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FATORES GENÉTICOS ENVOLVIDOS NO COMPORTAMENTO SUICIDA

GENETIC FACTORS INVOLVED IN SUICIDAL BEHAVIOR

FACTORES GENÉTICOS IMPLICADOS EN EL COMPORTAMIENTO SUICIDA

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RESUMO

O comportamento suicida (CS) é um problema global de saúde pública, sendo o suicídio um dos principais desafios que comumente está associado a transtornos mentais e alterações neurobiológicas e genéticas. O CS já foi descrito como uma interação complexa gene-ambiente que envolve a regulação emocional, cognição e respostas ao estresse, sendo o eixo hipotálamo-hipófise-adrenal (HPA) fundamental na regulação do estresse por intermédio da liberação de hormônios como o cortisol. Objetivou-se elencar as principais associações entre o genótipo e o CS. Para isso, foram buscados artigos de acesso aberto, em inglês, publicados entre 2021 e 2024, no PubMed usando os descritores "*Suicide*", "*Depression*", "*mental disorder*" e "*genetic*". Foram identificados 405 artigos, após os critérios de exclusão 13 artigos foram selecionados. Fatores envolvidos na modulação epigenética como a metilação do DNA e variantes em polimorfismos de nucleotídeo único, amplificam a suscetibilidade ao CS, principalmente em indivíduos previamente expostos a traumas. Tais alterações impactam a neuroplasticidade e regulam a os níveis de neurotransmissores fundamentais para o equilíbrio emocional. Apesar dos avanços que indicam a predisposição genética e epigenética como fortes influências nos distúrbios do HPA que desencadeiam respostas neuroquímicas e inflamatórias que por sua vez são associadas ao CS, ainda não se tem biomarcadores genéticos definitivos para a predição do CS. Logo, genes como *NR3C1*, *FKBP5*, *CRHR1* e *SKA2*, emergem como importantes alvos para a compreensão dos mecanismos subjacentes ao CS e podem impactar no desenvolvimento de estratégias de prevenção e terapias personalizadas.

Palavras-chave: transtono mental; eixo hipotálamo-hipófise-adrenal; epigenética.

ABSTRACT

Suicidal behavior (SB) is a global public health problem, with suicide being one of the main challenges commonly associated with mental disorders and neurobiological and genetic alterations. SB has been described as a complex gene-environment interaction involving emotional regulation, cognition, and stress responses, with the hypothalamic-pituitary-adrenal axis being fundamental in stress regulation through the release of hormones such as cortisol. The objective was to list the main associations between genotype and SB. For this, open-access articles in English published between 2021 and 2024 were searched on PubMed using the descriptors "Suicide", "Depression", "mental disorder" and "genetic". A total of 405 articles were identified, and after exclusion criteria, 13 articles were selected. Factors involved in epigenetic modulation, such as DNA methylation and variants in single nucleotide polymorphisms, amplify susceptibility to SB, especially in individuals previously exposed to trauma. These alterations impact neuroplasticity and regulate levels of neurotransmitters essential for emotional balance. Despite advances indicating genetic and epigenetic predisposition as strong influences on HPA disturbances that trigger neurochemical and inflammatory responses, which in turn are associated with SB, there are still no definitive genetic biomarkers for SB prediction. Therefore, genes like NR3C1, FKBP5, CRHR1, and SKA2 emerge as important targets for understanding the mechanisms underlying SB and may impact the development of prevention strategies and personalized therapies.

Keywords: mental disorder; hypothalamic-pituitary-adrenal, axis.

RESUMEN

El comportamiento suicida (CS) es un problema global de salud pública, siendo el suicidio uno de los principales desafíos que comúnmente se asocia con trastornos mentales y alteraciones neurobiológicas y genéticas. El CS ha sido descrito como una interacción compleja gene-ambiente que implica la regulación emocional, la cognición y las respuestas al estrés, siendo el eje hipotálamo-hipófisis-adrenal

fundamental en la regulación del estrés a través de la liberación de hormonas como el cortisol. El objetivo fue enumerar las principales asociaciones entre el genotipo y el CS. Para esto, se buscaron artículos de acceso abierto, en inglés, publicados entre 2021 y 2024, en PubMed utilizando los descriptores "Suicidio", "Depresión", "trastorno mental" y "genético". Se identificaron 405 artículos, y después de los criterios de exclusión, se seleccionaron 13 artículos. Los factores involucrados en la modulación epigenética, como la metilación del ADN y las variantes en los polimorfismos de un solo nucleótido, amplifican la susceptibilidad al CS, especialmente en individuos previamente expuestos a traumas. Estas alteraciones impactan la neuroplasticidad y regulan los niveles de neurotransmisores fundamentales para el equilibrio emocional. A pesar de los avances que indican la predisposición genética y epigenética como fuertes influencias en los trastornos del HPA que desencadenan respuestas neuroquímicas e inflamatorias que a su vez están asociadas con el CS, aún no se tienen biomarcadores genéticos definitivos para la predicción del CS. Por lo tanto, genes como *NR3C1*, *FKBP5*, *CRHR1* y *SKA2* emergen como importantes objetivos para la comprensión de los mecanismos subyacentes al CS y pueden impactar en el desarrollo de estrategias de prevención y terapias personalizadas.
Palabras-clave: transtorno mental; eje hipotálamo-hipófisis-adrenal; epigentics.

INTRODUÇÃO

Among the main causes of global mortality associated with Mental Disorders (MDs), high suicide rates stand out, making it a major public health issue. According to estimates from the World Health Organization, approximately 1 million people die annually due to this outcome, representing a significant challenge for healthcare systems and prevention policies (Hernández-Díaz, Y. et al., 2021).

It is essential to emphasize the difference between suicidal ideation and suicide attempts. Suicidal ideation is related to thoughts, desires, or plans to take one's own life, usually in a transient and superficial manner, meaning a mental elaboration of suicide without necessarily progressing to action. In contrast, a suicide attempt involves the actual act of trying to take one's own life, even if, for some reason (such as external intervention or failure of the method used), death does not occur. Suicide attempts are more prevalent among women, whereas suicide mortality is higher among men. This may be associated with the fact that men often use more aggressive and lethal methods, as well as the greater association with other MDs (Hernández-Díaz, Y. et al., 2021).

From a neuroscientific perspective, the relationship between MDs and structural and functional changes in the central nervous system (CNS) is widely documented. In depression, for example, there is evidence that regions such as the frontal lobe, cingulate gyrus, and hippocampus may undergo neuroplasticity-related modifications, influencing essential cognitive processes such as decision-making, memory, and emotional regulation (Zhang, et al.,

2018). Advances in molecular biology studies have enhanced our understanding of how these changes affect brain function, contributing to the onset and persistence of clinical symptoms (Sweatt, et al., 2016).

An individual's genotype has proven to be a crucial factor in susceptibility to suicidal behavior, prompting research focused on the genomics and epigenomics of patients. Recent studies indicate that the regulation of specific genes may increase the risk of suicidal behaviors due to neuroendocrine and neurotransmitter imbalances. Genes such as NCAN and SOX5, related to schizophrenia and depression, as well as genes involved in chronic stress pathways, such as NR3C1, FKBP5, CRHR1, and SKA2, have been linked to the modulation of hypothalamic-pituitary-adrenal (HPA) axis responses, potentially influencing suicidal thoughts and, consequently, suicide attempts. Although some evidence suggests these associations, studies are still in their early stages to establish genetic biomarkers capable of predicting suicidal behaviors, whether in individuals diagnosed with mental disorders or those without a diagnosis.

A deeper study of neurobiological and genetic factors could provide support for the development of more precise diagnostic protocols and targeted therapies, reducing the global impact of suicide and improving the quality of life for individuals at risk. In this context, the objective of this review is to synthesize the main findings on the genetic basis of suicidal behavior and highlight how key gene-environment interactions affect individual vulnerability.

METODOLOGIA

The selection of articles followed the PRISMA guidelines. Searches were conducted in the PubMed electronic database using the descriptors and terms "Suicide," "Depression," "mental disorder," and "genetic," in accordance with DeCS/MeSH recommendations. The Boolean operator AND was used, and the following inclusion filters were applied: publication period between 2021 and 2024, English language, open-access articles only, and original research articles only. Other types of publications and those that did not address the central theme of this review were excluded.

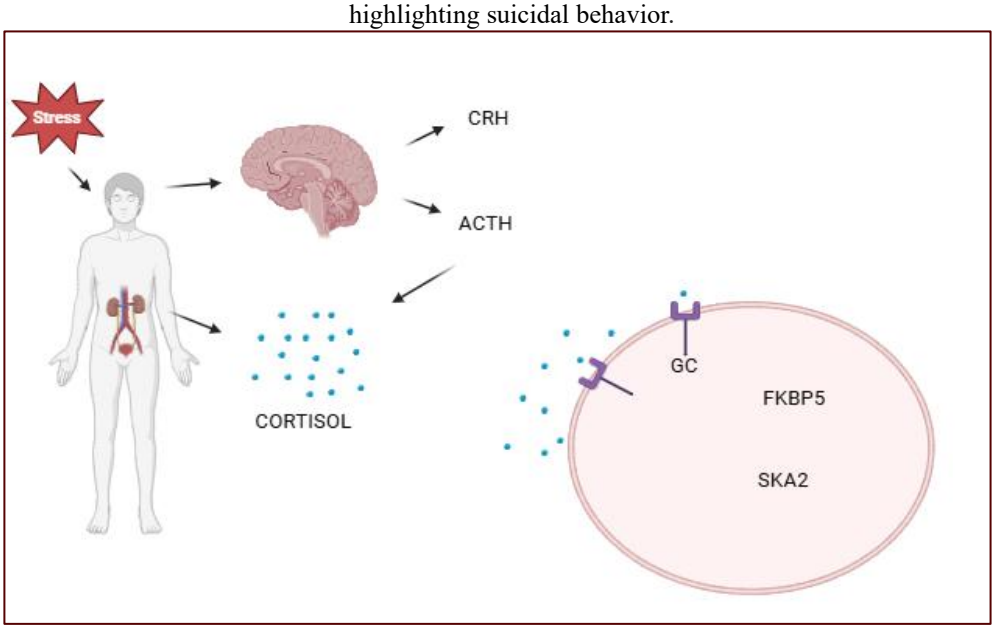
RESULTADOS E DISCUSSÃO

After searching for the defined terms in PubMed, 405 articles were identified. Of these, 392 were excluded for not meeting the inclusion criteria, while 13 articles met the established criteria and were selected for this review. Broadly, it was found that genetic predisposition can increase the risk of developing suicidal behavior (SB), regardless of mental disorders (MDs).

Under chronic stress conditions, the body activates a response mediated by the HPA axis (hypothalamic-pituitary-adrenal). This process is initiated by the action of CRH (corticotropin-releasing hormone) from the hypothalamus, considered the primary mediator of the brain's stress response. CRH stimulates the synthesis and release of ACTH (adrenocorticotropic hormone) by the pituitary gland, which, in turn, increases cortisol release from the adrenal glands (Hernández-Díaz, et al., 2021; Boscarino, et al., 2022; Hennings, et al., 2022).

Cortisol is one of the main stress hormones and plays a crucial regulatory role through a negative feedback mechanism, which inhibits the release of CRH and ACTH, helping modulate HPA axis activity. It directly affects neuroplasticity and neurotransmitters in the central nervous system, reducing BDNF levels under chronic conditions and altering glutamate, dopamine, and serotonin signaling, which can impact mood, cognition, and emotional regulation, contributing to neuronal damage. Additionally, cortisol activates various molecular mechanisms that regulate stress effects in the central nervous system, contributing to homeostasis maintenance. However, genetic and epigenetic alterations in HPA axis components may impair the effectiveness of this feedback, resulting in a dysregulated stress response and increasing vulnerability to suicidal behavior (Suh, et al., 2021; Derakhshanian, et al., 2021; Strumila, et al., 2023; Pereira, et al., 2024). These mechanisms are closely linked to stress regulation and vulnerability to suicidal behavior in predisposed individuals (Fig. 1).

Figure 1 - Image representing the HPA axis and stress pathway genes implicated in neuropathologies, highlighting suicidal behavior.



GENES ASSOCIATED WITH SUICIDAL BEHAVIOR

The activation of epigenetic factors associated with susceptibility to suicidal behavior (SB), which influence the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and its interaction with immune and inflammatory responses, can be modulated by internal or external stressors. Among the main genes associated with SB, NR3C1, FKBP5, CRHR1, and SKA2 stand out.

Due to its impact on HPA axis function and its high expression levels in patients with SB, the NR3C1 gene is one of the most strongly associated with SB. This gene encodes glucocorticoid receptors (GRs), which play a central role in regulating the HPA axis. Alterations in this gene, such as the rs6198 polymorphism, increase the expression of the GRβ isoform, which does not bind to cortisol, resulting in resistance to cortisol-mediated negative feedback and impairing HPA axis homeostasis. This mechanism contributes to the chronic dysregulation of the stress response, frequently observed in patients with SB (Amin, et al., 2022; Sanabrais-Jiménez et al., 2023). Given the crucial role of the HPA axis in stress response modulation and its interaction with emotional and cognitive circuits, studies detailing the regulatory pathways of these genes are highly relevant, as they are deeply implicated in the development of MDs and SB.

High cortisol levels in the brain can interact with the FKBP5 gene, inducing the production of the FKBP51 protein, which forms a protein complex with GRs, resulting in receptor resistance to cortisol. Methylation and SNP (single nucleotide polymorphism) polymorphisms rs1360780 and rs3800373 in the FKBP5/FKBP51 gene have been linked to an increased risk of developing SB (Zoladz, et al., 2017).

The CRHR1 gene is associated with the regulation of IL-1β levels, a pro-inflammatory cytokine, and an increased risk of SB. The CRHR1 receptor mediates the pro-inflammatory effect of CRH, promoting the release of high levels of IL-1β, which contributes to persistent HPA axis dysregulation (Miller, et al., 2018). Additionally, the rs110402 polymorphism in this gene has been linked to greater HPA axis dysregulation.

The expression of SKA2 is regulated by the transcription factors CREB and NF-κB, both essential for memory and learning processes. The SKA2 gene is expressed in the central nervous system (CNS) and plays a role in regulating GRs during stress responses mediated by the HPA axis (Xei, et al., 2019). Studies have identified a significant reduction in SKA2 expression in the prefrontal cortex of suicide victims, a region crucial for decision-making, a finding not observed in patients without SB (Pandey et al., 2016). Additionally, DNA

methylation and the SNP rs7208505 in the SKA2 gene have been associated with increased vulnerability to SB (Xei, et al., 2019).

The NR3C1, FKBP5, CRHR1, and SKA2 genes play critical roles in HPA axis regulation and are strongly associated with SB vulnerability. Genetic and epigenetic alterations in these genes impair cortisol negative feedback, dysregulate the stress response, and interact with inflammatory and neurochemical pathways, contributing to an increased risk of SB. However, further studies are needed to correlate the role of these genes with other MDs and additional SB-related pathways. Advancing the understanding of these genetic and epigenetic interactions could not only improve comprehension of the underlying mechanisms of SB but also guide the development of more effective and personalized prevention strategies and therapeutic interventions.

CONCLUSÕES

Genetic and epigenetic predisposition plays a crucial role in vulnerability to suicidal behavior, modulating the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and its interactions with inflammatory and neurochemical responses.

Genes such as NR3C1, FKBP5, CRHR1, and SKA2 emerge as key targets in understanding the molecular pathways involved in stress response and the development of suicidal behavior. These alterations compromise HPA axis homeostasis, impact emotional and cognitive regulation, and increase susceptibility in genetically predisposed individuals.

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