studies. While our understanding of these mechanisms is still evolving, there is evidence to suggest that stress can alter the physiology of the androgen system, leading to changes in sexual aggression-related behaviors.

Animal studies have provided valuable insights into the effects of stress on the physiology of the androgen system. For instance, research on rodents has demonstrated that exposure to chronic or acute stress can lead to alterations in the production and release of androgens, such as testosterone [98,99]. Stress can disrupt the hypothalamic-pituitary-gonadal (HPG) axis, which is responsible for

regulating androgen production. Studies have shown that stress can increase the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, subsequently leading to the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH, in turn, stimulates the release of glucocorticoids from the adrenal glands. These glucocorticoids can inhibit the HPG axis, resulting in decreased testosterone production [100,101].

Moreover, stress-induced alterations in the androgen system can extend beyond the HPG axis. Animal studies have demonstrated that stress can affect the enzymatic activity of key enzymes involved in androgen synthesis, such as 5-alpha-reductase and aromatase [102]. These enzymes are responsible for converting testosterone into more potent androgen dihydrotestosterone (DHT) and for converting testosterone into estrogen, respectively. Stress-induced changes in the activity of these enzymes can impact the levels and ratios of androgens and estrogens, leading to modifications in sexual aggression-related behaviors [103]. Human studies have also contributed to our understanding of the relationship between stress and the physiology of the androgen system. For instance, research on human subjects has shown that exposure to chronic stress can lead to alterations in androgen levels. Studies examining individuals in high-stress occupations or those experiencing chronic stressors have observed decreased testosterone levels [104,105]. Additionally, research has highlighted the role of stress-related hormones, such as cortisol, in modulating the physiology of the androgen system. Elevated cortisol levels, commonly observed during stress, have been associated with reduced testosterone levels and altered androgen signaling pathways [106,107]. However, a study found that testosterone levels increased after acute stress exposure in all groups, regardless of borderline personality disorder (BPD) or posttraumatic stress disorder (PTSD) status, suggesting that stress-related changes in testosterone release are not influenced by these disorders in young adult men [108].

The physiological alterations induced by stress in the androgen system can have significant implications for sexual aggression. Androgens, such as testosterone, are known to influence neural circuits involved in aggression, including those related to sexual aggression. Changes in androgen levels and the ratios of androgens to estrogens can influence the activation of these neural circuits and subsequently impact sexual aggression-related behaviors [109–111]. The relationship between stress and the androgen system is bidirectional, with stress leading to changes in androgen levels and androgens influencing the stress response. The relationship between androgens and sexual aggression is likely complex and influenced by a variety of factors, including individual differences in stress response, androgen sensitivity, genetic predispositions, and social context. Additionally, the interplay between other neurochemical systems, such as serotonin, further contributes to the intricate mechanisms underlying stress-induced sexual aggression. Lower levels of serotonin have been associated with increased aggression in humans and animals. Androgens have been shown to influence the serotonergic system, with testosterone administration leading to increased serotonin receptor expression in rats [112,113].

Bradford and McLean, 1984 investigated the relationship between testosterone levels and violent or sexually offensive behavior in a clinical population [114]. In the context of sexually offensive behavior, the study found a positive association between elevated testosterone levels and sexual aggression. It highlighted variations within the clinical population, and noted that certain subgroups of offenders, such as those who exhibited violent behavior, displayed notably higher testosterone levels. Individuals who were involved in sexually offensive behavior also had elevated testosterone levels, indicating a subgroup of sexual offenders with hormonal differences. This suggests that assessing testosterone levels in certain clinical populations, particularly individuals with a history of violent or sexual offending, may help identify those at higher risk of engaging in aggressive behaviors. It is however important that testosterone is not the sole determinant of aggressive or sexual offending behaviors. These behaviors result from complex interactions between biological, psychological, and social factors.

A study by O'Connor et al., 2004 which aimed to explore the effects of elevated testosterone levels on mood, aggression, and sexual behavior in young men, found that the increase in testosterone levels was associated with minor mood changes, including a significant increase in anger-hostility and a decrease in fatigue-inertia [115]. In the study, elevated testosterone levels were induced by administering a single 1000 mg testosterone undecanoate (TU) injection to participants and assessing various psychological and behavioral parameters. Importantly, TU treatment did not lead to increased aggressive or sexual behavior. These findings suggest that exogenous TU-induced elevations in testosterone, potentially used for male contraception, have limited psychological effects, but further research is needed to fully understand the implications of these minor mood changes.

Pope et al., 2000 also investigated the effects of supraphysiologic doses of testosterone on mood and aggression in normal men [116]. The results indicated that testosterone treatment led to a significant increase in manic scores, as measured by the Young Mania Rating Scale (YMRS) and daily diaries. Aggressive responses on the Point Subtraction Aggression Paradigm also increased with testosterone treatment. However, the drug response showed substantial variability, with most participants exhibiting minimal psychiatric effects. A minority of participants experienced hypomanic symptoms. However, the response to testosterone was highly variable, with most individuals showing little psychological change. The reasons for this variability in response remain unclear. A systematic review and meta-analysis, conducted by Chegeni et al., 2021 aimed to investigate the effects of anabolic-androgenic steroid (AAS) administration on self-reported aggression, and observer-reported aggression, in healthy males [117]. The results revealed that AAS administration was associated with a negligible increase in self-reported aggression under a random-effects model. However, this effect was not observed in the analysis of observer-reported aggression. Additionally, when the analysis was restricted to acute AAS administration, a slightly larger effect on self-reported aggression was observed. Still, this effect was not found for higher doses or long-term administration. The meta-analysis provides evidence of a small increase in self-reported aggression in healthy males following AAS administration in randomized control trials.

The role of testosterone in aggressive behavior, manifests in various forms from thoughts and verbal aggressiveness to physical violence. The interplay between subcortical brain structures (the amygdala and hypothalamus) and prefrontal cognitive centers determines aggressive behavior [118]. The influence of testosterone on aggression begins early in development, with genetic factors like the androgen receptor gene's CAG repeats playing a role [119]. Neuroimaging studies show that testosterone activates the amygdala,

but its effects are tempered by cortisol, which facilitates cognitive control, and serotonin, which regulates impulsivity, forming a complex interplay in the neuroendocrine influence on aggression [120]. Evidence from both animal and human studies supports the involvement of the androgen system in stress-induced sexual aggression. Stress can activate the androgen system, leading to changes in androgen levels and the expression and function of androgen receptors. These alterations, in turn, can influence the manifestation of sexual aggression. However, further research is needed to fully understand the underlying mechanisms and the intricate interplay between stress, the androgen system, and sexual aggression in both animal models and human populations.

1.7. Epigenetic modifications of neuromodulator systems modifications and sexual aggression

Epigenetic modifications of neuromodulator systems have emerged as a significant area of research in understanding the mechanisms underlying sexual aggression. Animal studies have demonstrated the impact of epigenetic modifications on neuromodulator systems and the consequent development of sexual aggression. For example, research conducted on rodents has shown that early-life stress can lead to epigenetic alterations in genes related to neuromodulator systems, including the HPA axis, the serotonergic system, and the androgen system. These epigenetic modifications can persist into adulthood and influence the function of these systems, resulting in altered sexual aggression-related behaviors [121]. Epigenetic modifications, such as DNA methylation and histone modifications, can regulate gene expression and alter the activity of neurotransmitter receptors and enzymes involved in the synthesis and metabolism of neuromodulators.

Research on rodents has demonstrated that early-life stress can lead to epigenetic changes in genes associated with the HPA axis, including the glucocorticoid receptor gene (NR3C1). These modifications can persist into adulthood and result in altered stress responses and behavioral outcomes, such as increased aggression [122,123]. Epigenetic modifications, such as DNA methylation and histone modifications, can regulate the expression of NR3C1, influencing the sensitivity to stress and the ability to regulate stress-related behaviors, including sexual aggression.

Human studies have also shed light on the relationship between epigenetic modifications of the HPA axis and sexual aggression. Research investigating individuals with a history of trauma or adverse experiences has revealed associations between epigenetic modifications and HPA axis dysregulation. For example, studies have observed altered DNA methylation patterns in the NR3C1 gene in individuals with a history of sexual aggression, indicating epigenetic changes that can influence HPA axis functioning [124,125]. These modifications can disrupt the stress response system, affecting cortisol regulation and stress-related behaviors, potentially contributing to sexual aggression.

Epigenetic modifications of the HPA axis can influence sexual aggression by impacting various aspects of HPA axis functioning. Dysregulation of the stress response and altered cortisol levels resulting from epigenetic modifications can disrupt the balance between the HPA axis and other neurochemical systems involved in aggression, such as the serotonergic and dopaminergic systems [126]. Changes in gene expression within the HPA axis can affect the feedback regulation of cortisol, leading to altered stress reactivity and emotional responses, which can manifest as sexual aggression [127].

Epigenetic modifications of the SLC6A4 gene, which encodes the serotonin transporter, have been investigated in animal and human studies to understand their role in sexual aggression. As previously mentioned, serotonin plays a crucial role in regulating mood, impulsivity, and aggression, and alterations in serotonin levels or function have been implicated in aggressive behavior, including sexual aggression. Epigenetic modifications of the SLC6A4 gene can influence serotonin transporter expression, subsequently impacting serotonin levels and function [128,129]. Epigenetic modifications, such as DNA methylation and histone modifications, can regulate the transcriptional activity of the SLC6A4 gene, altering serotonin reuptake and availability. Research on rodents has shown that early-life stress can induce epigenetic alterations in the SLC6A4 gene, leading to changes in serotonin transporter expression and function. These modifications can impact serotonin signaling and neurotransmission, which in turn can influence behaviors related to sexual aggression [130,131].

Human studies have also investigated the association between epigenetic modifications of the SLC6A4 gene and sexual aggression. Research conducted on individuals with a history of early-life trauma or exposure to adverse experiences has revealed differences in DNA methylation patterns in the SLC6A4 gene [132]. These Epigenetic modifications of the SLC6A4 gene can affect serotonin reuptake, leading to imbalances in serotonin availability and compromised neurotransmission, which may contribute to the manifestation of sexual aggression [133,134]. Altered serotonin transporter activity due to epigenetic modifications can disrupt the balance of serotonin in neural circuits involved in aggression regulation, leading to an increased risk of sexual aggression [92,135]. Epigenetic modifications of the SLC6A4 gene can influence sexual aggression through their impact on serotonin neurotransmission.

The relationship between epigenetic modifications of the SLC6A4 gene and sexual aggression is multifaceted, influenced by genetic variations, environmental context, and individual differences. Moreover, the interplay between the serotonergic system and other neurochemical and neuromodulator systems adds complexity to the mechanisms underlying sexual aggression. However, additional research is necessary to gain a better understanding of the specific epigenetic mechanisms involved and to unravel the intricate interactions between epigenetic modifications, the serotonergic system, and other contributing factors in sexual aggression.

Serotonin plays a significant role in various psychiatric conditions and antisocial/aggressive personality. Serotonin concentration in the brain is regulated by serotonin transporter SLC6A4 and monoamine oxidase A (MAOA). Hypo-functioning of serotonin neurotransmission has been linked to a higher risk of aggressive behaviors [136]. This includes reduced SLC6A4 expression in impulsive-aggressive individuals, and childhood stress and aversive experiences that can lead to epigenetic changes in SLC6A4. For example, childhood stress, such as bullying victimization, has been associated with increased methylation of the SLC6A4 promoter [137,138]. Similarly, individuals who experienced physical abuse in childhood tend to have increased SLC6A4 methylation in peripheral white cells, which is correlated with an elevated risk of developing antisocial personality disorders [139]. These epigenetic

changes can also affect serotonin synthesis in the brain, amygdala reactivity, and brain morphology. Additionally, orbitofrontal cortex activity and morphology have been linked to aggressive behavior, and exposure to peripubertal stress in a rat model led to changes in amygdala connectivity and MAOA expression, which was accompanied by epigenetic modifications in the prefrontal cortex [140]. These findings suggest a complex interplay between serotonin pathway genes, early-life stressors, and aggressive behavior, with epigenetic mechanisms playing a crucial role in these relationships.

Rawat et al., 2022 explored how early life stressful experiences impact aggressive behavior in adulthood through changes in transthyretin (TTR) expression and function [141]. The research conducted on male mice exposed to peripubertal stress found that TTR, a thyroid hormone transporter, plays a key role in regulating escalated aggressive behavior. Changes in TTR gene expression, thyroid hormone availability, and DNA methylation patterns in the prefrontal cortex and hypothalamus were identified as underlying mechanisms. This research suggests that TTR could be a potential target for addressing escalated aggression and related psychiatric conditions triggered by early-life stress. Konar et al., 2019 also investigated the link between early-life stress, sexual dimorphism, and aggressive behavior, focusing on the epigenetic regulation of the MAOA gene [142]. Researchers found that peripubertal stress led to escalated aggression in adult males but increased social exploration in females. Epigenetic changes, such as methylation patterns and Sirt1 binding to the MAOA promoter, were linked to these behavioral differences, highlighting the complex interplay between epigenetic mechanisms, sex-specific responses, and aggressive psychopathology.

Kruger et al., 2019 examined child sexual offenders (CSOs) and pedophiles to investigate the role of the androgen system in child sexual offending [143]. The research, involving 194 subjects, including CSOs, pedophiles, and controls, found that CSOs, irrespective of their sexual preference, exhibited elevated prenatal androgen exposure compared to non-offending pedophiles and controls. The study also observed higher methylation of the androgen receptor gene in CSOs, indicating reduced functionality of the testosterone system, along with lower peripheral testosterone levels. These findings suggest that alterations in the androgen system at prenatal, epigenetic, and endocrine levels are associated with child sexual offending, supporting theories of testosterone-related brain development abnormalities in delinquent behavior [144]. In another study investigating the serotonergic system's role in pedophilia and CSO, the methylation rates of HTR3A (serotonin receptor) showed significant differences between child sexual offenders and non-offenders, with child sexual offenders having lower methylation rates. These rates also correlated negatively with experiences of sexual violence and the number of sexual offenses committed. Additionally, pedophilia-related alterations in 5HT3A and SLC6A4 methylation rates were observed, suggesting epigenetic changes may be involved in pedophilia and child sexual offending, as well as personal experiences of sexual violence [145].

Research, including a meta-analysis, has consistently shown that low cortisol levels are associated with antisocial behavior. Low basal cortisol levels have been linked to externalizing behavior in childhood and adolescence, as well as reduced self-control, delinquent behavior, and both proactive and reactive aggression during adolescence [146]. Moreover, individuals with a history of child abuse and neglect tend to have lower HPA activity and higher levels of trait and state aggression in adulthood, indicating that HPA hypo-activity may serve as a mediator between early-life environment and long-term aggressive behavior [147]. Recent studies have confirmed the relationship between early adverse family environments and epigenetic changes in NR3C1, leading to augmented inhibitory control of the HPA axis. These epigenetic alterations persist into adulthood, significantly affecting neurodevelopment, stress response, and self-regulation, all of which contribute to a predisposition to aggressive behavior [141]. These studies suggest a crucial role for NR3C1 in shaping the risk of aggressive behavior.

While these studies provide insights into the epigenetic regulation of genes involved in different neuromodulator systems and their influence on social behavior, the direct link between epigenetic modifications of these systems and sexual aggression is yet to be established. Further research is needed to investigate the specific epigenetic changes within these systems that may contribute to sexual aggression in both animal models and human populations. Additional studies focusing on epigenetic modifications within these systems and their association with sexual aggression will contribute to a better understanding of the complex mechanisms underlying this behavior.

1.8. Adaptive and maladaptive aspects of stress, sexual aggression, and animal behavior

Sexual and aggressive behaviors, while often considered in the context of human society, also have important adaptive functions in the animal kingdom. These behaviors are shaped by evolutionary processes and serve critical roles in ensuring the survival and reproductive success of various species. Understanding the adaptiveness of these behaviors in animals provides valuable insights into their complexity and diversity.

Neuromodulator pathways, such as the HPA axis, can influence an animal's ability to engage in competitive behaviors. The release of stress hormones like cortisol can enhance an individual's preparedness for competition [148]. This heightened state of alertness and readiness can be beneficial when animals are competing for mates or defending territories. For example, in the animal kingdom, competition for access to mates is fierce. Male animals often display aggressive behaviors to establish dominance and secure mating opportunities. This competition can enhance the reproductive success of the fittest males, leading to the transmission of their genes to the next generation [149]. Epigenetic modifications have been identified as mechanisms through which animals can adapt to environmental stressors. These modifications can influence gene expression without altering the DNA sequence, allowing for rapid and reversible changes in behavior and physiology [150]. In the context of sexual aggression, epigenetic adaptations may allow animals to adjust their aggressive behaviors based on environmental cues. This flexibility can be advantageous for animals living in dynamic or unpredictable environments. In some species, sexual and aggressive behaviors are closely intertwined in complex courtship rituals. Stress-induced neurochemical changes may help individuals navigate these rituals effectively. These behaviors can influence mate selection and courtship success, allowing animals to optimize their reproductive strategies [151]. The modulation of aggressive and

sexual behaviors under stress may enable animals to balance their reproductive efforts strategically.

While it is evident that the involvement of neuromodulator pathways and epigenetics in the context of stress and sexual aggression can be adaptive in some situations, there are important limitations and potential negative consequences to consider. Over-activation of neuromodulator pathways due to chronic stress can lead to maladaptive behaviors. An exaggerated stress response may result in aggressive behaviors that are no longer contextually relevant or beneficial. These behaviors could consume energy and resources, leading to a reduced overall reproductive fitness [152]. Engaging in aggressive or sexually competitive behaviors can be energetically costly for animals. The allocation of resources to support these behaviors might reduce the energy available for other essential functions, such as foraging or self-maintenance. Excessive investment in aggression or courtship may lead to a decrease in overall fitness if the costs outweigh the benefits [153]. Aggressive behaviors, particularly in confrontations between individuals, may result in injuries, which can be detrimental to an animal's survival and reproductive prospects. In addition, the conspicuous courtship behaviors that are meant to attract mates may also attract predators or competitors. This increased risk may compromise the safety and survival of the individuals involved. Intraspecific competition driven by aggressive or sexual behaviors can result in population-level challenges. For example, over-competition for limited resources or mates can lead to increased stress, reduced population sizes, and in some cases, intra-specific violence. This underscores the potential drawbacks of excessive aggression and sexual competition [154].

The involvement of neuromodulator pathways and epigenetics in the relationship between stress and sexual aggression represents a complex interplay of adaptive and potentially maladaptive processes. The adaptiveness of these behaviors depends on factors such as the environment, the species, and the individual's ability to fine-tune their responses to stressors. While there are clear advantages to enhancing competitive abilities and reproductive strategies through these mechanisms, there are also inherent risks and potential negative consequences that must be considered. The balance between adaptability and maladaptation remains a central theme in understanding the role of these pathways in animal behavior.

2. Conclusion

Biological theories of sexual aggression have focused on factors such as brain abnormalities, hormone levels, genetics, and intellectual functioning to explain the etiology of sexual aggressive behavior. Several studies have reported the presence of brain abnormalities in some sexual offenders. However, it is crucial to note that such abnormalities are not consistently found in the majority of cases [155–157]. This suggests that while brain abnormalities may be present in some offenders, they are not a universal characteristic of sexual offenders. Research has explored the link between hormonal abnormalities, especially testosterone, and sexual offending. However, studies to date have not provided conclusive evidence of a direct association between hormone levels and sexual offending behavior [158,159]. This indicates that the relationship between hormone levels and sexual offending is not straightforward. There has been consideration of genetic and epigenetic factors that may predispose individuals to engage in aggressive sexual behavior. However, research in this area has been limited by small sample sizes, and more extensive studies are needed to establish causal relationships between epigenetics and sexual offending [160]. Biological studies of sexual aggression have generated findings that are inconclusive or limited in various aspects, including brain abnormalities, hormonal influences, epigenetics, and intellectual functioning.

These findings emphasize the complexity and heterogeneity of sexual offending behavior, suggesting that it cannot be solely explained by one factor, but rather results from a combination of factors. More extensive research is needed to gain a comprehensive understanding of the biological underpinnings of sexual offending behavior. Therefore, comprehending the intricate interplay between stress, neuromodulator systems, and epigenetic modifications concerning sexual aggression carries profound implications for both law and society. Sexual aggression remains a grave public health concern, with global estimates indicating that as many as one in three women will confront sexual violence at some point in their lives [161]. While this exploration has offered valuable insights into potential avenues for intervention and prevention, it is paramount to underline that the present manuscript does not aim to establish direct causal relationships between the discussed biological systems and sexual aggression. Rather, it serves as a crucial step in advancing our knowledge and awareness of these multifaceted issues.

One implication of this understanding is that it may provide a scientific basis for the development of new pharmacological treatments for sexual aggression. Research has already identified several potential targets for intervention, including the serotonergic system, the androgen system, and the HPA axis [162,163]. By targeting these systems with specific drugs, it may be possible to reduce the incidence of sexual aggression. However, further research is needed to better understand the efficacy and safety of such interventions.

Another implication is that this understanding can inform legal proceedings related to sexual aggression. For instance, if epigenetic modifications are found to be associated with sexual aggression, this information could find utility as evidentiary support in legal proceedings. A better understanding of the physiological and neurological effects of stress can offer valuable insights for the legal system's response to sexual violence-related crimes. This can include the development of more informed legal policies and interventions for offenders, as well as support and protection for victims who have experienced trauma. Such insights might contribute to more equitable sentencing and rehabilitation programs for those involved.

Furthermore, grasping the link between stress and sexual aggression may illuminate avenues for prevention. Should stress emerge as a significant contributor to sexual aggression, interventions designed to mitigate stress levels might effectively deter such behaviors. This could encompass the provision of stress-reduction techniques like mindfulness or cognitive-behavioral therapy to individuals at risk.

Lastly, understanding the role of neuromodulator systems and epigenetic modifications in sexual aggression could help diminish the stigma historically associated with this issue. Sexual aggression has often been perceived as a moral failing or character flaw. Yet,

this growing understanding suggests that sexual aggression may result from intricate physiological and psychological factors that extend beyond an individual's complete control. Recognizing the contributions of these systems enables society to approach the issue with greater compassion and knowledge.

In conclusion, the exploration of stress, neuromodulator systems, and epigenetic modifications in the context of sexual aggression has far-reaching implications for law and society. While it identifies potential targets for intervention, informs legal proceedings, supports prevention efforts, and combats stigma and victim-blaming related to sexual violence, it must be stressed that these associations are intricate and multifaceted. Continued research is vital to deepen our understanding, unravel the complexities, and develop effective interventions in the ongoing pursuit of mitigating sexual aggression and fostering a more supportive and enlightened society.

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Data availability

No data was used for the research described in this article. No data associated with this manuscript has been deposited into a publicly available repository.

CRediT authorship contribution statement

Ngala Elvis Mbiydzenyuy: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation, Conceptualization. **Sian Megan Joanna Hemmings:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Thando W. Shabangu:** Writing – review & editing, Writing – original draft, Conceptualization. **Lihle Qulu:** Writing – review & editing, Writing – original draft, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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