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Dynamics Of Changes In Natriuretic Hormone During Immobilization Stress

Nasirillayeva O.B., Toshtemirova P.Z.
Tashkent State Medical University

ABSTRACT. This literature review examines in detail the effects of natriuretic hormones during immobilization stress and the dynamics of their changes. It also provides information on the types of natriuretic hormones and their influence on the activity of other hormones. Experiments conducted on this topic and their results are described. The findings show that significant changes in natriuretic hormone secretion occur at the early stages of immobilization stress, and this process is closely associated with cardiac activity and stress hormones. Additionally, the activation of the neuroendocrine system and the heart's endocrine responses under stress were assessed.
Keywords: Blood pressure, cortisol, hypothalamic-pituitary-adrenal system, renin-angiotensin-aldosterone, atrial natriuretic peptide, stress.
АННОТАЦИЯ. В данном обзоре литературы подробно рассматриваются эффекты натрийуретические пептиды в процессе иммобилизационного стресса и динамика его изменений. Также представлена информация о типах натрийуретические пептиды и его влиянии на активность других гормонов. Описаны проведенные по данной теме эксперименты и их результаты. Полученные результаты показывают, что на ранних стадиях иммобилизационного стресса происходят значительные изменения в секреции натрийуретические пептиды, и этот процесс тесно связан с сердечной активностью и гормонами стресса. Оценена активация нейроэндокринной системы и эндокринные реакции сердца под воздействием стресса.
Ключевые слова: артериальное давление, кортизол, гипоталамо-гипофизарно-надпочечниковая система, ренин-ангиотензин-альдостероновая система, предсердный натриуретический пептид, стресс.
ANNOTATSIYA. Ushbu adabiyotlar tahlilida natriy uretik gormonning immobilizatsion stress jarayonidagi ta'siri va o'zgarishlar dinamikasi keng yoritilgan. Natriy uretik gormonning turlari va bundan tashqari boshqa gormonlar faoliyatiga ta'siri haqida ham ma'lumotlar keltirilgan. Shu mavzuda olib borilgan tajribalar va ularning natijalari yoritilgan.Olingan natijalar immobilizatsion stressning dastlabki bosqichlarida natriy uretik gormonlar sekretsiyasida sezilarli o'zgarishlar yuz berishini, bu jarayon yurak faoliyati va stress gormonlari bilan chambarchas bog'liqligini ko'rsatadi. Stress ta'sirida neyroendokrin tizim faollashuvi va yurak endokrin javoblari baholangan.
Kalit so'zlar: Qon bosimi, kortizol, gipotalamus-gipofiz-buyrakusti bezi, renin-angiotenzin-aldosteron, atrial nartiyuretik peptid, stress.

Introduction

Currently, stress is considered one of the major causes of many diseases, and it primarily leads to changes in hormonal activity in the body. One of these hormones is the natriuretic peptide. Natriuretic peptides were first isolated from the brain of pigs and represent a group of hormones produced in the atria and ventricles of the heart. They regulate fluid balance, electrolytes, and sodium levels in the body, and reduce blood pressure. These peptides increase the excretion of sodium (Na^+) and chloride (Cl^-) ions through the kidneys, decrease the production of hormones such as renin and aldosterone, relax blood vessels, and thereby lower arterial pressure.[1]

There are three main types of natriuretic peptides: atrial natriuretic peptide (ANP), which is produced in the atria of the heart; brain natriuretic peptide (BNP), which is mainly produced in the ventricles, especially in the left ventricle; and C-type natriuretic peptide (CNP), which is also found in other tissues. Atrial natriuretic peptide (ANP), also known as atrial natriuretic factor, atrial natriuretic hormone, atriopeptin, or atriopeptide, is a peptide hormone secreted by cardiomyocytes and is a potent vasodilator. It plays an important role in regulating water–electrolyte balance and lipid metabolism and is synthesized in the atrial muscle cells in response to increased blood pressure.

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Although BNP is mainly produced in the heart, it has also been identified in certain regions of the brain, where its expression has been shown to be significantly higher than that of ANP. In animal models, endogenous ANP released from the hypothalamus during stress has been found to suppress the secretion of adrenocorticotropic hormone (ACTH)[2].

This suggests that central BNP may also be involved in neuromodulatory systems that regulate emotional behavior and stress hormones. Over the past decade, a growing body of evidence has demonstrated the involvement of BNP in regulating hypothalamic–pituitary–adrenal (HPA) axis responses in various stress models. However, the limited number of studies investigating the effects of natriuretic peptides on HPA axis modulation have mainly been conducted in animal models and have focused primarily on the roles of ANP and C-type natriuretic peptide (CNP). While there is available information in the medical literature regarding BNP responses to acute physical stress, data on its systemic response to acute psychological stress remain very limited. [2]. In addition, the endocrine response of the heart may be regulated differently depending on the type of stress factors. This hormone performs several important functions. It promotes sodium and water excretion by increasing the elimination of sodium (Na^+) and chloride (Cl^-) ions through the kidneys. It lowers blood pressure by relaxing the smooth muscles of small blood vessels, thereby reducing arterial pressure. It also regulates hormonal activity by suppressing the effects of blood pressure–increasing hormones such as renin, aldosterone, and angiotensin II.

During immobilization stress, the dynamics of natriuretic peptides (especially ANP) are closely associated with the body's neurohumoral responses and are determined by changes in the activity of atrial mechanoreceptors, the renin–angiotensin–aldosterone system (RAAS), and the sympathetic nervous system. At the onset of stress exposure, sympathetic activity sharply increases, leading to elevated heart rate and blood pressure. As a result, atrial volume rises, and ANP secretion initially shows a slight increase.

As immobilization continues, peripheral vasoconstriction and fluid retention intensify, which increases venous return and further stretches the atria, leading to a rise in ANP and, to some extent, BNP levels. These hormones enhance natriuresis and diuresis, acting as compensatory mechanisms against stress-induced disturbances in hydro-electrolyte balance.

However, in prolonged stress conditions, excessive activation of the renin–angiotensin–aldosterone system may reduce the compensatory effect of ANP, decrease its sensitivity, and lead to a relative decline in hormone levels over time. Thus, during immobilization stress, ANP levels initially increase, remain elevated during ongoing stress, and although their effect may weaken in prolonged stress due to RAAS activation, their secretion generally remains above physiological baseline levels.

Considering that natriuretic peptides regulate hemodynamics, body fluid, and electrolyte balance through strong physiological effects, and exert inhibitory influences on neurohormonal and immune systems, it is important to determine their role in the response to acute psychological stress[2,3]. Several experimental studies on this topic have been conducted in different countries. Scientists from Charles University in Prague carried out an experiment on two different strains of rats. In this study, the localization of ANP and the possible role of hypothalamic–pituitary–adrenal (HPA) axis activity in the expression of the cardiac proANP gene were investigated.

Adult male rats of Sprague–Dawley (SD) and Lewis (LE) strains (Charles River Laboratories, Sulzfeld, Germany) were used in the experiment. Their initial average body weight was approximately 200 grams. The animals were provided with standard pellet food and water ad libitum. Rats were housed five per cage (42 × 26 cm^2) under controlled environmental conditions, including a 12-hour light/12-hour dark cycle, constant temperature (22 ± 1 °C), and relative humidity of 50–70%.

Behavioral tests were conducted between 8:00 AM and 1:00 PM. All procedures involving the rats were carried out in accordance with the European Community guidelines for the care and use of laboratory animals. The study was approved by the Ethics Committee of the First Faculty of Medicine, Charles University in Prague.

The studies were conducted on both control (non-stressed) and stress-exposed animals. Considering the potential relationship between HPA axis activity and natriuretic peptides, two rat strains with differing stress responsiveness were selected: Sprague–Dawley (SD) rats, a widely studied standard reference group, and Lewis (LE) rats, which are characterized by a blunted HPA axis response to stress.

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All animal groups were subjected to two types of acute stress in a single session: immobilization (restraint) and immobilization combined with cold exposure. Following stress exposure, a relatively high density of ANP immunoreactivity was observed in the atria of the heart in both types of animals. At the initial stage, no significant changes were observed in the hypothalamic–pituitary–adrenal system; however, with prolonged stress, activation of the HPA axis led to a reduction in ANP activity.

In this context, ANP appears to play a protective role for the heart, acting as a compensatory mechanism aimed at maintaining cardiovascular stability under stress conditions.

Upon dissection of stress-exposed animals, staining was observed in the atrial regions of the heart, whereas no significant changes were detected in the ventricles in either strain. Both strains of animals were subjected to two types of acute stress.

Immobilization stress alone was induced by fixing the rat's forelimbs and hindlimbs using adhesive tape lined internally with soft material (gauze) to prevent pain. The animal was then placed into a tightly fitting plastic mesh, which was adjusted according to the size of each animal and secured in place with a bandage.

In the case of immobilization combined with water immersion (ICS), the stressed rats were placed in a water bath at 22 °C in such a way that approximately the upper one-quarter of the animal's body remained above the water surface. After 60 minutes of stress exposure, the rats were dried and returned to their home cages for recovery periods of either 60 minutes (IS1, ICS1) or 180 minutes (IS3, ICS3).

Animals in the control group were not subjected to any procedures and were used in the experiment immediately after being removed from their home cages. From each experimental group, frozen heart tissues from four animals were sectioned using a cryostat (Leica CM1850, Germany). Tissue sections with a thickness of 10 μm were mounted onto gelatin-coated microscope slides and stored until incubation.

Sections were first preincubated for 30 minutes with normal goat serum diluted 1:25 in PBS, followed by incubation with primary antibodies. Immunofluorescent staining was performed using a rabbit anti-ANP antibody (1:100, Millipore, Temecula, CA, USA) in a humid chamber at room temperature overnight. After thorough washing, the primary antibodies were directly labeled with Texas Red–conjugated secondary goat anti-rabbit serum (1:200, Calbiochem, Darmstadt, Germany) for 1 hour at room temperature.

These directly labeled preparations were subsequently used for double incubation and were incubated with a mouse monoclonal antibody against protein gene product (PGP) 9.5 (1:100, UltraClone Limited, UK), a general neuronal marker. This incubation was also carried out overnight at room temperature.

The second incubation was performed with biotin-labeled goat anti-mouse IgG (1:200, 1 hour at room temperature; Sigma, St. Louis, MO, USA), followed by the application of fluorescein isothiocyanate (FITC)-labeled streptavidin (1:200, 1 hour at room temperature; Calbiochem, San Diego, CA, USA).

After careful washing, the preparations were mounted in glycerol buffered to pH 8.6 with diazabicyclooctane (DABCO, Sigma, USA). The sections were evaluated using an epifluorescence microscope equipped with appropriate filter combinations (Olympus BX60, Germany). Some slides were subsequently stained with alum hematoxylin for 10 minutes, washed, and re-evaluated to confirm the localization of immunopositivity.

Cardiac natriuretic peptides (NPs) play an important role in regulating blood pressure and fluid homeostasis. The biological effects of ANP and BNP released from the heart are similar. They counteract systems that tend to increase extracellular fluid volume and blood pressure, such as the renin–angiotensin system and the sympathetic nervous system [4].

Under conditions of chronic hemodynamic load, the expression, synthesis, and secretion of ANP and BNP in the heart are enhanced by mechanical and neuroendocrine stimuli. Acute stress activates the brain's noradrenergic system, which interacts with the hypothalamic–pituitary–adrenal (HPA) axis—the main neuroendocrine effector of the stress response. Therefore, activation of the HPA axis plays a crucial integrative role in adaptation to and coping with stress.

Stress factors can lead to various cardiovascular disturbances, including ventricular arrhythmias, coronary vasoconstriction, increased heart rate, and elevated blood pressure.

These pathological conditions have been shown to be associated with increased levels of natriuretic peptides in the blood. It has also been established that emotional stress factors and chronic harmful influences can enhance the expression of natriuretic peptide (NP) genes in the heart and lead to increased secretion of ANP. However, there is limited information regarding the effect of HPA system activity on cardiac NP expression

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under acute stress conditions. Moreover, it remains unclear whether changes in NP expression in cardiomyocytes are directly involved in the acute stress response [5].

In addition, a related study was conducted at the Wingate Institute in Israel. This study investigated the effects of stress on natriuretic peptide concentrations and cortisol levels. Psychological stress is highly prevalent in modern society. Students, in particular, often experience various stressors such as academic pressure, social challenges, financial difficulties, and uncertainty about the future. The brain responds to such stress by activating physiological mechanisms, leading to stimulation of the hypothalamic–pituitary–adrenal (HPA) axis, which ultimately results in the release of the stress hormone cortisol from the adrenal cortex.

The nature and extent of biological changes depend on the severity and duration of the stressor, as well as on the coping strategies employed. In this regard, psychological stressors that do not pose a direct physical threat to homeostasis generally elicit a relatively limited physiological response. Numerous studies indicate that the HPA axis response to such stressors is regulated by various brain structures.

The experiment was conducted on completely healthy students during an examination period. Before the assessment, the students' stress levels, blood pressure, heart rate, cortisol levels, and blood concentrations of natriuretic peptides were measured. The same parameters were reassessed 10–15 minutes before the exam, and the results were compared.

The main finding of this study was that circulating levels of the natriuretic peptide NT-proBNP decreased in response to a common psychological stressor in undergraduate students—namely, anticipation of a major written university examination. The presence of pre-exam stress (based on subjective stress assessments) was confirmed by objective indicators, including increased blood cortisol levels, as well as corresponding changes in heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

Stressful life events have long been suggested to stimulate specific neuroendocrine activity, and acute stress is associated with increased cortisol secretion. Studies show that cortisol levels rise during anticipation of stressful events such as oral or written academic examinations. In our study, elevated cortisol levels in students on the day of the exam clearly indicate activation of the hypothalamic–pituitary–adrenal (HPA) axis [6].

In addition, similar to other researchers, we observed a significant increase in SBP, DBP, and HR in response to exam-related stress. Notably, in the group of female students, blood cortisol levels showed a significant correlation with subjectively assessed stress levels, whereas previous studies had not found a clear relationship between psychological stress indicators and hormonal levels.

Taking into account both subjective and objective stress indicators, the main aim of our study was to analyze changes in circulating NT-proBNP levels in response to a common daily stressor. To our knowledge, this study is the first to describe the NT-proBNP profile in response to academic stress in healthy students.

It is worth noting that the heart may possess two distinct endocrine systems: one primarily located in the atria, responsible for the production of ANP and related peptides, and another mainly in the ventricles, responsible for the secretion of BNP and related peptides.

Furthermore, it has been suggested that the endocrine response of the heart may vary depending on whether the stressor is acute, subacute, or chronic. Under normal conditions, the ventricular myocardium produces only limited amounts of BNP in response to acute stimuli, whereas in chronic cardiac dysfunction, BNP secretion becomes more pronounced compared to ANP.

This is because BNP is predominantly produced in the ventricular myocardium, which has a greater mass. In healthy individuals, most of the circulating ANP and BNP originates from the atria. Therefore, BNP is considered a biomarker of cardiac diseases, while ANP is regarded as a better indicator of acute hemodynamic load.

Since ANP levels are highly sensitive to rapid hemodynamic changes, such as body position, and given that our study was conducted on healthy students, we preferred to measure BNP-related peptides. Although BNP is a more accurate indicator of the activity of the cardiac natriuretic system compared to NT-proBNP, its levels in healthy individuals are often very low or even undetectable. In contrast, NT-proBNP is more stable and has a wider measurable range. Therefore, NT-proBNP was selected to more precisely assess stress-induced changes.

Previous studies in animal models have shown that the HPA axis is inhibited at multiple levels by ANP, whereas CNP stimulates cortisol release. There is also clinical and experimental evidence suggesting that ANP

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has anxiolytic (anxiety-reducing) effects. However, there is very limited information regarding the role of BNP in the human brain and its neuromodulatory effects during psychological stress.

In our study, we found that the mean plasma level of NT-proBNP significantly decreased in individuals exposed to psychological stress.

These results are consistent with findings from animal models suggesting that BNP may suppress stress-induced increases in cortisol levels. Interestingly, a significant correlation was found in males between the magnitude of cortisol changes and the difference in NT-proBNP levels between resting and stress conditions.

The endocrine system of the heart is complex and responds differently to various types of stressors. Psychological stressors, which do not pose a direct physical threat to homeostasis, generally elicit a more limited physiological response (Kiecolt-Glaser et al., 1992). Therefore, acute psychological stress—such as anticipation of an important examination—may affect cardiac endocrine activity through mechanisms distinct from those involved in physical нагрузка or pathological conditions.

Many previous studies have shown that physical stress activates the autonomic nervous system, leading to increased blood pressure and heart rate, as well as elevated levels of ANP and BNP. In contrast, our findings demonstrate a decrease in NT-proBNP levels prior to academic stress. This pattern is fundamentally different from the increase in BNP typically observed following physical stress.

It should also be noted that there is a distinction between brain-derived BNP and circulating BNP in the bloodstream. Natriuretic peptides released from the hypothalamic–pituitary system suppress ACTH secretion, indicating that central and peripheral natriuretic systems may function independently. Accordingly, circulating NT-proBNP levels primarily reflect cardiac origin.

Since NT-proBNP and cortisol were measured simultaneously in this study, it is not possible to determine which parameter changes first. Additionally, other factors influencing NT-proBNP levels cannot be excluded. Therefore, further studies are required to better understand the underlying mechanisms involved.

It was also found that NT-proBNP levels were higher in female students compared to males. Numerous studies have shown that age and sex are independently associated with natriuretic peptide levels. In addition, previous research has reported that cortisol responses during academic examinations are also gender-dependent, which is consistent with our findings [5,7].

Conclusion. In conclusion, under conditions of immobilization stress, dynamic changes in natriuretic peptide secretion are observed. Stress not only affects blood pressure and heart rate but also influences the heart, brain, and other organs. It impacts the heart by increasing the levels of natriuretic peptides. During prolonged stress, activation of the renin–angiotensin–aldosterone system and increased cortisol levels are observed. Under the influence of these hormones, long-term stress may lead to a decrease in natriuretic peptide levels; however, their levels generally remain higher than those observed under resting conditions.

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