DOI: 10.24412/2311-1623-2024-42-42-49

Non-specific adaptive defense reactions of the body in the development of panic attacks and primary prevention of cardiovascular diseases

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Aim of the study. The aim of this review is to explore the neurobiology of stress and fear, to summarize the conceptual views of panic attacks (PA) and their association with cardiovascular diseases (CVD), to provide a further strategy for clinical research on PA, and to optimize prevention and treatment interventions.

Methods. Scientific articles up to and including 2024 were searched in six electronic medical databases ("Web of Science", "Scopus", "MEDLINE/PubMed", "EMBASE", "elibrary.ru", "cyberleninka.ru"). Inclusion criteria were: keywords "anxiety disorders, autonomic disorders, COVID-19, PA, CVD, neurobiology of stress and anxiety, non-specific adaptive defense mechanisms and reactions (NADMR) of the organism, non-specific methods of treatment and prevention", cardiovascular diseases, coronary heart disease; types of scientific papers "original clinical studies"; period of research for the last 5 years. Scientific papers with psycho-organic diseases, severe somatic diseases and/or their complications were excluded. The dialectical and systematic approach was used as the methodological framework to address the objectives. The exploratory method of analysis was applied in the review of titles, abstracts and full texts. The deductive method was used to identify private patterns of different concepts. In case of discrepancies, possible solutions were synthesized.

Results. The analysis of studies devoted to different concepts of PA etiology, neurobiology of fear and evolution of views on the pathogenetic relationship between PA and CVD allowed to identify their relationship with NADMR, in which non-linear "mediator" effect would influence the development of PA and CVD. The analysis and synthesis of data from different PA concepts showed that there is no contradiction between the concepts and proposed a PA concept with a broader spectrum of nonlinear "mediator" mechanism of PA. With these results, the author substantiates the association of NADMR with PA and CVD through a nonlinear "mediator" mechanism.

Conclusion. The study of NADMR is important for the improvement of the general physical and mental health and well-being of the population in the long term, especially in conditions of aggressive environmental factors. It also

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makes it possible to emphasize the need to study complex methods of treatment, including "non-specific", the results of which should be reflected in new standards of treatment of this nosology.

Keywords: non-specific adaptive defense mechanisms and reactions, panic attacks, neurobiology of stress and fear, COVID-19, cardiovascular diseases, coronary heart disease.

Conflict of interests: none declared.

Recieved: 22.03.2024
Accepted: 16.05.2024

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For citation: Vodopianov V.A. Non-specific adaptive defense reactions of the body in the development of panic attacks and primary prevention of cardiovascular diseases. International Journal of Heart and Vascular Diseases. 2024. 12(42):42-42. DOI: 10.24412/2311-1623-2024-42-42-49

Introduction

Mental and physical distress are a part of human evolution that can enhance mental and physical performance. Depending on the period of human history, the nature and quality of stressors may vary [1].

As humanity progresses, the modern world is filled with new anthropogenic stressors that can not only deteriorate but also ruin human health. For this reason, some researchers point to the impossibility of harmonious human existence in the anthropogenic environment [2].

Depending on a variety of exogenous and endogenous factors, a certain part of the population develops panic attacks (PA), with statistical evidence of a high prevalence among all population groups worldwide [3].

Therefore, further study of the mechanisms of development of psychovegetative disorders will improve the prevention and treatment of PA and reduce the prevalence of cardiovascular diseases (CVD).

Any non-standard situation for a human being is a stress, a biological concept that was proposed by Hans Sellier. He introduced the definition of stress as "a non-specific reaction of the organism to any demand on it" [4]. The definition of stress was based on the "general adaptation syndrome", which includes three stages: initial symptoms, adaptation to stress and manifestation when stress does not end. Some authors previously referred to the unexplored component (mechanism) of stress as "non-specific". Studies in recent years have shown that the "non-specific response" is a non-linear reaction of "mediators", where abnormal activity of one of the "mediators" disturbs and distorts the rest of the network and has a cumulative effect [5].

Therefore, it is now quite acceptable to refer to such mechanisms and reactions as non-specific adaptive defense mechanisms and reactions (NADMR), which Hans Sellier called "adaptive evaluations whose significance is genetically determined". More recent work on stress has used different definitions depending on the stimulus or response to it. This leads to confusion when stress is confused with stressors (triggers/stressors). Therefore, a number of researchers, based on the discoveries of recent years, have proposed the need to define stress as a combination of external factors (stressor) and internal factors (stress perception and emergence) [6].

Hans Sellier distinguished two types of stress: acceptable ("eustress") and negative ("distress"), regardless of the stressor, which are still used today [7]. Later, new data on the effects of stressors on the body made it possible to propose a new definition of stress: "good, bad and very bad stress" [8].

According to "allostatic load" studies, the duration of stress depends on the combination of external and internal factors that determine the positive adaptive and harmful effects of stress. Short-term (acute) stress can last from one minute to two hours [9, 10], and long-term (chronic) stress can last from a few hours a day to weeks or months [11]. Chronic stress determines the ultimate spectrum of adverse effects [6], which depends on the nature of the adaptive responses: adaptive, compensatory, and maladaptive [12].

Chronic stress is also associated with functional strain, which can lead to exhaustion of the organism. Exhaustion leads to NADMR breakdown and maladaptation. The increase or decrease in NADMR depends on the combination of internal and external stressors, which determines the boundary of the stress dichotomy [12].

It can be assumed that the boundary between positive and negative stress will shift towards adaptation

DOI: 10.24412/2311-1623-2024-42-42-49

or maladaptation depending on the functional state of the organism, as a "stress threshold" [13].

In order to increase stress resistance and, as a result, the functional state of the organism, it is recommended to use widely dosed mental and physical exercise for preventive purposes, increasing the resistance and endurance of all body systems [14].

The "stress threshold" is individual for each person, when it is exceeded, there are violations of regulatory systems. The severity of disorders in the functioning of organs and systems of the organism and the time of their occurrence depend on the nature of the stressor and individual constitutional features of a person, which determine the reaction and perception of stressors [15-17].

The "stress and coping theory" has also been proposed [18]. Cognitive interpretation plays a key role in this theory, acting as a mediator between stressor and response. According to this theory, the body is unable to cope with emerging events due to impaired cognitive interpretation. The "stress and coping theory" is reflected in recent work on Gestalt phenomenology [19].

Stressors can lead to anxiety and, in extreme cases, to very severe fear, loss of behavioral control (coping), and even suicide if the person does not receive timely help [20, 21].

A sudden onset of intense fear or discomfort, exacerbated by intense autonomic arousal and peaking within a few minutes, is defined by the DSM as PA. It is accompanied by at least four somatic symptoms with the background of a sense of imminent threat to health or life without apparent cause. It is characterized by an association with physical (non-cognitive) fear and anxiety [19, 22].

In the ICD-10 classification of the Russian Federation, PA is a type of anxiety disorder in the form of spontaneous anxiety attacks not clearly associated with specific situations or objects, accompanied by a sharp increase in the level of anxiety and numerous somatic symptoms.

The prevalence of PA varies from 2% to 25% depending on the country. On average, 100,000 people represent 7-9% of the world's population, according to the WHO. This difference in statistics may be due to cultural differences (such as referral to a specialist or adherence to traditional non-drug treatments). In addition, constitutional features of the psyche and aggressive factors of the human environment differ in different regions [23].

Aggressive environmental factors include phenomena such as the COVID-19 pandemic and military conflicts, the escalation of which worldwide in recent years will contribute to an increase in delayed psychiatric disorders [15], including PA, the treatment of which may become more resistant to pharmacotherapy [20].

A person who has experienced social, personal, or other shocks may require long-term rehabilitation treatment to return to a normal rhythm of life, as conscious stressors may shift to unconscious ones or have delayed effects [21]. Therefore, people affected by severe stressors are particularly in need of long-term rehabilitation.

As a matter of fact, unconscious stressors make anxiety disorders more uncomfortable because the source of danger cannot be identified. In these primary care patients, anxiety may be overlooked during assessment, contributing to the development of chronic anxiety disorders [24].

High risk factors for the development of PA have been identified, despite the lack of obvious causes and a direct link between the level of social stability/protection and bad habits/dependencies (smoking, alcohol and other psychoactive substances). Individuals exposed to these risk factors, according to the study of PA history, show more unstable psychoemotional states in their absence in the body [25].

Persistent attempts to obtain psychoactive substances increase mental arousal. On the one hand, this encourages continued smoking and addiction, and on the other hand, it provokes PA in the absence of these substances in the blood. Managing PA in this population requires a unique treatment approach.

According to the American Psychiatric Association in 2013, PA reflect, but are not limited to, an abrupt autonomic surge of marked discomfort and extreme fear or a sense of impending doom accompanied by a strong urge to escape or fight [26].

As a result, PA may be a risk factor for several forms of psychopathology. These include, major depressive disorder, generalized anxiety disorder, personality disorders, substance use disorders and severe mental illness [27, 28].

Methods

Scientific articles up to and including 2024 were searched in six electronic medical databases ("Web of Science", "Scopus", "MEDLINE/PubMed", "EMBASE",

"elibrary.ru", "cyberleninka.ru"). Inclusion criteria were: keywords "anxiety disorders, autonomic disorders, COVID-19, PA, CVD, neurobiology of stress and anxiety, non-specific adaptive defense mechanisms and reactions (NADMR) of the organism, non-specific methods of treatment and prevention", cardiovascular diseases, coronary heart disease; types of scientific papers "original clinical studies"; period of research for the last 5 years. Scientific papers with psycho-organic diseases, severe somatic diseases and/or their complications were excluded.

The dialectical and systematic approach was used as the methodological framework to address the objectives. The exploratory method of analysis was applied in the review of titles, abstracts and full texts. The deductive method was used to identify private patterns of different concepts. In case of discrepancies, possible solutions were synthesized.

Results

Until the 2000s, there were many different theories, with neuroanatomical ones being the most popular. However, there is still no absolute consensus on the neurobiology of PA.

The study of the pathogenetic mechanisms of PA in a neuroanatomical model revealed the so-called "fear network", the core of which is the amygdala body. The septo-hippocampal system in interaction with the amygdala is involved in the formation of adaptation through emotional memory to stress [29] and neuroplasticity of synapses (remodeling of dendrites) due to cortisol, for which receptors are present in the dentate gyrus of the hippocampus. These results were recorded in the brain as genomic and epigenomic signatures.

In the new definition of "good, tolerant, and toxic" stress, compared to the old "good, bad, and very bad," the researchers replaced the term "bad" with "tolerant" because the end result of this condition is not deterministic and is conditionally pathological. Because "tolerant stress" can be considered a compensatory type of stress response and a borderline state between "good and toxic stress", the end result of which is determined by the totality of the non-linear action of "mediators" as adaptive ("good stress") and maladaptive ("toxic stress").

Not all scientists share this view on the development of PA. An alternative hypothesis for the etiology of PA is related to the panic system, based on the clinical findings of Gestalt phenomenology versus those of affective neuroscience. Researchers propose to consider PA as "an acute attack of loneliness that is not adequately recognized by the patient due to the interference of a dissociative component that makes it impossible to integrate all the neurophysiological responses activated by the panic/dissociation brain system into a coherent emotional sensation" [19].

Meanwhile, Russian scientists talk about the lack of a common neurobiological concept [30, 31]. This may indicate more concepts or a more complex model of PA, which in turn indicates the prospects for further clinical research [32, 33].

In addition, there are other studies that suggest the involvement of cognitive interpretation of external stimuli in the development of pathological anxiety. Normally, fear is an evolutionarily inherited protective emotion. If the perception and cognitive interpretation of this emotion is disturbed, PA may develop [20].

While the etiology of PA remains controversial, it is already clear that there is an association between PA and CVD [34].

Traditionally, scientists considered a panic attack to be a "functional" arousal and identified it only after careful exclusion of "organic" causes. Today, even psychiatrists reject the term "functional disorders" as applied to mental illness. Functional and organic disorders can occur in somatic pathology and psychiatric disorders. In addition, there is a growing body of literature supporting the existence of a clear link between mental and physiological processes [35].

For a long time, researchers denied such a link between psychological and physiological processes. For example, until the 2000s, studies by a group of scientists from the National Heart Foundation of Australia found no direct causal relationship between coronary heart disease (CHD) and anxiety-depressive disorders or PA. The researchers attributed the increased risk of CHD to factors such as smoking, dyslipidemia, alcohol consumption, and arterial hypertension [36].

In the early 2000s, a systematic review of prospective cohort studies found a mixed association between CHD and PA, with no significant established risk of CHD in PA. Preliminary evidence links PA to myocardial ischemia through two pathophysiological mechanisms: reduced heart rate variability and myocardial ischemia. Therefore, researchers have suggested further prospective studies to prove the association between PA and CHD [37].

DOI: 10.24412/2311-1623-2024-42-42-49

In another systematic review and meta-analysis of recent years, researchers concluded that there is no risk of developing CHD with the background of PA. They explained the etiologic relationship between them by the fact that PA precedes CHD, but in reality CHD could be misdiagnosed and interpreted as PA. However, due to several "limitations" at the time of the systematic review, including the small number of original studies, the results cannot exclude the association of PA with CHD and the increased risk of developing the latter [38]. They may serve to refine the design of further original studies.

Indeed, in 2012, the first study of myocardial perfusion in PA without established CHD was conducted, showing an association of PA with myocardial ischemia.

Another original study from the Baker Institute's Human Neurotransmitter Laboratory in Melbourne found that mental stress triggers cardiovascular events. Due to the fact that PA have "forms of sympathetic nervous system amplification", they increase the risk of CVD. It is noteworthy that the authors of this article emphasize the lack of specific prevention of cardiovascular triggers, one of which is PA [38]. Therefore, the study of NADMR may be a promising area of clinical research in the prevention of PA.

The combination of CVD risk factors such as alcohol, tobacco, psychoactive substances, etc. together with PA will accumulate a pathogenetic effect. Such a cumulative effect even increases the risk of acute coronary syndrome, which also mimics the clinical picture of PA and leads to a more severe course of it [39].

Consequently, the treatment of PA can be considered as primary prevention of CVD [38].

General treatment protocols for mental disorders favor a holistic biopsychosocial approach, excluding acute CVD. The National Institute for Health and Clinical Excellence (NICE 2017) treatment protocols recommend the following modular treatment regimen in descending order of evidence of greatest effectiveness: psychotherapy, pharmacological intervention, and non- pharmacological intervention [40].

Cognitive-behavioral therapy is the method of choice for PA in psychotherapy. However, in the long-term course of PA, psychotherapy and pharmacotherapy can be supplemented with physiotherapy, acupuncture, organic preparations to restore the neurotransmitter deficit due to long-term depletion of the chronic course of the pathological process, correction of the psychoemotional background, Ericksonian hypnosis, and the use of a new method of metacognitive therapy [41-43].

At the moment of an acute anxiety attack, which can provoke PA, relaxation techniques of concentration on breathing and relaxation of involuntarily tensed muscles will help to control it [44].

According to the 2017 NICE guidelines, anxiolytics, neuroleptics or benzodiazepines are recommended for the treatment of PA. Depending on the severity of the course of PA, anxiolytics or selective serotonin reuptake inhibitors (SSRIs) may be the first line of treatment for anxiety. Tetracyclic antidepressants may sometimes be more effective. Benzodiazepines are used for generalized anxiety disorder [20].

Discussion

Perhaps there is no contradiction between the described theories of the origin of PA, and the problem is not only the dissociative component that interferes with the formation of a "coherent emotional feeling". It is possible that the link in these views is the septo-hippocampal gyrus, where a false emotion is formed after activation by an acute stressor or sensitization by a chronic stressor of the fear brain network. One of the triggers would be separation/loneliness. The separation/loneliness would then transform into an anxiety attack, and the constructs of emotional memory in childhood may not contradict the example of Parkinson's disease in old age on which the findings of Gestalt phenomenology are based.

Thus, the example described above may also support the author's view that the problem is not just a matter of cognitive interpretation of the single emotion of loneliness. Rather, it is more likely that the cognitive interpretation of various/single emotions triggers a non-linear cascade of "mediators", the end result of which determines NADMR.

Such seemingly conflicting scientific evidence on the etiology of PA may be different parts of the same whole, pointing to a much more complex and non-linear neurobiology of NADMR stress tolerance than a disruption in an individual brain's fear network or a faulty cognitive interpretation of external stimuli. The establishment of an interdisciplinary panel would help advance the study of PA.

In 2019, an interdisciplinary commission addressed the issue of stress resilience, the results of which,

after editing and harmonization, were published in August 2020. The proposed definitions of stress resilience were all different. However, the commission unanimously affirmed that stress resilience is a multilevel process, from the neurobiological level to the level of social structure. This takes the study of stress resilience to a new level and suggests a non-linear response of NADMR "mediators" in the formation of stress tolerance [45].

Despite the differentiated approach to the treatment of anxiety-depressive disorders, there are still emerging forms resistant to pharmacotherapy that are still poorly understood [46]. It is possible that with prolonged use of SSRIs and persistence of a psychotraumatic factor, endogenous serotonin is depleted. As a result, non-selective tetracyclic antidepressants and benzodiazepines show better results than SSRIs in generalized anxiety disorder.

In the future, a possible solution to the problem of imperfect drug therapy in the form of the emergence of drug-resistant forms of anxiety-depressive disorders will be further study of the role of neuropeptides. They are involved in neuromodulation of behavioral disorders: corticotropin-releasing factor, galanin, oxytocin, vasopressin, neuropeptide Y and orexins[47]. Neuropeptides can be used as markers in clinical trials of new or complex PA treatments.

Specific and non-specific rehabilitation methods are recommended as prophylaxis for universal (no risk group), selective (high risk group) and indicative (minimal risk group) groups [48].

Specificity consists of excluding or limiting PA-provoking factors. Specific prophylaxis is short-term and effective when used episodically. Non-specific methods of prevention are increasing and strengthening the mental and physical functional capabilities of the organism, normalization of biorhythms, avoidance of bad habits, proper nutrition, audiotherapy with sounds of nature, pleasant music, meditative recordings, helpful relaxation and other methods of recovery [49, 50].

Conclusion

Since mental disorders may contribute to impaired autonomic function, which creates favorable conditions for the development of CVD, early diagnosis and treatment of PA would be a prevention of CVD, and increasing stress tolerance would be a prevention of PA. Therefore, further study of NADMR will contribute to a better understanding of the mechanism of "non-linear mediator" effects in the development of PA and its causal relationship with CVD.

Thus, the presented results summarizing the different concepts of PA and their relationship with CVD, the results of research on the neurobiology of stress and anxiety in the long term may have implications for improving the overall physical and mental health and well-being of the nation in the long term. Especially by integrated therapies in the face of aggressive environmental factors. The results of the NADMR studies will allow the design of subsequent clinical trials on PA, CVD and "non-specific" methods of treatment of these diseases in order to increase the functional activity of the organism and improve adaptive capabilities.

Conflict of interests: none declared.

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