Review Article
http://mjiri.iums.ac.ir
Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2025 (27 Jan);39.15. https://doi.org/10.47176/mjiri.39.15

Biological Basis for the Formation of Suicidal Behavior: A Review

Roza Tatayeva[1]*, Yerbol Nurkatov[2] Lyailya Akbayeva[1], Oralbek Ilderbayev[1], Akmaral Makhanova[3], Ainash Suleimenova[1]

Received: 6 Apr 2024 Published: 27 Jan 2025

Abstract

Background: The article addresses one of the pivotal issues in the formation of suicidal behavior, namely the function of central and peripheral neurotransmitter systems and the mechanisms of neuroendocrine regulation. This article presents the relationship between alterations in lipid metabolism and suicidal behavior, as well as candidate genes of the serotonergic system involved in suicidal behavior.

Methods: The present study is a review of a number of published completed papers by systematically searching original articles in English in the following electronic databases: PubMed, SCOPUS, Mendeley, Google Scholar, and ScienceDirect between 2013 and 2023.

Results: A total of 126 sources were used in the scientific literature review, covering findings from a range of disciplines, including biology, neurochemistry, anatomy, neurohormones, and serotonergic system candidate genes relevant to suicidal behavior.

Conclusion: The identification of neurobiological indicators of suicidality is of significant importance for the understanding of the pathophysiology of suicidality and for the search for peripheral markers that could be utilized to clarify risk, prediction, and, ideally, suicide prevention. The findings of this review underscore the intricate biological underpinnings of suicidal behavior, underscoring that suicidality is not merely a psychological or social phenomenon but rather a complex and deeply rooted system of neurobiological processes. The review suggests that biological markers should be integrated with existing psychological assessments to create a multidimensional profile of suicide risk.

Keywords: Suicide, Serotonin, Cortisol, Lipid Profile, Candidate Genes

Conflicts of Interest: None declared
Funding: This research work was carried out with the support of the targeted funding program—BR18574196—Study of genetic mechanisms in the formation of suicidal behavior to develop strategies for predicting and preventing suicide, Ministry of Science and Higher Education of the Republic of Kazakhstan.

Cite this article as: Tatayeva R, Nurkatov Y, Akbayeva L, Ilderbayev O, , Makhanova A, Suleimenova A. Biological Basis for the Formation of Suicidal Behavior: A Review. *Med J Islam Repub Iran.* 2025 (27 Jan);39:15. https://doi.org/10.47176/mjiri.39.15

Introduction

The biological basis of suicidality represents a distinct area of inquiry within the field of suicidology. This area of study encompasses an array of biological mechanisms, including the functional characteristics of the brain, its mediator systems, the various links of neuroendocrine regulation involved in the stress reaction, and other biological processes that may contribute to the development of suicidal behavior. The neurobiological model of stress vul-

Corresponding author: Dr Roza Tatayeva, rktastana23@mail.ru

1. Department of General Biology and Genomics, L.N. Gumilyov Eurasian National University, Astana , Kazakhstan
2. Department of Health and Wellness Center, Nazarbayev University, Astana, Kazakhstan
3. Medical University of Karaganda, Karaganda, Kazakhstan

↑What is "already known" in this topic:
While discussing biological factors and pathophysiological mechanisms of suicidal behavior, processes in the central nervous system were analyzed. As evidenced by numerous data, various peripheral processes are involved in pathological chains - the metabolic systems of the body (in particular, peripheral serotonin, tryptophan, neurokynurenines, etc.).

→What this article adds:
This review article examines the stress response that affects the entire body and physiological processes responsible for the formation of suicidal behavior, including serotonin system candidate genes, lipid metabolism, neurohormonal responses, as well as components of inflammation - the gut-brain axis to elucidate the risk, prediction and prevention of suicide.

[DOI: 10.47176/mjiri.39.15]

nerability is currently the most developed in modern suicidology. This model is supported by studies that have primarily focused on the neurotransmitter systems of the central nervous system and the central mechanisms of neuroendocrine regulation (1).

Death by suicide is a complex behavioral phenomenon influenced by a combination of inherited traits and environmental factors. Suicide is a behavioral event that reflects a complex heritable phenotype with diverse clinical and environmental risk factors. Annually, approximately 703,000 individuals worldwide die by suicide (2). As indicated in the 2021 World Health Organization report, Kazakhstan is among the countries with the highest suicide rates globally, ranking 20th (3). Indeed, the actual figures are likely to be considerably higher, given that a significant proportion of suicides are recorded as deaths from other causes, including cardiovascular disease, road accidents, accidents, and accidental poisoning. The presented statistics on completed suicides only partially reflect the true extent of the problem. The ratio of completed suicides, suicide attempts, and trends is approximately 1:10:100 on average. In the Republic of Kazakhstan, 4,500 individuals attempted suicide in 2021, and 3,700 individuals attempted suicide in 2022. Consequently, suicide is regarded as a significant public health concern, prompting a comprehensive review of the existing scientific literature to elucidate its underlying neurobiological mechanisms.

The stress diathesis theory of suicide posits that there are predisposing and provoking risk factors for suicide attempts. Genetics, inflammation, serotonergic systems, peripheral biomarkers such as cholesterol, and changes in the hypothalamic-pituitary-adrenal (HPA) axis may be involved in the biological diathesis of suicidal behavior (4-6).

There are numerous models that differ in their emphasis on the role of psychological factors. Nevertheless, a significant number of models place considerable emphasis on the role of psychological, social, psychiatric, and neurobiological factors in predicting suicide risk (7). The stress-diathesis component, which posits that suicidal behavior results from the interaction of acute stressful events and a predisposition to suicidal behavior (diathesis), is central to many of these models.

It is of significant interest to examine the processes associated with suicidal behavior (or mental disorders that are important risk factors for suicide) in this context. This may include an examination of the peripheral link of neurotransmitter systems, such as serotonergic and noradrenergic, the role of cholesterol and other lipids, the role of the immune system in general and inflammation in particular, the state of the neurohumoral stress response system and other body systems, as well as their genetic base. The appeal of research in this domain lies not only in the pursuit of a deeper understanding of the underlying mechanisms of suicidal behavior but also in the potential for identifying sensitive and readily assessable peripheral markers (potentially predictive) of suicide. The identification of such peripheral biomarkers, for example, at the level of psychophysiological reactions or suicide-associated genetic polymorphisms (or their combinations), could provide a significant supplement and clarification to the existing psychological instruments, suicide risk questionnaires, and assessment scales, the number of which is constantly growing. However, the predictive value of these instruments is believed to remain low, as previously stated (8).

Concurrently, the examination of the most investigated biological factors associated with suicide encompasses disorders of neurotransmitter processes, the hypothalamic-pituitary-adrenal axis (HPA), trophic factors, lipid metabolism, neuroimaging, and postmortem morphology of the brain. In conclusion, research into genetic markers of suicidal behavior is becoming increasingly important, which is beyond the scope of this review.

The role of the hypothalamic-pituitary-adrenal (HPA) axis in suicidal behavior is a topic of considerable research interest, with a substantial body of evidence emerging from various studies (9-11). Moreover, there is a suggestion that the hypothalamic-pituitary-thyroid (HPT) and hypothalamic-pituitary-gonadal (HPG) axes may also play a role in suicidal behavior. Furthermore, the potential correlation between suicidal behavior and alterations in neuropeptide levels is a topic of investigation (11).

The goal of the review is to clarify the role of candidate genes, changes in neuropeptide levels, lipid metabolism, and hormones in the formation of suicidal behavior.

Methods

Search strategy

The literature was collected in the PubMed, SCOPUS, Mendeley, Google Scholar, and ScienceDirect databases to identify pertinent studies published between 2013 and 2023. A systematic review was conducted through a comprehensive search of the literature in the PubMed, SCOPUS, Mendeley, Google Scholar, and ScienceDirect databases, with the objective of identifying relevant studies published from 2013 to 2023. The following keywords were included in the search: "suicide," "hypothalamic-pituitary-adrenal axis," "neurotransmitters," "hormones," "serotonin," "cortisol," "lipid profile," and "hypothalamic-pituitary-thyroid axis," "candidate genes." In addition, MeSH terms, truncation, wildcards, and proximity operators were used to refine the search. A total of 1123 articles were initially identified for review. Following the application of the inclusion and exclusion criteria, 165 articles were subjected to assessment, with 126 ultimately included in the final analysis. The methods summary did not provide detailed information about the specific study participants or groups. However, the studies included different groups according to the various neurobiological factors of suicidality under investigation.

This approach allowed us to minimize subjectivity and increase the reliability of article selection. A standard checklist such as the PRISMAA standard checklist and the PRISMA standard checklist should be used for transparency. These checklists help assess the quality of the included studies, identify potential sources of bias, and assess the reliability of the results (Figure 1).

[DOI: 10.47176/mjiri.39.15]

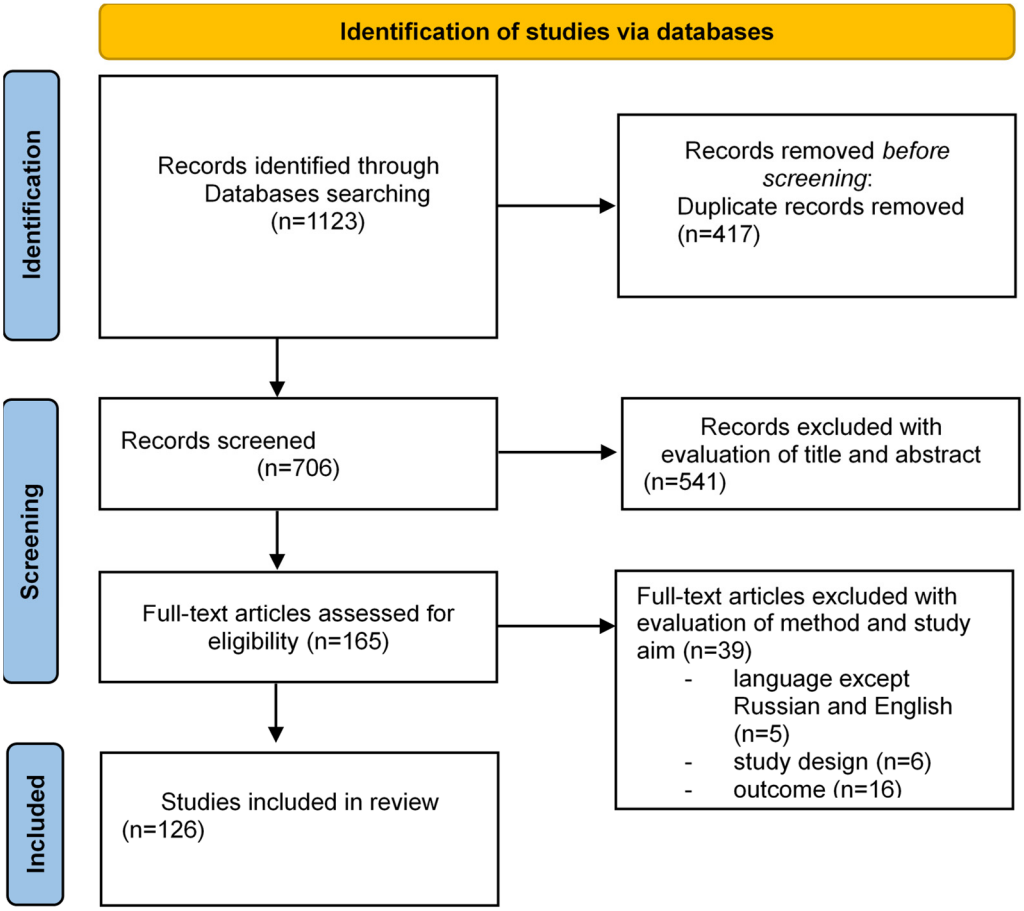

Figure 1. PRISMA flow chart of the studio selection process

One thousand one hundred twenty-three articles were found by searching the databases. As a result, 126 articles were used. The review includes articles that meet the following criteria: 1) full-text articles, 2) English-language articles and, 3) Russian articles, 4) suicide-related articles. Exclusion criteria were writing, conference proceedings, comments, debates, and editorials. The initial search strategy yielded 1123 published articles that were selected for possible inclusion in the review. A total of 165 full-text articles were assessed for eligibility, 126 of which were included in the review. The final list of articles was reviewed by two independent authors using full-text articles. In the case of disagreement, they reached a consensus during the discussion.

The hypothalamic-pituitary-adrenal (HPA) axis

The hypothalamic-pituitary-adrenal (HPA) axis represents the most crucial element in the human response to stress. It has been demonstrated that the corticotropin-releasing hormone (CRH) and vasopressin hormones, when acting in concert, stimulate the corticotropic cells of the anterior pituitary gland, thereby triggering the release of adrenocorticotropic hormone (ACTH). ACTH stimulates the synthesis of cortisol, which regulates vegetative, cognitive, and behavioral reactions in response to stress. In the process of inhibiting the stress response, the inhibition occurs in the following order: CRH, then ACTH. CRH, a neuropeptide comprising 41 amino acids and two G-protein-linked proteins, is a hormone of the HPA axis that plays a pivotal role in regulating this axis. Elevated CRH levels in the limbic system over an extended period of time have been linked to the development of stress and depressive disorders. Elevated CRH levels have been observed in the hypothalamus of individuals who have committed suicide (12).

Another hormone that plays a role in the HPA axis is cortisol, which is secreted by the adrenal cortex. It is established that the HPA axis is activated in response to stress, resulting in the release of cortisol from the adrenal glands. Once released, cortisol fulfills several crucial functions, including enhancing access to energy reserves, accelerating the mobilization of proteins and fats, and regulating the intensity and duration of inflammatory responses. The HPA axis has been demonstrated to demonstrate circadian oscillations, thereby establishing a link between glucocorticoid synthesis and diurnal patterns. Consequently, in humans, serum cortisol concentrations exhibit a diurnal rhythm, with peak levels occurring in the morning and lowest levels at night. The HPA axis is the primary stress response system responsible for the adaptive component of the stress response, which attempts to

[DOI: 10.47176/mjiri.39.15]

restore homeostasis. Dysregulation of the stress response has been linked to a wide range of pathologies, including autoimmune diseases, hypertension, mood disorders, and major depression (13). There is evidence to suggest that childhood trauma is associated with dysregulation of the cortisol stress response in adulthood.

The present study was the inaugural investigation to ascertain whether childhood trauma, daily stressors, and emotional states were correlated with daily cortisol levels over a seven-day period in individuals at elevated risk for suicidal behavior (14).

Cortisol has been the subject of study in patients who have attempted suicide, and in some studies, its increase has been associated with either an increase or decrease in HPA axis activity. In a study of 35 patients and 16 healthy controls who had attempted suicide, the patients exhibited lower evening salivary cortisol levels than the controls. Additionally, low cortisol levels were found to be correlated with the severity of psychiatric symptoms. Suicidal levels of cortisol have been identified in individuals with bipolar disorder who have attempted suicide, as evidenced by elevated cortisol levels in nighttime saliva. Cortisol levels are increased in individuals who attempt suicide, and higher cortisol concentrations in plasma regard to depression and more attempts of suicide (15).

Adrián Alacreu-Crespo and Emilie Olié (2020) also posit that the dexamethasone suppression test (DST), which demonstrates an increase in HPA axis activity in the absence of suppression, may serve as a biological marker of suicidal behavior (16). Additionally, T. Beauchaine et al. (17) investigated the cortisol levels following the dexamethasone test in female patients aged 13-17 years. They observed a deviation from the normal range in patients with suicidal ideation and a history of self-harm.

The hypercortisolemia resulting from increased HPA axis activity has been demonstrated to reduce glucose entry into the brain while also inhibiting the function of serotonin and glutamate receptors in the hippocampus. This has been demonstrated to enhance its toxicity and suppress the expression of brain-derived neurotrophic factor (BDNF), which is also a glucocorticoid receptor. It has been documented that elevated cortisol levels resulting from CRH and ACTH resistance are unable to suppress CRH, leading to a continued increase in HPA axis activity. The ambiguous role of cortisol in suicidal behavior may be attributed to the fact that glucocorticoid receptors are expressed throughout the body, yet there is considerable heterogeneity in glucocorticoid sensitivity and biological responses across tissues. The prevailing notion that glucocorticoids exert their effects through a single GR protein has been challenged and significantly revised in light of the discovery of a diverse array of receptor isoforms (18). Furthermore, post-translational modifications of these GR isoforms contribute to the expansion of the potential for heterogeneity in glucocorticoid signaling.

In light of the disparate findings, O'Connor and colleagues (2016) undertook a meta-analysis of all extant studies that compared participants with at least one previous suicide attempt with a comparison group with no history of suicide attempts (19). A total of 27 studies (n=2226; 779 suicides and 1447 suicide attempts) were identified that met the inclusion criteria. In general, no notable impact of the suicide group on cortisol levels was discerned. Nevertheless, a notable correlation between cortisol levels and suicide attempts was discerned across all age groups. In studies where the mean sample age was below 40 years, the association was positive (i.e., higher cortisol levels were associated with suicide attempts; $r = 0.234$, $P<0.001$). In contrast, in studies where the mean age was 40 years or above, the association was negative (i.e., lower cortisol levels were associated with suicide attempts). The authors thus concluded that the meta-analytic results support the hypothesis that HPA axis activity, as indicated by age-related changes in natural cortisol levels, is associated with suicide attempts.

Another study (20) revealed elevated cortisol levels in the suicide attempt group when compared to healthy controls ($F=7.26$, $P=0.008$). However, no statistical differences were observed between the suicide attempt group and the psychiatric disorders group ($P=0.22$). The data revealed elevated cortisol levels in individuals diagnosed with depression ($P=0.004$) and in individuals with two or more documented suicide attempts ($P<0.001$).

Therefore, the relationship between HPA axis status and suicidality can be defined as follows: this system mediates the effects of stressful stimuli, thereby forming a specific background for the development of suicidality. Stress and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, as indicated by cortisol levels, represent significant additional risk factors for suicide.

Serotoninergic neurotransmitter system

The serotonergic neurotransmitter system, which is frequently linked to suicidality in scientific literature, merits particular attention. It plays a pivotal role in regulating a multitude of social behaviors, neuroendocrine rhythms, sleep patterns, cognitive functions, and emotions. In light of the conflicting findings in the scientific literature (21), there is a prevailing view that depression, mania, and anxiety are associated with a reduction in serotonin bioavailability in the central nervous system (22). The results of numerous studies employing diverse methodologies, including autopsy and in vivo techniques, indicate disruptions in the serotonin neurotransmitter system and the stress response system of the hypothalamic-pituitary-adrenal axis in individuals with a predisposition to suicidal behavior. These disturbances manifest as impaired cognitive control of mood, pessimism, reactive aggression, impaired problem-solving abilities, an exaggerated response to negative social cues, excessive emotional distress, and suicidal ideation, which may ultimately result in suicidal behavior (23).

Neurobiological risk factors for suicidal behavior were evaluated, which will play an important role in suicide prevention, as well as in the regulation of treatment algorithms and in the follow-up of treatment (24). The serotonin system of the PFC is closely associated with analogous neurons in the brainstem, particularly in the pons and the raphe nuclei (caudal and dorsal). In this nucleus, an in-

[DOI: 10.47176/mjiri.39.15]

crease in the activity of tryptophan hydroxylase (a regulated enzyme of 5-HT biosynthesis) and an increase in the number of 5-HT1A autoreceptors are observed in individuals who have committed suicide (25). Serotonin (5-hydroxytryptamine, 5-HT) is a biogenic amine that acts as a neurotransmitter in the nervous system. Additionally, this molecule functions as a hormone. In the brains of vertebrates, the cell bodies of serotonergic neurons are located in the wall of the third ventricle and in the ancient brainstem, where they constitute the so-called raphe nuclei. Their processes innervate extensive regions of the central nervous system (CNS) (26).

The current study investigated the effects of a six-week multimodal rehabilitation stay on the KYN pathways and their association with treatment response (responder versus non-responder). Observable changes in these pathways were found in both groups over time. These findings implicate a necessity to clarify the relevance of the KYN pathways and the related inflammatory processes in the etiopathology of depression. Specifically, their changeability through multimodal interventions, which are the common treatment option for depression, should gain more interest in research. Investigating the amount of treatment time needed to elicit changes in the biological underpinnings of depression could lead to better clinical management and more effective treatment interventions (27, 28). It has been demonstrated that approximately 90% of the TRP ingested by humans is converted to kynurenine for subsequent metabolism, a process designated as the kynurenine pathway ("KP"). The remaining TRP is metabolized to serotonin and indole (29). Concomitantly, the dysregulation of TRP metabolites, including serotonin, quinolinic acid (QUIN), and kynurenic acid (KYNA), has been associated with depressive behavior in both animal models and humans. Consequently, dietary TRPs are degraded via three principal pathways: the serotonin pathway, which involves the conversion of tryptophan hydroxylase-1; the tryptophan-indole pathway, which acts on aromatic hydrocarbon receptors and comprises four subpathways; and the KP pathway, which involves the conversion of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) (30).

The dysfunction of kynurenine metabolism represents a potential mechanism of depression, linking two prominent etiological hypotheses within the field: the "cytokine hypothesis" and the "receptor hypothesis." The primary mechanism may be the excessive activation of indoleamine 2,3-dioxygenase in the entire body and in the brain due to chronic inflammation. This results in an increase in the rate of kynurenine metabolism, which ultimately leads to an accumulation of quinolinic acid (QUIN) and a reduction in kynurenic acid (KYNA) in the brain. The neurotoxic effects of QUIN impact glial cells and neurons, contributing to the development of inflammation-induced depression (31).

The most socially significant aspect is the role of serotonin in psychological disorders in humans. The evolution of theories concerning the role of biogenic amines in the pathophysiology of mental disorders has led to a consensus that depression, mania, and anxiety states are associated with decreased bioavailability of serotonin in the central nervous system (32, 33).

Data are provided on a decrease in the level of the main serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the brain tissue of suicides, and in those who have attempted suicide, a reduced level of 5-HIAA in the cerebrospinal fluid (CSF) (34-36).

Despite the abundance of data on serotonergic system disturbances in suicidality, the question of whether this is a characteristic of the "suicidal brain" or a reaction of the normal brain to external stress factors that cause a decrease in serotonin levels remains unresolved (37).

Genes associated with the function of the serotonergic system

The majority of these disturbances are associated with a genetically determined trait that is inherent in individuals who engage in suicidal behaviors. Given the unusually wide gene diversity observed in the human population, it is plausible that there may be individuals with an initially reduced level of brain serotonin (38). This may be attributed to certain gene polymorphisms that result in the synthesis of kynurenines from tryptophan derived from food instead of serotonin, a reduction in the formation of tryptophan hydroxylase-2, which synthesizes brain serotonin from its precursor, or an elevated level of the MAO-A enzyme, which metabolizes serotonin, among other factors (39).

Genetic variations in the serotonergic system, including single nucleotide polymorphisms (SNPs), variable number tandem repeats (VNTRs), and alleles, have been demonstrated to be strongly associated with aggressive and suicidal behavior. In particular, variations in tryptophan hydroxylase (TPH), serotonin transporter (5-HTT), serotonergic receptors, and monoamine oxidase (MAOA) have been demonstrated to influence these behaviors. The application of genome-wide association studies (GWAS) has significantly enhanced our comprehension of the genetic underpinnings of psychiatric disorders. Large-scale studies have demonstrated that these conditions are influenced by a multitude of common genetic variations, with each variation contributing a relatively minor risk factor (40). Moreover, it has become evident that numerous genes exert influence over a multitude of psychiatric disorders, underscoring the intricate and intertwined genetic underpinnings of these conditions (41).

Twin studies have demonstrated a substantial genetic influence on the risk of suicidal behavior. A meta-analysis conducted by Lopes and colleagues (2019) revealed a significantly higher concordance for completed suicide in identical than in fraternal twin pairs. The heritability of suicide among twins has been estimated to range from 21% to 50% (42).

The investigation of key candidate genes includes the study of genes encoding the serotonin transporter, serotonin receptors (5-HT2A, 5-HT1A, 5-HT1B), tryptophan hydroxylases I and II, and monoamine oxidase A (43). Furthermore, gene-environment interactions, particularly in the context of stressful events, have been identified as a

[DOI: 10.47176/mjiri.39.15]

significant risk factor for suicidal behavior (44). Dysfunctions of the serotonergic system have been repeatedly linked to a range of psychiatric disorders, including depression, anxiety, aggression, and suicidality (45-47).

Postmortem analyses of individuals who committed suicide and suffered from depression have revealed a reduction in the number of serotonin transporters in various brain regions, including the prefrontal cortex, hypothalamus, occipital cortex, and brainstem (48).

The study by Xiang, Chunchen et al. (2019) underscores the association between specific genetic variations, including A128C in TPH1, A138G in 5-HT2A, and type L in the VNTR of MAOA, and both aggression and suicide (49).

The TPH1 gene is primarily expressed in peripheral tissues, particularly in enterochromaffin cells of the gastrointestinal tract, where it plays a crucial role in the synthesis of peripheral serotonin. This is in contrast to TPH2, which is predominantly active in the central nervous system (50). Serotonin has been demonstrated to enhance the activation of immune cells that respond to tissue damage (51, 52). The study by González-Castro (2022) also confirmed a significant association between TPH-1 gene polymorphisms (A218C and A779C) and suicidal behavior (SB) in fixed effects models, indicating a potential risk of SB manifestation at the clinical level. No significant association was identified between SB and TPH-2 gene polymorphisms (G-703T, A-473T, and G19918A) (53, 54). The A218C polymorphism has been demonstrated to exert influence over several phenotypic traits, a phenomenon that can be attributed to a pleiotropic effect whereby there is a propensity towards anger and the capacity to regulate its outward expression. The TPH1 A218C gene variant and recent stressful life events were found to be independently associated with suicide attempts in Serbian psychiatric patients (55).

The A allele of the TPH1 rs1800532 and rs1799913 polymorphisms may result in alterations to TPH1 activity, which subsequently impacts serotonin synthesis (56).

A reduction in serotonin levels may contribute to a reduction in gray matter volume, particularly in regions associated with emotional regulation and cognitive functions, such as the precentral and postcentral gyri. These changes may precipitate suicidal ideation and behavior, which elucidates the observed correlation between diminished gray matter volume and the presence of the A allele of these polymorphisms in patients with depressive disorder and suicide attempts. Some studies have demonstrated that the genetic marker TPH2 rs4641528 C is associated with an increased susceptibility to post-stroke depression (PSD) among Korean patients (57). The rs4641528 C polymorphism has the potential to either enhance or weaken the activity of tryptophan hydroxylase-2, which in turn affects the availability of serotonin in the brain.

Another polymorphism, rs7305115, of the TPH-2 gene was found to be associated with an elevated risk of suicidal behavior in the Mexican population. Additionally, specific haplotypes (combinations of genetic variants) of the TPH-2 gene have been linked to an elevated risk of suicide attempts (58).

The A-1438G (rs6311), T102C (rs6313), and His452Tyr (rs6314) polymorphisms of the 5HT2A gene have attracted the greatest attention in the context of suicidal behavior. Prior research has examined all single-nucleotide polymorphisms (SNPs) within the gene (59). The 5-HT2A gene 102C/C genotype has been linked to an elevated risk of suicidal behavior. It has been demonstrated that individuals with the 102 C/C genotype have experienced a considerable number of stressful events and losses throughout their lives. Conversely, the A1438G and C1354T polymorphisms in this gene did not demonstrate a statistically significant association with the risk of suicide or the number of stressful events and losses (60). Conversely, the authors M. Li have posited that this polymorphism is not associated with suicidal behavior in adult women with depression (61).

The relationship between suicidal behavior and genetic predisposition has been extensively investigated, as has the influence of childhood abuse on future mental health. For example, one study identified a potential interaction between the HTR2A gene and a history of childhood abuse. Individuals with the A/A or A/G genotypes exhibited a markedly elevated incidence of suicide attempts relative to those with the G/G genotype. However, this disparity was exclusively observed among those who had endured childhood abuse (62).

A systematic review by González-Castro (63) revealed a significant interaction effect between HPA axis genes and traumatic events on suicidal behavior. The majority of the included studies demonstrated a positive correlation between trauma exposure and suicidal behavior, emphasizing the necessity of early diagnosis and intervention to prevent suicidal outcomes in vulnerable individuals. Gene-environment interactions, particularly for CRHR1, CRHR2, and FKBP5, indicate that genetic factors may modify the body's response to stress, thereby enhancing suicidal tendencies. However, no significant results were observed for the CRH, NR3C1, MC2R, and POMC genes in terms of gene-environment interactions. This indicates a need for further research to elucidate their role in the mechanisms underlying the development of suicidal behavior. Another gene of note is MAOA (monoamine oxidase A), which encodes an enzyme involved in the metabolism of neurotransmitters such as serotonin, dopamine, and norepinephrine and is primarily localized in the catecholaminergic cells of the central nervous system. Monoamine oxidase A (MAOA) plays a pivotal role in regulating the levels of these monoamines by breaking them down, thereby controlling their concentration in the central nervous system (CNS) (64). MAOA plays a pivotal role in maintaining neurochemical equilibrium, which is essential for optimal brain function. An incorrect breakdown of monoamines can result in either an excess or deficiency of these substances, which is associated with psychopathological conditions.

MAOA polymorphisms, particularly those associated with low enzyme activity, may impair the body's capacity to regulate neurotransmitter levels, such as those of serotonin and dopamine. This may render individuals more susceptible to aggressive responses to stressful or traumatic events (65).

[DOI: 10.47176/mjiri.39.15]

In a study of women with affective disorder who had previously attempted violent suicide, an elevated level of the AA genotype for the rs5906957 single nucleotide polymorphism of the MAOA gene was observed in comparison to the control group (66).

The findings of the Balestri M study indicate that the A allele of the MAOA gene rs6323 is linked to heightened harm avoidance in female suicides, while the A allele of the MAOB gene rs2205655 is associated with elevated levels of cooperativeness in healthy women. In male suicides, the A allele of the MAOA gene rs909525 has been linked to an increased tendency toward reward dependence. These genes may exert an influence on personality traits that are associated with suicidal behavior (67).

The study conducted by Murdoch JD revealed a notable global diversity of the SLC6A4 gene, encompassing a range of repeat variants and single nucleotide polymorphisms in its vicinity. Significant SNPs, including rs25531, rs25532, and rs6355, are associated with specific haplotypes and exhibit geographic variation. It is imperative to consider the ethnic specificity and diversity of polymorphisms in the SLC6A4 gene when conducting association studies, as this will facilitate a more accurate understanding of their role in serotonin-related biological processes (68).

It is crucial to acknowledge the discrepancies in study design, inclusion criteria, and data analysis techniques highlighted in this review, which have resulted in conflicting findings.

Therefore, the genes of the serotonergic system represent a promising avenue for therapeutic intervention. Strategies aimed at increasing or enhancing their signaling may prove beneficial in the development of new, effective treatments for mental disorders.

Hypothalamic-pituitary-thyroid axis.

The HPT axis may be involved in the pathophysiology of suicide. It is another hormonal system that is secreted by the hypothalamus. Thyrotropin-releasing hormone (TRH) is released from the anterior pituitary gland via the pituitary portal circulation, which stimulates the release of the pituitary hormone thyroid stimulating hormone (TSH). TSH then stimulates the production of thyroxine (T4) and triiodothyronine (T3) from the thyroid gland. Additionally, T4 can be converted to T3 through a process known as deiodination, which occurs in surrounding tissues. There is evidence to suggest that the HPT axis may play a role in the pathophysiology of suicide (69). In the context of thyroid disease, the primary effects of this condition include fatigue, depression, and suicidal ideation. Secondly, some psychiatric symptoms, such as a tendency towards subclinical hypothyroidism, were observed in patients who did not respond to antidepressant treatment. Some patients with depression demonstrated an inadequate TSH response to TRH. These circumstances facilitated the investigation of the HPT axis in individuals exhibiting suicidal behavior. Thyroid function test measurement may be used as discriminative cut-offs between suicide attempts and healthy subjects. None of the thyroid hormones indicated future suicide attempts. FT4, TSH, and lower FT3/FT4 levels are independently associated with suicide attempts. FT4 may be a useful marker to predict current suicide attempts (70).

The activity of the HPT axis in individuals attempting suicide showed changes in most patients. Various theories have been proposed to explain the pathophysiology. One such theory is that HPT axis dysfunction develops to balance the reduced central 5-HT neurotransmission that develops in the axis. Another theory is that TRH increases serotonin transmission via 5-HT1 receptors (71).

Hypothalamic pituitary gonadal axis.

The HPG axis is a complex system that plays a pivotal role in the development of primary and secondary sexual characteristics and reproduction in humans. In addition to their physical effects, the hormones of the HPG axis also influence mood and behavior in humans. Along with the postpartum period, perimenopause is a “window of vulnerability” for depression development because a decline in estrogen level accounts for the extinction of reproductive function, emotional disorders, and genitourinary menopausal syndrome, which are combined with non-endocrine risk factors, such as decreasing income levels, low social support, and stress (72).

Testosterone has been identified as a contributing factor in the etiology of suicidal behavior in both men and women with bipolar disorder and other psychiatric conditions. The effects of testosterone on psychological traits are complex. It affects mood and behavior, including social interactions. Testosterone plays a regulatory role in both proactive and reactive aspects of aggression. It seems plausible that both elevated and depressed testosterone levels may contribute to the neurobiology of suicide in different patient groups (73).

In patients who have attempted suicide, studies have been conducted to elucidate the pathophysiology of suicide about HPG axis hormones, with variable results. A reduction in follicular stimulating hormone (FSH) levels has been observed in female patients with suicidal ideation and a history of suicide attempts, particularly in those under the age of 45 (74).

Another study has indicated that suicide attempts are more prevalent during the follicular phase of the menstrual cycle when follicle-stimulating hormone (FSH) levels are at their lowest (75).

By regulating intracellular calcium levels, serotonin stimulates the release of GnRH. In light of the aforementioned information, it was concluded that serotonergic dysfunction observed in depressed patients may result in decreased FSH levels by affecting the HPG axis.

The effect of testosterone on suicidal behavior is a topic of ongoing debate in the scientific community. Testosterone levels may predict suicidal behavior in women with bipolar disorder (76).

The number of major depressive episodes, the maximum lethality of suicide attempts, and the testosterone levels were higher in men compared to women. Current suicidal ideation scores were higher in women compared to men (77).

Lipid profile and suicidal behavior

[DOI: 10.47176/mjiri.39.15]

A significant number of authors have identified a correlation between blood cholesterol levels and suicidal behavior in humans (78-81). A study of a large sample of patients revealed a three- to four-fold decrease in cholesterol levels among those who had committed suicide compared to the control group (82). These findings suggest that differential consideration of serum total cholesterol levels according to age group may have clinical utility for predicting suicidality in patients with depressive disorders. However, because research participants came from a single hospital, the generalizability of findings may be limited (83). A retrospective study conducted by Japanese scientists on a cohort of patients who had committed suicide revealed that the risk of suicide increased in conjunction with a decline in cholesterol levels over a three-year period preceding the event. In this study, a decrease in average cholesterol by 0.5 mmol/L was associated with an 18% increase in the risk of suicide (84).

A correlation has been identified between low cholesterol and an increased risk of memory loss, cognitive impairment, mood disorders, and suicidal behavior (85).

A reduction in cholesterol levels may result in the alteration of synapses, as proposed by (86), which could potentially contribute to suicidal behavior.

Nevertheless, it is conceivable that the reduction in peripheral cholesterol in humans occurs concurrently with alterations in cholesterol in diverse synaptic lipid rafts in neurons (via a shared regulatory mechanism).

As previously stated, the neurotransmitter serotonin plays a pivotal role in inhibiting aggressive behavior within the central nervous system. Currently, a hypothesis posits a correlation between serum cholesterol levels and the reduction of serotonergic activity in the brain. Consequently, in a study, monkeys with experimentally reduced cholesterol levels exhibited higher concentrations of serotonin metabolites than monkeys fed a high-cholesterol diet. A reduction in serotonergic communication activity results in the manifestation of instinctive reactions and violent suicidal behavior (87). The aforementioned "cholesterol-serotonin" theory is also supported by evidence indicating that a deficiency of total cholesterol can lead to central neuroinflammation, which in turn affects the serotonergic system and increases aggressiveness and impulsivity. A total of 65 studies, comprising 510,392 participants, were included in the analysis. In comparison to non-suicidal patients, those who had suicidal ideation exhibited significantly reduced serum TC levels. Furthermore, when suicidal patients were compared to healthy controls, a significant difference was observed in TC, HDL-C, and LDL-C levels between the two groups (88).

Abnormalities in PUFA status have been linked to an increased risk of developing neuropsychiatric disorders, including major depression, bipolar disorder, schizophrenia, Alzheimer's disease, and attention deficit hyperactivity disorder. Pathophysiological mechanisms may include not only suboptimal PUFA intake but also metabolic and genetic abnormalities, defective liver metabolism, and diffusion and transport problems. A reduction in cholesterol levels results in an elevated n-6:n-3 PUFA ratio, thereby promoting neuroinflammation since n-3 PUFAs exhibit anti-inflammatory properties, while n-6 PUFA levels exhibit proinflammatory activity and disinhibit the two inflammatory processes. Some researchers posit that abnormal monoaminergic neurotransmission, in conjunction with neuroinflammation, represents the primary biological factors underlying suicidal behavior (89).

An intriguing hypothesis has recently been proposed by researchers suggesting a potential link between the well-documented process of cholesterol metabolism and the neurobiological underpinnings of suicide risk through the capacity to remove cholesterol specific to ABCA1 (90). It has been demonstrated that cholesterol-lowering drugs may exert an antidepressant effect through anti-inflammatory pathways (91). Individuals who had attempted suicide within the previous month exhibited significantly reduced triglyceride (TG) levels and elevated high-density lipoprotein cholesterol (HDL-C) levels compared to those who had never attempted suicide (92). Regarding the variety of depressive symptoms, no significant differences were observed in plasma lipid levels between subjects exhibiting mild, moderate, and severe depressive symptoms.

It has been demonstrated that in patients with depression, a cholesterol level in the blood plasma of less than 3.47 mmol/l may indicate an increased risk of suicidal behavior (93). A study conducted by Belarusian scientists indicated that the lowest levels of total cholesterol (TC) in the blood serum were observed in men who utilized "highly lethal" methods of self-harm (94). In a subsequent investigation into the hormonal and metabolic profiles of individuals who had attempted suicide, the same research team observed lower levels of TC and LDL in the blood serum, irrespective of gender (95). However, Turkish scientists, in their study of women who had attempted suicide, reached the conclusion that the levels of TC, LDL, and TG were significantly lower in the group that had attempted suicide, while the level of HDL was significantly higher (96).

It is believed (97) that clinicians pay attention to a decrease in total cholesterol (TC) below 4.5 mmol/L and to the emotional state of patients with such levels of TC. New hypotheses regarding the neurochemical mechanisms underlying the effects of cholesterol on impulsivity and aggression, associated with the modulation of neurosteroid and brain-derived neurotrophic factor (BDNF) metabolism, appear to be emerging (98).

Although the majority of researchers concur that low cholesterol levels are associated with suicidal behavior, there are studies that have identified a correlation between high cholesterol levels and suicidal tendencies. In a Japanese study comprising a substantial number of participants, it was observed that women with elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) exhibited an elevated risk of suicidal behavior (99). In addition, several studies have failed to identify a correlation between suicidal behavior and cholesterol levels (100).

This study demonstrated that in comparison to non-suicide attempters, suicide attempters in young patients with major depressive disorder exhibited elevated levels of fasting blood glucose (FBG), total cholesterol (TC), and low-

[DOI: 10.47176/mjiri.39.15]

density lipoprotein cholesterol (LDL-C) (all $P<0.05$), while displaying reduced levels of high-density lipoprotein cholesterol (HDL-C) ($P<0.001$). Subsequent logistic regression analysis indicated that suicide attempts were associated with elevated FBG, reduced HDL-C, disease course, HAMD scores, and overt anxiety (101).

The literature suggests an association between individuals with lower cholesterol levels and suicidal behavior. This may be caused by changes that induce failures in synaptic transmission or because low cholesterol levels seem to induce an inflammatory response in the nervous system. Additionally, lower serum cholesterol levels have been associated with violent methods used in suicide attempts. The presence of the ApoE4 allele, which has been associated with less cholesterol redistribution in the central nervous system, should also be considered due to the mechanisms already described. Therefore, more research is needed to understand the mechanism that associates serum cholesterol levels and suicidal behavior. In addition, research on how serum cholesterol affects CNS cholesterol metabolism should be conducted to fully establish the role of cholesterol in suicidal behavior (102).

Therefore, the role of cholesterol in the development of suicidal behavior in humans appears to be an interesting research question and maybe a promising direction in the study of this problem.

Conclusion

The hypothalamic-pituitary-adrenal (HPA) axis plays a pivotal role in the regulation of stress responses. The interaction of the hypothalamus, pituitary gland, and effector endocrine glands is carried out with the participation of numerous peptide factors, the most significant of which are corticotropin-releasing factor, adrenocorticotropic hormone, and cortisol.

The relationship between the function of the HPA axis and the propensity for suicidal behavior can be understood by considering the role of this system in mediating the impact of stress stimuli, thereby establishing a potential background for the emergence of suicidal tendencies.

The primary neurotransmitter system that may be linked to suicidality is the serotonergic system, which plays a pivotal role in regulating diverse social behaviors, neuroendocrine rhythms, sleep patterns, cognitive functions, and emotions. A disruption of the latter is closely associated with changes in the function of the serotonin system of the midbrain. A reduction in serotonin system function in the prefrontal cortex has been observed in various forms of antisocial behavior, including some instances of autoaggression and homicide.

In conclusion, it can be stated that the role of the serotonergic system in the implementation of suicidal behavior is mediated by a decrease in serotonin metabolism, a change in the number and affinity of certain types of serotonin receptors, and a decrease in the affinity of the serotonin transporter of neurons, which ensures the reuptake of the neurotransmitter. These changes are primarily observed in the prefrontal cortex. The level of serotonin in the nervous tissue is dependent upon the active transport of tryptophan to the brain. Furthermore, its metabolism is associated with the functioning of specific enzymes, including tryptophan hydroxylase, aromatic amino acid decarboxylase, and monoamine oxidase. Psychopharmacological studies have demonstrated that the effects of serotonin are mediated by its interaction with specific receptors, which may be subject to modification.

The collective findings from the cortisol reactivity studies indicate that a blunted or decreased activity of the HPA axis may elevate the risk of suicide attempts among individuals who are vulnerable to such behavior. The results also indicate that the HPA axis stress response system may be dysregulated in individuals who have attempted suicide, which may consequently elevate the risk of future suicide attempts by impairing their capacity to cope and adapt to acute and non-acute stressors. A review of the literature indicates that both types of observations (hyper-reactivity and under-reactivity) may be valid and consistent in their relationship between cortisol levels and suicide attempts. However, this relationship may be explained by age-dependent exposure to stress over time. Nevertheless, further research is required to elucidate how fluctuations in the cortisol-suicidal vulnerability correlation evolve over time.

The results of our literature review indicated inconsistencies in the findings regarding cholesterol. Nevertheless, over half of the studies analyzed confirm the existence of a relationship between cholesterol levels and suicidal behavior.

A variety of peripheral processes are implicated in pathological chains, including metabolic systems, immunity, neurohormonal reactions, and intestinal microflora as a component of the "gut-brain" axis. All of these factors are ultimately associated with suicidal behavior, from suicidal ideation to completed suicide. The identification of these associations is of great importance for the understanding of the pathophysiology of suicidality and for the search for peripheral markers that could be used to clarify the risk, prediction, and, in an ideal case, prevention of suicide. Such a prospect is particularly promising when strategies are employed to integrate social, psychological, biochemical, psychophysiological, and genetic testing. Further data accumulation, particularly of a genetic nature, and improvement of strategies analogous to convergent functional genomics are essential.

The advantage of utilizing neurobiological markers of suicidality over clinical indicators and socio-psychological predictors is their relative independence from the researcher's opinion. The identification of a set of biological characteristics in a patient that are typical for patients with a high risk of committing a suicide attempt could facilitate prognosis and the timely initiation of treatment.

Authors' Contributions

R.T. contributed to the conceptualization, writing, methdology; Y.N. contributed to the formal analysis, O.I contributed to the editing; L.A. and A.E. contributed to the data curation. L.A. and A.M. contributed to the preparation of literature sources. All authors have read and agreed with the published version of the manuscript.

[DOI: 10.47176/mjiri.39.15]

Ethical Considerations

The process of collecting information and writing the article has not required contact with patients and their identities or any private information, nor has any intervention been applied.

Acknowledgment

Declared none.

Conflict of Interests

The authors declare that they have no competing interests.

References

1. Rozanov VA. Peripheral biological factors and biomarkers of suicide. Suicidology. 2018;9(1):3-22.
2. World Health Organization [Internet]. Suicide. Available from: https://www.who.int/news-room/fact-sheets/detail/suicide. Accessed 17 Sep 2022.
3. Inform.kz [Internet]. Available from: http://www.inform.kz.
4. Serafini G, Parisi VM, Aguglia A, Amerio A, Sampogna G, Fiorillo A, et al. A specific inflammatory profile underlying suicide risk? Systematic review of the main literature findings. Int J Environ Res Public Health. 2020;17:393.
5. Aguglia A, Amerio A, Asaro P, Caprino M, Conigliaro C, Giacomini G, et al. High lethality of suicide attempts associated with platelet to lymphocyte ratio and mean platelet volume in psychiatric inpatient setting. World J Biol Psychiatry. 2021;22:119-27.
6. Aguglia A, Solano P, Giacomini G, Caprino M, Conigliaro C, Romano M, et al. The association between dyslipidemia and lethality of suicide attempts: a case-control study. Front Psychiatry. 2019;10:70.
7. O'Connor DB, Gartland N, O'Connor RC. Stress, cortisol and suicide risk. Int Rev Neurobiol. 2020;152:0074-7742.
8. Oquendo MA, Bernanke JA. Suicide risk assessment: tools and challenges. World Psychiatry. 2017;16(1):28.
9. Eren I, Özbek S. İntihar Patofizyolojisinde Hormonların Rolü. Turkiye Klinikleri J Psychiatry-Special Topics. 2014;7(3).
10. Davidovsky SV, Ibragimova JA, Goncharik AV, et al. Analysis of hypothalamic-pituitary-adrenal system parameters in individuals who committed parasuicide. Medical Journal. 2021;(3).
11. Serafini G, Pompili M, Lindqvist D, Dwivedi Y, Girardi P. The role of neuropeptides in suicidal behavior: a systematic review. Biomed Res Int. 2013;2013:687575.
12. Qin XY, Shan QH, Fang H, Wang Y, Chen P, Xiong ZQ, et al. PSD-93 up-regulates the synaptic activity of corticotropin-releasing hormone neurons in the paraventricular nucleus in depression. Acta Neuropathol. 2021;142:1045-64.
13. Walker JJ, Spiga F, Gupta R, Zhao Z, Lightman SL, Terry JR. Rapid intra-adrenal feedback regulation of glucocorticoid synthesis. J R Soc Interface. 2015;12:20140875.
14. O'Connor DB, Green JA, Ferguson E, O'Carroll RE, O'Connor RC. Effects of childhood trauma on cortisol levels in suicide attempters and ideators. Psychoneuroendocrinology. 2018;88:9-16.
15. Genis-Mendoza AD, Dionisio-García DM, Gonzalez-Castro TB et al. Increased Levels of Cortisol in Individuals With Suicide Attempt and Its Relation With the Number of Suicide Attempts and Depression. Front Psychiatry. 2022;10;13.
16. Alacreu-Crespo A, Olié E, Girod C, Cazals A, Chaudieu I, Courte P. Dexamethasone suppression test may predict more severe/violent suicidal behavior. Front Psychiatry. 2020;11:97.
17. Beauchaine TP, Crowell SE, Hsiao RC. Post-dexamethasone cortisol, self-inflicted injury, and suicidal ideation among depressed adolescent girls. J Abnorm Child Psychol. 2015;43(4):619-32.
18. Ramamoorthy S, Cidlowski JA. Corticosteroids - mechanisms of action in health and disease. Rheum Dis Clin North Am. 2017;1-20.
19. O'Connor DB, Ferguson E, Green J, O'Carroll R, O'Connor RC. Cortisol levels and suicidal behavior: a meta-analysis. Psychoneuroendocrinology. 2016;63:370-9.
20. Genis-Mendoza D, Dionisio-García DM, Gonzalez-Castro TB, et al. Increased levels of cortisol in individuals with suicide attempts and its relationship with the number of suicide attempts and depression. Front Psychiatry. 2022;13:912021.
21. Moncrieff J, Cooper RE, Stockmann T, et al. The serotonin theory of depression: a systematic umbrella review of the evidence. Mol Psychiatry. 2022;28(8):1-14.
22. Cowen PJ, Browning M. What has serotonin to do with depression? World Psychiatry. 2015;14(2):158-60.
23. Heeringen van K, Mann JJ. The neurobiology of suicide. Lancet Psychiatry. 2014;1(1):63-72.
24. Hocaoglu C. Editorial: The neurobiology of suicide: the 'suicidal brain'. Front. Psychiatry 2023; 14:1215902.
25. Mann JJ. The serotonergic system in mood disorders and suicidal behaviour. Philos Trans R Soc Lond B Biol Sci. 2013;368(1615):20120537.
26. Karkusova MD. Biological effects of serotonin. J New Med Technol e-edition. 2022;6 [cited 2022 Dec 22]. Available from: http://www.medtsu.tula.ru/VNMT/Bulletin/E2022-6/3-12.pdf. DOI: 10.24412/2075-4094-2022-6-3-12. Russian.
27.Mazo G, Dubinina EE, Krizhanovskiĭ AS. Inflammation and depression: the role of oxidative stress, hormonal and cellular factors. S.S. Korsakov Journal of Neurology and Psychiatry. 2014;114(1):80□84. (In Russ.)
28. Reininghaus EZ, Lenger M, Schönthaler EMD, Fellendorf FT, Stross T, Schwarz M, Moll N, Reininghaus B and Dalkner N. Changes in tryptophan breakdown associated with response to multimodal treatment in depression. Front. Psychiatry. 2024;15:1380620
29. Badawy AA-B. Kynurenine pathway of tryptophan metabolism: regulatory and functional aspects. Int J Tryptophan Res. 2017;10:1-20.
30. Agus A, Planchais J, Sokol H. Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe. 2018;23(6):716-24.
31. Chen LM, Bao CH, Wu Y, et al. Tryptophan-kynurenine metabolism: a link between the gut and brain for depression in inflammatory bowel disease. J Neuroinflammation. 2021;18:135.
32. David DJ, Gardier AM. Les bases de pharmacologie fondamentale du système sérotoninergique: application à la réponse antidépressive. Encephale. 2016;42(3):255-63.
33. Bamalan OA, AlKhalili Y. Physiology, serotonin [Updated 2021 Mar 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545168
34. Deurwaerdère DP, Giovanni DG. Serotonin in health and disease. Int J Mol Sci. 2020;21(10):3500.
35. Jones LA, Sun EW, Martin AM, Keating DJ. The ever-changing roles of serotonin. Int J Biochem Cell Biol. 2020;125:105776.
36. Francescangeli J, Karamchandani K, Powell M, Bonavia A. The serotonin syndrome: from molecular mechanisms to clinical practice. Int J Mol Sci. 2019;20(9):2288.
37. van Heeringen K, Mann JJ. The neurobiology of suicide. Lancet Psychiatry. 2014;1(1):63-72.
38. Kovalzon VM. Modern view on the serotonin theory of depression. On the 90th anniversary of the outstanding Soviet and Russian psychopharmacologist Izyaslav Petrovich Lapin (1930–2012). Russ Neurol J. 2020;(3).
39. Oxenkrug GF. Serotonin-kynurenine hypothesis of depression: historical overview and recent developments. Curr Drug Targets. 2013;14(5):514-21.
40. Sullivan PF, Geschwind DH. Defining the genetic, genomic, cellular, and diagnostic architectures of psychiatric disorders. Cell. 2019;177(1):162-83.
41. Brainstorm Consortium, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, et al. Analysis of shared heritability in common disorders of the brain. Science. 2018;360(6395).
42. Lopes F, McMahon F. The promise and limits of suicide genetics. Am J Psychiatry. 2019;176:600-2.
43. Menon V, Kattimani S. Suicide and serotonin: making sense of evidence. Indian J Psychol Med. 2015;37(3):377-8.
44. Antypa N, Serretti A, Rujescu D. Serotonergic genes and suicide: a systematic review. Eur Neuropsychopharmacol. 2013;23(10):1125-42.
45. Bortolato M, Pivac N, Muck Seler D, Nikolac Perkovic M, Pessia M, Di Giovanni G. The role of the serotonergic system at the interface of aggression and suicide. Neuroscience. 2013;236:160-85.
46. Mann JJ. The serotonergic system in mood disorders and suicidal behaviour. Philos Trans R Soc Lond B Biol Sci. 2013;368(1615):20120537.
47. Glick AR. The role of serotonin in impulsive aggression, suicide, and

[DOI: 10.47176/mjiri.39.15]

homicide in adolescents and adults: a literature review. Int J Adolesc Med Health. 2015;27(2):143-50.
48. Patodia S, Somani A, Liu J, Cattaneo A, Paradiso B, et al. Serotonin transporter in the temporal lobe, hippocampus and amygdala in SUDEP. Brain Pathol. 2022 Sep;32(5):e13074. doi: 10.1111/bpa.13074.
49. Xiang C, Liu S, Fan Y, Wang X, Yunbo J, Li L, et al. Single nucleotide polymorphisms, variable number tandem repeats and allele influence on serotonergic enzyme modulators for aggressive and suicidal behaviors: a review. Pharmacol Biochem Behav. 2019;180.
50. Sinenko SA, Kuzmin AA, Skvortsova EV, Ponomartsev SV, Efimova EV, Bader M, et al. Tryptophan hydroxylase-2-mediated serotonin biosynthesis suppresses cell reprogramming into pluripotent state. Int J Mol Sci. 2023;24(5):4862.
51. Najjar S, Hung L, Margolis K. Serotonergic control of gastrointestinal development, motility, and inflammation. Compr Physiol. 2023;13:4851-68.
52. Imamdin A, van der Vorst E. Exploring the role of serotonin as an immune modulatory component in cardiovascular diseases. Int J Mol Sci. 2023;24:1549.
53. González-Castro TB, Genis-Mendoza AD, Hernández-Díaz Y, Tovilla-Zárate CA, Castillo-Avila RG, López-Narváez ML, et al. Association between TPH1 polymorphisms and the risk of suicide behavior: an updated meta-analysis of 18,398 individuals. Front Psychiatry. 2022;13:932135.
54. González-Castro TB, Juárez-Rojop I, López-Narváez ML, Tovilla-Zárate CA. Association of TPH-1 and TPH-2 gene polymorphisms with suicidal behavior: a systematic review and meta-analysis. BMC Psychiatry. 2014;14:196.
55. Karanović J, Ivković M, Jovanović VM, Pantović M, Pavlović-Janković N, Damjanović A, et al. Tryptophan hydroxylase 1 variant rs1800532 is associated with suicide attempt in Serbian psychiatric patients but does not moderate the effect of recent stressful life events. Suicide Life Threat Behav. 2016;46(6):664-8.
56. Lee SM, Lee S, Kang WS, Jahng GH, Park HJ, Kim SK, et al. Gray matter volume reductions were associated with TPH1 polymorphisms in depressive disorder patients with suicidal attempts. Psychiatry Investig. 2018;15(12):1174-80.
57. Ko M, Choi-Kwon S, Jun S, Kim JH, Cho K, Nah H, et al. Poststroke emotional disturbances and tryptophan hydroxylase 2 gene polymorphisms. Brain Behav. 2018;8(2).
58. López-Narváez ML, Tovilla-Zárate CA, González-Castro TB, Juárez-Rojop I, Pool-García S, Genis A, et al. Association analysis of TPH-1 and TPH-2 genes with suicidal behavior in patients with attempted suicide in Mexican population. Compr Psychiatry. 2015;61:72-7.
59. Ben-Efraim YJ, Wasserman D, Wasserman J, Sokolowski M. Family-based study of HTR2A in suicide attempts: observed gene, gene × environment and parent-of-origin associations. Mol Psychiatry. 2013;18(7):758-66
60. Ghasemi A, Seifi M, Baybordi F, Danaei N, Samadi Rad B. Association between serotonin 2A receptor genetic variations, stressful life events and suicide. Gene. 2018;658:191-7.
61. Li M, Wang H, Li J, Deng Y, Yu C. Peer victimization, depression, and non-suicidal self-injury among Chinese adolescents: the moderating role of the 5-HTR2A gene rs6313 polymorphism. Child Adolesc Psychiatry Ment Health. 2022;16:108.
62. Shinozaki G, Romanowicz M, Mrazek DA, Kung S. HTR2A gene-child abuse interaction and association with a history of suicide attempts among Caucasian depressed psychiatric inpatients. J Affect Disord. 2013;150(3):1200-3.
63. González-Castro TB, Juárez-Rojop IE, Tovilla-Zárate CA, Ovando-Ricárdez JA, Hernández-Díaz Y, López-Narváez ML, et al. Gene-environmental interaction between HPA-axis genes and trauma exposure in suicide behavior: a systematic review. J Psychiatr Res. 2023;164:162-70.
64. Kolla NJ, Bortolato M. The role of monoamine oxidase A in the neurobiology of aggressive, antisocial, and violent behavior: a tale of mice and men. Prog Neurobiol. 2020;194:101875.
65. Shah SS, Mohyuddin A, Colonna V, Mehdi SQ, Ayub Q. Monoamine oxidase A gene polymorphisms and self-reported aggressive behaviour in a Pakistani ethnic group. J Pak Med Assoc. 2015;65(8):818-24.
66. Ludwig B, Carlberg L, Kienesberger K, Swoboda P, Mitschek MM, Bernegger A, et al. Monoamino oxidase A gene single-nucleotide polymorphisms and methylation status and the risk of violent suicide attempts in affective disorder patients. Front Psychiatry. 2021;12:667191.
67. Balestri M, Calati R, Serretti A, Hartmann AM, Konte B, Friedl M, et al. MAOA and MAOB polymorphisms and personality traits in suicide attempters and healthy controls: A preliminary study. Psychiatry Res. 2017;249:212-7.
68. Murdoch JD, Speed WC, Pakstis AJ, Heffelfinger CE, Kidd KK. Worldwide population variation and haplotype analysis at the serotonin transporter gene SLC6A4 and implications for association studies. Biol Psychiatry. 2013;74(12):879-89.
69. Toloza FJK, Mao Y, Menon L, George G, Borikar M, Thumma S, et al. Association of thyroid function with suicidal behavior: A systematic review and meta-analysis. Medicina (Kaunas). 2021;57(7):714.
70. Ozcan H, Yucel A, Atis O, Yucel, et al. Thyroxin Levels Associated with Current Suicide Attempts: A Case Control and Follow-Up Study. Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology, 2016; 26(3), 278–286.
71. Duval F, Mokrani MC, Erb A, Gonzalez F, Danila V, et al. Relationship between melatonergic and thyroid systems in depression. Endocrinol Diabetes Metab J. 2019;3(5):1-4.
72. Blinov DV, Akarachkova E, Ampilogova DM, et al. Depression in postmenopause: interdisciplinary approach in management and perspectives for rehabilitation. Akusherstvo, Ginekologia i Reprodukcia = Obstetrics, Gynecology and Reproduction. 2021;15(6):738–754.
73. Sher L. Testosterone and suicidal behavior in bipolar disorder. Int J Environ Res Public Health. 2023;20(3):2502.
74. Kim B, Kang ES, Fava M, Mischoulon D, Soskin D, Yu BH, et al. Follicle-stimulating hormone (FSH), current suicidal ideation and attempt in female patients with major depressive disorder. Psychiatry Res. 2013;210(3):951-6.
75. Kim B, Kang ES, Fava M, Mischoulon D, Soskin D, Yu BH, et al. Follicle-stimulating hormone (FSH), current suicidal ideation and attempt in female patients with major depressive disorder. Psychiatry Res. 2013;210(3):951-6.
76. Sher L, Grunebaum MF, Sullivan GM, Burke AK, et al. Association of testosterone levels and future suicide attempts in females with bipolar disorder. J Affect Disord. 2014;166:98-102.
77. Sher L, Sublette ME, Grunebaum MF, Mann JJ, Oquendo MA. Plasma testosterone levels and subsequent suicide attempts in males with bipolar disorder. Acta Psychiatr Scand. 2022;145(2):223-225.
78. Li H, Zhang XY, Sun Q, Zou R, Li ZJ, Liu SY. Association between serum lipid concentrations and attempted suicide in patients with major depressive disorder: A meta-analysis. PLoS One. 2020;15(12).
79. Messaoud A, Mensi R, Mrad A, Mhalla A, Azizi I, Amemou B, et al. Is low total cholesterol levels associated with suicide attempts in depressive patients? Ann Gen Psychiatry. 2017;16:20.
80. Segoviano-Mendoza M, Cardenas-de la Cruz M, Salas-Pacheco J, Vazquez-Alaniz F, La Llave-Leon O, Castellanos-Juarez F, et al. Hypocholesterolemia is an independent risk factor for depression disorder and suicide attempt in northern Mexican population. BMC Psychiatry. 2018;18:7.
81. Shrivastava A, Johnston M, Campbell R, De Sousa A, Shah N. Serum cholesterol and suicide in first episode psychosis: A preliminary study. Indian J Psychiatry. 2017;59(4):478-82.
82. Aguglia A, Solano P, Giacomini G, Caprino M, Conigliaro C, Romano M, et al. The association between dyslipidemia and lethality of suicide attempts: A case-control study. Front Psychiatry. 2019;10:70.
83. Wonsuk C, Hee-Ju K, et al. Age-specific associations between serum cholesterol levels and suicidal behaviors in patients with depressive disorders: A naturalistic prospective observational cohort study. 2023; 14 (1).
84. Chen SM, Mizoue T, Hu HH, Kuwahara K, Honda T, Yamamoto S, et al. Serum cholesterol levels preceding suicide death in Japanese workers: A nested case-control study. Acta Neuropsychiatr. 2019;31(5):266-9.
85. González-Castro TB, Genis-Mendoza AD, León-Escalante DI, et al. Possible association of cholesterol as a biomarker in suicide behavior. Biomedicines. 2021;9:1559.
86. Freemantle E, Mechawar N, Turecki G. Cholesterol and phospholipids in frontal cortex and synaptosomes of suicide completers: Relationship with endosomal lipid trafficking genes. J Psychiatr Res. 2013;47:272-9.
87. da Graça Cantarelli M, Tramontina AC, Leite MC, Gonçalves CA. Potential neurochemical links between cholesterol and suicidal behavior. Psychiatry Res. 2014;220:745-51.
88. Wu S, Ding Y, Wu F, Xie G, Hou J, Mao P. Serum lipid levels and suicidality: meta-analysis of 65 epidemiological studies. J Psychiatry Neurosci. 2016;41:56.

[DOI: 10.47176/mjiri.39.15]

89. Liu JJ, Green P, John Mann J, Rapoport SI, Sublette ME. Pathways of polyunsaturated fatty acid utilization: implications for brain function in neuropsychiatric health and disease. Brain Res. 2016;1597:220–46.
90. Engel DF, de Oliveira J, Lopes JB, Santos DB, Moreira ELG, Farina M, et al. Is there an association between hypercholesterolemia and depression? Behavioral evidence from the LDLr/mouse experimental model. Behav Brain Res. 2016;311:31–8.
91. Knowles EEM, Curran JE, Meikle PJ, Huynh K, Mathias SR, Goring HHH, et al. Disentangling the genetic overlap between cholesterol and suicide risk. Neuropsychopharmacology. 2018;43:2556–63.
92. Baek JH, Kang ES, Fava M, Mischoulon D, Nierenberg AA, Yu BH, et al. Serum lipids, recent suicide attempt and recent suicide status in patients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2014;51:113–8.
93. Messaoud A, Mensi R, Mrad A, Mhalla A, Azizi I, Amemou B, et al. Is low total cholesterol levels associated with suicide attempt in depressive patients? Ann Gen Psychiatry. 2017;16:20.
94. Davidovskii SV, Ibragimova ZhA, Kartun LV. Features of the content of cholesterol and its lipoprotein fractions in the peripheral blood of persons who have committed suicide attempts. Lab Diagn. 2019;8(4):461–9.
95. Features of hormonal and metabolic status in persons who have committed a suicide attempt. Lab Diagn. 2021;10(2):130–45.
96. Emet M, Yucel A, Ozcan H, Gur STA, Saritemur M, Bulut N, et al. Female attempted suicide patients with low HDL levels are at higher risk of suicide re-attempt within the subsequent year: A clinical cohort study. Psychiatry Res. 2015;225(1-2):202–7.
97. Rozanov VA. Peripheral biological factors and biomarkers of suicide. Suicidology. 2018;9(2):7–32.
98. Cantarelli MG, Tramontina AC, Leite MC, et al. Potential neurochemical links between cholesterol and suicidal behavior. Psychiatry Res. 2014;220(3):745–51.
99. Svensson T, Inoue M, Sawada N, Charvat H, Mimura M, Tsugane S, Grp JS. High serum total cholesterol is associated with suicide mortality in Japanese women. Acta Psychiatr Scand. 2017;136(3):259–68.
100. Bartoli F, Di Brita C, Crocamo C, Clerici M, Carra G. Lipid profile and suicide attempt in bipolar disorder: A meta-analysis of published and unpublished data. Prog Neuropsychopharmacol Biol Psychiatry. 2017;79:90–5.
101. Zhao K, Zhou SY, Shi X, Chen JJ, Zhang YY, Fan KL, et al. Potential metabolic monitoring indicators of suicide attempts in first episode and drug naive young patients with major depressive disorder: A cross-sectional study. BMC Psychiatry. 2020;20(1):387.
102. González-Castro TB, Genis-Mendoza AD, León-Escalante DI, et al. Possible association of cholesterol as a biomarker in suicide behavior. Biomedicines. 2021;9(11):1559.

[DOI: 10.47176/mjiri.39.15]