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Review

Neurobiological Basis of Suicidal Behavior in Adolescents

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The importance of studying the biological basis of suicidal behavior (SB) is beyond doubt, as suicidal behavior contradicts the basic physiological foundations of the instincts of survival and self-preservation. Research into this issue is of particular importance in adolescents, as this is the age group in which the frequency of SB increases sharply. This leads to the need to search for reliable biomarkers of SB for valid assessment of suicide risk and for developing approaches to its prevention. This review reflects results from modern biological research in the main areas of genetics, neurochemistry, neuroimmunology, and neuroimaging and reflects the most significant abnormalities associated with SB. Comprehensive research into anomalies in all the above areas will allow a combination of the most significant of them to be identified. In addition, knowledge of different pathogenetic pathways of SB formation will lead to the development of new effective approaches to prevention.

Keywords: suicidal behavior, adolescents, biology of suicide, neuroinflammation, prevention.

Suicidal behavior (SB), which includes suicidal thoughts, suicide attempts, and death by suicide, accompanies a variety of mental and physical illnesses. Suicides account for 8.5% of deaths among adolescents and young adults (15–29 years old) and are the second leading cause of death among this age group worldwide. Suicides are committed by young men three times more often than by young women, while the opposite pattern is seen for suicide attempts [1].

In adolescents, the onset of puberty is associated with a sharp increase in the frequency of SB, which is a particular point of evidence that suicide has a biological basis [2, 3]. Moreover, adolescence often marks the onset of a variety of mental disorders, including mood and personality disorders [4], and this is also a risk factor for SB.

SB is currently regarded as an independent multifactorial pathology caused by a multiplicity of sociodemographic, biological (including genetic), and environmental factors [5, 6]. Understanding the pathogenetic basis of suicide attempts and completed suicides is crucial for more effective identification of at-risk groups and preventive intervention.

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Research indicates that the neurobiological basis of suicide includes genetic, neurochemical, neuroimmunological, biochemical, hormonal, and structural-functional changes in the brain.

The objective of this review is to analyze the scientific literature on the biological basis of suicide. Particular attention is paid to studies examining the possibility of using various biological markers to predict suicide.

Genetic Factors. The past few decades have seen publication of results from many studies addressing the genetic basis of suicide, and significant progress has been made in this area. A key discovery was that suicide is a polygenic disease in which risk is influenced by multiple genetic loci with different effects. Candidate genes associated with suicide are mostly located in the serotonergic, dopaminergic, and glutamatergic systems [7]. Genes controlling the cytokine response (*SP110*) [8], stress reactivity genes (*FKBP5*, *CRHR1*, *AGBL2*) [9], and genes associated with energy metabolism (*SUCLA2*), etc. [10] are also regarded as candidate genes for SB. Interpretation of the complex phenotype of SB is made more difficult by the involvement of multiple genetic factors and the heterogeneity of interacting genetic loci. Thus, genome-wide association studies (GWAS) are currently promising, though final results remain to be established.

Neurochemical Factors. Neurochemical abnormalities in SB are a key aspect of understanding the biological

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basis of this behavior. The serotonin system is the most extensively studied in this regard. Decreases in the concentration of the main serotonin metabolite, 5-hydroxyindoleacetic acid, along with paradoxical increases in the number of serotonergic neurons and the key enzyme in serotonin synthesis, tryptophan hydroxylase, in the cerebrospinal fluid were found in individuals who attempted suicide [11]. The serotonin model, which seeks to explain these results, suggests the simultaneous coexistence of low serotonin levels and a compensatory increase in the activity of serotonergic receptors aimed at increasing the bioavailability of serotonin. Low levels of hydroxyindoleacetic acid in the cerebrospinal fluid have been proposed as a marker of SB, regardless of psychiatric diagnosis [12, 13]. In addition, low levels of hydroxyindoleacetic acid correlate with the choice of the most lethal suicide methods [14].

The involvement of noradrenaline in SB was initially hypothesized not because of data showing changes in its levels in individuals who have attempted suicide, but because of the effectiveness of antidepressants that act on the noradrenergic system [15] and because of its important role in the regulation of arousal, attention, cognitive functions, and stress reactions [16]. Data have now been obtained showing increased noradrenaline levels and decreased binding of α2-adrenergic receptors in the prefrontal cortex [17]. Clinically, increased noradrenaline levels lead to increased anxiety and irritability, along with an enhanced stress response, which increases the risk of SB [18]. This pathogenetic pathway appears to be the most important and requires special study in adolescence, when age-related, clinically determined hypernoradrenalinemia-induced impulsivity and aggressiveness become significant factors in the development of SB [19].

Dopamine dysregulation associated with anhedonia, another important clinical factor in SB, is also of interest in studies of the biological basis of adolescent suicide. Current data demonstrate a link between suicidal intent and a decrease in central dopaminergic neurotransmission. Thus, individuals who have attempted suicide have been found to have decreased levels of homovanillic acid (a dopamine metabolite) in the cerebrospinal fluid [20]. Deficiency in dopamine transmission has been confirmed by data showing a decrease in the bioavailability of the dopamine transporter, due to chronic weakening of dopamine neurotransmission in the mesolimbic pathways [21]. Numerous studies in animal models have also demonstrated a link between dopamine system deficiency and the development of depressive symptoms and suicidal behavior, with the involvement of the physiological reward system in the pathological process and the development of so-called learned helplessness, with a reduced ability to avoid the action of a stressor [22].

More recently, research attention has been drawn to gamma-aminobutyric acid (GABA), which is the main inhibitory neurotransmitter in the central nervous system (CNS) and is involved in the regulation of emotions and behavior [23]. Neuroimaging data have been obtained showing GABA deficiency in key areas of the brain responsible for the regulation of the emotions, impulse control, and related cognitive processes: the prefrontal cortex, hippocampus, and corpus callosum [24]. Clinically, this deficiency leads to a decrease in stress tolerance and the emergence of extreme types of behavior, including suicide [25]. From a practical perspective, the results of a recent study reported by Shao et al. [26] are important – these demonstrated a significant decrease in the serum GABA level in individuals with depression and suicidal thoughts as compared with a group of depressed patients without suicidal thoughts and a group of healthy individuals, which allows serum GABA estimation to be used as a biomarker of suicide risk.

Glutamate, as the main excitatory neurotransmitter in the central nervous system, also takes part in forming SB, as evidenced by studies in recent years [27]. Studies on animal models have evidenced the catalytic role of the glutaminergic system in the formation of aggression [28]. Subsequent studies traced a relationship between CSF glutamate concentrations and levels of impulsivity and aggressive impulsivity in humans [27]. It was proposed that data on the role of the glutamate-glutamine cycle and the enzymatic system supporting it should be used to create new therapeutic targets for the prevention of SB.

Polyamines. Polyamines are aliphatic molecules containing two, three, or four amino groups. The best known of these are agmatine, putrescine, spermine, and spermidine, each of which participates in its own signal pathway [29]. Polyamines have been shown to influence neurotransmitter systems, including GABA and glutamate activity, shaping the neurobiology of SB. Studies in animal models and postmortem examination of the brains of individuals who committed suicide while depressed showed decreased polyamine levels in the hippocampus [29]. Recent years have seen an increasing number of studies supporting the polyamine stress response theory [30], which suggests a rapid and transient increase in polyamine synthesis in response to stressful stimuli. Chronic stress factors, however, lead to persistent changes in polyamine concentrations. Thus, spermidine and spermine levels remain unaltered after single stressful events but gradually increase after repeated stimuli, suggesting that they have an adaptive role in protecting the CNS [30]. Experimental work reported by Zomkowski et al. [31] showed that putrescine had efficacy in relieving depressive symptoms, comparable to that of the antidepressant imipramine. Given that polyamines are able to penetrate the blood–brain barrier, this opens up opportunities for their systemic use to achieve therapeutic goals in the prevention of SB.

Neuroimmunological Factors. The role of inflammation in SB was suggested by a study by Nassberger et al. [32], who found persistent increases in the concentration of soluble interleukin-2 receptor (S-IL-2R) in the plasma of individuals who had attempted suicide, reflecting T-lymphocyte activation. Subsequent studies also demonstrated increases

in proinflammatory factors such as tumor necrosis factor (TNF)-α, kynurenic acid (KYN), and interleukins (IL)-1β and IL-6 [33]. Attempts were made to find biological differentiation of depression with and without suicidal ideation based on the extent of increases in the concentrations of inflammatory markers such as IL-2 and IL-6, TNF-α, S100 protein, and C-reactive protein (CRP) [34].

The main serum inflammation biomarkers include CRP, IL-6, and the most promising marker of chronic inflammation – soluble urokinase-type plasminogen activator receptor (suPAR) [35]. suPAR was found to reflect a long-term inflammatory response, in contrast to the two markers noted above, which are associated with the acute-phase reaction.

Excessive and/or prolonged activation of proinflammatory factors has been shown to lead to increased permeability of the blood–brain barrier, activation of microglia, and the development of neuroinflammation [36, 37].

A unique immunological study of a group of adolescents (mean age 15.0 years) with suicidal thoughts established similar biological profiles for 41 indicators in all individuals with current or past suicidal tendencies, regardless of the number of suicide attempts, which indicates stable immunological abnormalities in this contingent and opens up the possibility of using them as biological markers of suicide risk [38]. The study showed that the following indicators have the greatest predictive potential: Flt-3L is a proinflammatory cytokine involved in the production of monocytes, natural T-killers, and B-cells; GM-CSF is a growth factor that induces granulocyte and macrophage proliferation; IFN-γ is a cytokine that interacts with other proinflammatory agents to enhance the overall immune response.

Chronic neuroinflammation is seen as a universal trigger of SB in individuals with and without mental disorders. Neuroinflammation contributes to disrupting the transmission of nerve spikes and neuroplasticity; it provokes maladaptive behavioral patterns [39]. In recent years, hematological coefficients, such as the neutrophil:lymphocyte or platelet:lymphocyte ratios, have been proposed for predicting suicide in risk groups; these ratios have been shown to correlate with SB [40].

Mitochondrial Dysfunction. Neuroinflammation associated with increased synthesis of proinflammatory cytokines and free radicals contributes to damage to mitochondrial membranes and DNA, leading to impairment of their functional activity [41].

Alterations in the expression of genes associated with mitochondrial dysfunction and neuroinflammation have been identified in the brains of individuals who committed suicide [42]. Significant biochemical changes in the enzyme NADPH oxidase, which transfers electrons across mitochondrial membranes, have been found in postmortem brain samples from individuals who committed suicide [43], which also indicates mitochondrial dysfunction.

Markers of mitochondrial dysfunction, such as fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15) [44], as well as elevated levels of modified purines and pyrimidines, which are components of RNA, have been identified in the blood of patients with major depressive disorder and SB [45].

Thus, mitochondrial dysfunction leading to disruption of intracellular bioenergetics is seen as one of the biological factors contributing to the development of SB and may become a potential target for new diagnostic and therapeutic methods [46].

Neurotrophic Factors and Neuroplasticity. Brain-derived neurotrophic factor (BDNF) is a neurotrophin – a growth factor involved in the regulation of structural and synaptic plasticity and maintenance of neuronal function. Numerous external and internal stimuli (stress, physical activity, diet, head injury, etc.) have been shown to regulate the expression of BDNF [47]. Numerous postmortem studies of brain samples from individuals who died by suicide have demonstrated decreases in the concentration of this factor in the brain. Established correlations between blood and brain BDNF levels allow this factor to be used as a marker for SB [48]. Low BDNF levels correlate with atrophy of the hippocampus and prefrontal cortex as detected by MRI in suicidal individuals.

Lipid Metabolism. Cholesterol and polyunsaturated fatty acids (the omega-3 and –6 classes), together with sphingolipids, form so-called lipid rafts, a key component of membrane lipids in the CNS which support neurotransmitter signals [43]. A correlation has been established between the lipid profile and suicidal tendencies. Thus, a meta-analysis of 65 studies by Wu et al. [49] revealed significantly lower levels of triglycerides and cholesterol in depressed patients with suicidal thoughts as compared with depressed patients without suicidal thoughts and the control group. Moreover, comparison of individuals with the highest and lowest triglyceride levels showed that the risk of suicidal tendencies in the latter was 112% higher, the risk of attempted suicide was 123% higher, and the risk of completed suicide was 85% higher.

A study of individuals who had attempted suicide (n = 100) and control patients (n = 100) treated in the intensive care unit for injuries resulting from accidents revealed decreased eicosapentaenoic acid levels in the phospholipids of erythrocytes in suicides [50]. Another study proposed use of the docosahexaenoic acid level and the ratio of omega-6 to omega-3 polyunsaturated fatty acids as biomarkers for suicide risk, as a decrease in the former and an increase in the latter were noted in a group of patients with depression and suicidal thoughts [51]. Later work confirmed the involvement of polyunsaturated fatty acid deficiency in the formation of the set of risks of SB, including the severity of depression, aggression, and impulsivity in patients with self-harming behavior and a tendency to abuse psychoactive substances [52].

Vitamin D. Vitamin D has been shown to have a special role in relation to the formation of SB. Vitamin D is involved in the transcription of more than 1000 genes regulating neurotrophic and neuroprotective effects [53], and

also shifts the balance of T-helpers towards a less proinflammatory phenotype, leading to a decrease in suicide risk [54]. Data have been obtained showing a statistical relationship between vitamin D levels, the presence of mental disorders, and a history of suicide attempts [55]. A recent meta-analysis of 13 studies by Yu et al. [53] associated vitamin D deficiency with a 1.6-fold increase in the risk of suicide. These results suggest that vitamin D intake should be included in comprehensive suicide prevention programs in adolescents.

Hormones. There is extensive evidence that changes in the hypothalamic-pituitary-adrenal axis (HPA) with impairments to final glucocorticoid synthesis may predispose to suicide [56], increasing the risk of suicide by a factor of more than 4.5 [57]. While studies of adult cohorts have yielded conflicting results, a review by Miller et al. [58] of data from adolescents showed a link between low cortisol levels and suicide risk. Thus, adolescents who attempted suicide had lower blood and hair cortisol levels than those who had only suicidal thoughts, while in adolescent girls suffering from depression and prone to self-harming behavior, low cortisol levels after the dexamethasone test were associated with a higher frequency of suicidal thoughts. In general, it is now understood that both high and low cortisol levels indicate disruption of the response of the HPA axis to stress and determine increased vulnerability to acute stress with the formation of SB [58].

Sex hormones are known to influence the neurobiology of affective disorders and to determine the sex-related characteristics of SB.

Studies of the influence of female sex hormones on the risk of suicide showed that this risk is greater in the luteal phase of the menstrual cycle [59]. This study also obtained data showing increased progesterone levels in women with repeated (more than three) suicide attempts. As regards male sex hormones, a positive correlation was found between testosterone concentrations and the risk of suicide: an increase in the level of this hormone by 10 ng/dL in women increased the risk of suicide by a factor of 16.9 [60]. At the same time, an inverse relationship was found in men: individuals who attempted suicide had lower testosterone levels, and an analogous relationship was observed in relation to the choice of suicide method: low hormone levels determined more violent methods of ending life [61].

Thyroid dysfunction is associated with mental symptoms such as depression and anxiety and may determine SB [62]. A meta-analysis of 13 studies involving 826 individuals with SB conducted by the authors showed significantly lower levels of free triiodothyronine and total thyroxine compared with controls. No differences were found in other hormones associated with thyroid function. A later study by Zhu et al. [63] showed significant increases in thyroid-stimulating hormone levels in young people with suicidal thoughts. The data obtained require verification in future studies.

Consideration of the involvement of the hormonal system in the formation of SB in adolescents requires another hormone synthesized in adipose tissue to be mentioned; this is leptin, and is important because the problem of obesity is currently relevant in this age group. Leptin receptors have been shown to be present in the HPA axis and to be involved in modulating the stress response; they also affect the dopaminergic and serotonergic systems [64]. A meta-analysis of nine case-control studies by González-Castro et al. [65] revealed decreased leptin levels in individuals with SB.

Structural and Functional Changes in the Brain. The frontal and prefrontal areas of the cortex play an important role in suicide because they are involved in cognitive processes, stress responses, and the inhibition of impulsivity [66]. Patients with a history of suicide attempts show changes in the activation patterns of the prefrontal regions associated with impaired decision-making, assessment of risk and reward, and social evaluation.

The anterior cingulate cortex, responsible for negative self-perception and processing of emotional stimuli, is closely associated with suicidal tendencies [67]. As compared with the reference group, individuals who committed suicide attempts showed greater activation of the anterior cingulate cortex when viewing emotionally expressive faces, indicating different processing of emotional stimuli [68].

fMRI studies have confirmed the role of dysfunction of the ventral and dorsal prefrontal cortex in the pathophysiology of suicide in response to emotional and hedonic stimuli [69]. Structural MRI studies have shown that adults who attempted suicide had smaller gray matter volume and neuron density in the ventral prefrontal cortex, as well as smaller hippocampal volume, than a reference group with mental disorders [69]. Furthermore, decreased orbitofrontal cortex activity during risky and safe decision-making is consistent with alterations in decision-making processes [68].

Conclusions. This literature review found significant differences in neurobiological parameters in individuals with SB in different areas of pathophysiology. These anomalies are particularly important in adolescence, when the immaturity of the body's functional systems makes imbalance in response to various external and internal provocatory factors the basis for suicide. Future research should seek to find sets of biomarkers, including genetic abnormalities, mono- and polyamines, inflammatory factors, lipid profile components, vitamins, enzymes, hormones, and structural features of the brain, such that key combinations will allow reliable prediction of suicide risk and, through timely correction of disrupted links in pathogenesis, implementation of its specific prevention.

The authors declare no conflict of interest.

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