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EFFECT OF MALE GONADAL HORMONES ON CHANGES IN THE CARDIOVASCULAR SYSTEM CAUSED BY ACUTE COLD INJURY

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Gender differences in the functioning of the human body are considered the basis of the development of gender pharmacology. The peculiarities of the structure of the male and female bodies produce a wide range of physiological and psychological reactions that ensure each species' biological role. It is known that in extreme conditions, which include low temperatures, the mental and physical reactions of individuals of different sexes differ. The main target organs of cold injury are the central nervous and cardiovascular systems. The state of the cardiovascular system depends on many factors, one of which is the level of sex hormones. It is known that men tolerate low temperatures worse, and the survival rate of rats under conditions of acute general cooling increases when the testosterone level decreases. However, information on changes in the cardiovascular system's work under different levels of body saturation with testosterone is unclear and needs clarification. The studies show changes in the electrocardiograms of rats, changes in the hormonal background of males, and changes in heart rate, R and S wave amplitudes, and QT and ST intervals. When an acute cold injury was simulated, the electrocardiogram changes became more extensive: the R amplitude statistically decreased, and the S amplitude increased. In addition, the PQ, RS, QT, and ST intervals were statistically lengthened. The performed gonadectomy reduced the expressiveness of the changes on the electrocardiogram and restored some parameters to those considered within the limits of statistical error. Thus, the expressiveness of changes in the electrocardiogram under the influence of cold in males with a normal testosterone level was significantly greater than in animals after castration. A similar trend was observed in the analysis of blood pressure changes in male rats with different hormonal backgrounds.

Key words: gender, cold injury, ECG, blood pressure, testosterone, rats, experiment.

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ВПЛИВ ЧОЛОВІЧИХ ГОНАДНИХ ГОРМОНІВ НА ЗМІНИ СЕРЦЕВО-СУДИННОЇ СИСТЕМИ, ВИКЛИКАНІ ГОСТРОЮ ХОЛОДОВОЮ ТРАВМОЮ

Статеві відмінності функціонування організму людини вважаються основою розвитку гендерної фармакології. Особливості будови чоловічого та жіночого організму формують цілий ряд як фізіологічних, так і психологічних реакцій, що забезпечують біологічну роль кожного виду. Відомо, що в екстремальних умовах, до яких належить і низькі температури психічні й фізичні реакції у особин різних статей відрізняються. Основними органами мішенями холодової травми є центральна нервова система та серцево-судинна. Стан серцево-судинної системи залежить від багатьох факторів, серед яких рівень статевих гормонів посідає почесне місце. На даний час відомо що чоловіки гірше переносять низьку температуру, а показник виживання у щурів за умови гострого загального охолодження збільшується при умові зниження рівня тестостерону. Однак відомості щодо змін в роботі серцево-судинної системи за умови різного рівня насиченості організму тестостероном не однозначні та потребують уточнення. Проведені дослідження свідчать про зміни на електрокардіограмі щурів зі зміною гормонального фону самців, відзначались зміни в показниках частоти серцевих скорочень, амплітудах зубців R, S та інтервалах QT, ST. При моделюванні гострої холодової травми зміни на електрокардіограмі ставали більш масштабними: статистично знижувалась амплітуда R, збільшувалась амплітуда S, крім того, статистично подовжувались інтервали PQ, RS, QT, ST. Проведена гонадектомія зменшувала виразність змін на електрокардіограмі та відновлювала деякі показники до таких які вважались в межах статистичної похибки. Таким чином виразність змін на електрокардіограмі під впливом холоду у самців з нормальним рівнем тестостерону була значно більша ніж у тварин після кастрації. Схожу тенденцію було прослідковано при аналізі змін артеріального тиску у самців щурів з різним гормональним фоном.

Ключові слова: стать, холодова травма, ЕКГ, артеріальний тиск, тестостерон, щури, експеримент.

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Gender determination is an important medical and social aspect of human existence. It is known that depending on gender, a person's worldview and behavior are formed in normal and extreme conditions. The pattern of behavior depends on many factors, one of which is the level of sex hormones. The peculiarities of female and male organisms form a wide range of physiological and psychological reactions that ensure each species' biological role. Given this, the male body is physically more developed, resulting in greater physical strength and endurance than the female body. Still, while androgens provide constitutive features, they also affect behavioral and cognitive reactions [2, 4]. In extreme conditions, the male body is often characterized by a tendency to aggression, making it difficult to think consistently and logically. As

well as with an increased level of stress hormones in emergencies, men are characterized by an underestimation of real threats to life, which can even lead to death [2]. Women, in turn, are more prudent in extreme conditions and are not inclined to make adventurous decisions. Therefore, in difficult, extreme conditions, women are more inclined to preserve life [2]. These features of behavioral reactions lead to the fact that the male gender is a risk factor under the influence of extreme conditions, which include too high or too low environmental temperature, humidity, radiation, etc. In addition, the peculiarities of the structure and functioning of female and male organisms formed the basis of the concepts of gender diseases and gender pharmacotherapy. Thus, some diseases are considered "female", and some – are "male". Examples of "female" diseases are migraine, systemic lupus erythematosus, and rheumatoid arthritis, while gout and oncological diseases of the intestines, kidneys, and bladder are considered "male" [2]. Among these diseases, a special role is played by diseases of the cardiovascular system. It is known that men are more susceptible to coronary heart disease and heart attack than women at puberty, and therefore, increased testosterone levels are a risk factor for cardiovascular diseases. It is known from literary sources that the level of testosterone in the blood of men decreases with age and with the development of cardiovascular diseases. It is believed that the mechanism of testosterone reduction is compensatory, and an artificial increase in its level sharply increases the risk of developing cardiovascular pathology [4]. Cold injury also causes several changes in the cardiovascular system's function. Still, it is unknown how different levels of testosterone saturation affect ECG and blood pressure indicators under extremely low temperatures [1].

The ability to survive extreme conditions with minimal damage depends on the coordinated work of all the organs and systems of the human body. In addition to the central nervous system, the cardiovascular system plays one of the most critical roles. The coordinated work of the cardiovascular system provides oxygen and nutrients to vital organs and fills the entire body with necessary substances [12].

The purpose of the study was to establish changes in the work of the cardiovascular system of male rats under the influence of extremely low temperatures, depending on the level of sex hormones.

Materials and methods. Experimental studies were performed on 56 sexually mature male rats of the Wistar line weighing 280–300 g based on an accredited experimental laboratory for the preclinical study of pharmacological substances of the Department of Pharmacology of the National Pirogov Memorial Medical University. The animals were obtained from the vivarium of the Institute of Pharmacology and Toxicology of the National Academy of Sciences of Ukraine. After a two-week quarantine, the animals were divided into 8 groups of 7 rats. To determine the role of sex hormones, some animals underwent bilateral orchidectomy. Operative interventions were carried out according to the generally accepted methodology and in compliance with the rules of asepsis. After anesthetization with a ketamine solution (Farmak, Ukraine) at the rate of 10 mg/kg, the animals were fixed on a special table for surgical interventions, and thorough epilation of the abdominal area was performed. The operative field was treated three times with solutions of iodine and alcohol according to the Grossich-Filonchikov method. Operative access was provided by performing a lower-middle laparotomy, after which the main surgical procedure was performed. The main operative technique involved removing the testicles from the wound and applying ligatures to the spermatic cord on one side and the ligament of the cremaster muscle on the other. Subsequently, the formations between the ligatures were cut, and the testicles were removed. After removing the testicles, the laparotomy wound was sutured in layers, the muscles were sutured with catgut, and the skin was sutured with monofilament suture material according to the Donatti method. After the surgery, 7 animals were placed in cages, and the postoperative wound was treated daily with a betadine solution (EGIS Pharmaceutical Plant, Hungary). According to methodological recommendations, the rats were left for 21 days until the remaining testosterone was removed from the body [2].

The state of the cardiovascular system was assessed using ECG parameters, and blood pressure was measured invasively on the tail artery. To determine the ECG parameters, the animals were anesthetized with a ketamine solution and fixed on the operating table. Electrodes were placed on special clips on the animals' front and back legs. The ECG was recorded in real-time using a cardiogram recording unit, ECG-100 equipment, from Biopack Systems Inc., USA. To determine blood pressure parameters, animals were placed in a special box in a prone position after anesthesia. The tail artery was catheterized (an Ultraflon catheter, Medicare G24), and a strain gauge was connected. Blood pressure was measured using the TSD104A unit of Biopack Systems Inc., USA. Acute cold injury (ACI) was reproduced by methodological recommendations [1]. After adaptation, the animals were taken into the experiment after 20 minutes of staying in the boxes at a low temperature. The obtained data were statistically processed using descriptive statistics, non-parametric using the basic data, and the STATISTICA 6.0 program. The results were presented as the arithmetic mean value and the mean square deviation $M \pm \delta$. Differences with a value of $p \leq 0.05$ were considered reliable.

Results of the study and their discussion. Analysis of the heart rate in male rats with different hormonal backgrounds showed that the heart rate in the control group of male rats corresponded to an average of 380.71±12.46 (p≤0.05). However, after gonadectomy, against the background of a critical decrease in testosterone, the average heart rate increased by 6.9 %. Later, when changes in the heart rate parameter were determined after an acute cold injury, it was found that in the group of animals with a normal level of testosterone, the decrease in heart rate was 32.2 %, which was more pronounced in comparison with animals after gonadectomy (25.9 %, (p≤ 0.05)). It should be noted that changes in heart rate in rats after castration against the background of acute cold injury were not critical and did not go beyond the normal heart rate in animals of this species.

Acute cold injury causes a slowing down of the heart and other disturbances in its functioning. A comparison of the amplitude of the P, R, S, and T waves on the ECG in male rats with different hormonal backgrounds against acute cold injury showed that the saturation of the body with testosterone changes the contractility of the heart's ventricles and conduction through the conduction system (Fig. 2).

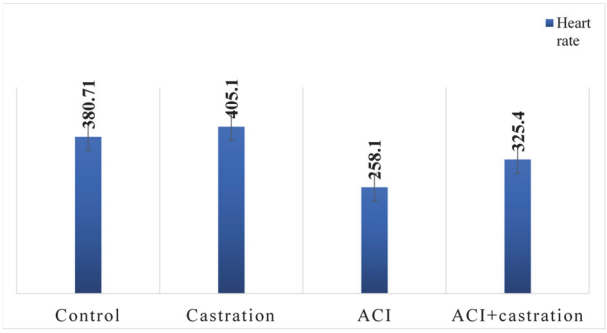

Fig. 1. Determination of heart rate in male rats with different hormonal backgrounds against acute cold injury.

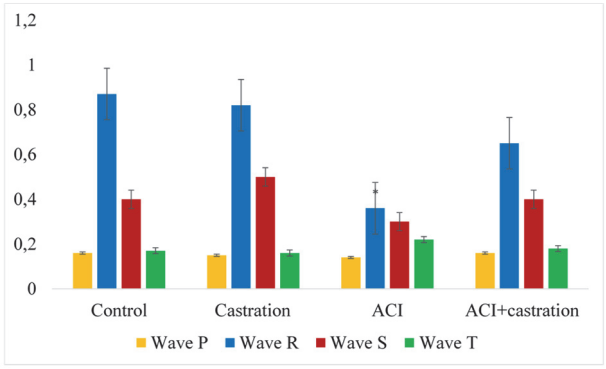

Fig. 2. Amplitudes of primary waves in male rats under conditions of different levels of sex hormones against the background of acute cold injury.

After gonadectomy in male rats, the amplitudes of the P, S, and T waves on the ECG practically did not change, while the amplitude of the R wave slightly decreased (by 5.7 %), and the average value of the S wave, on the contrary, increased by 20.0 %. The wave sizes decreased after an acute cold injury, but not to the same extent. The most significant deprivation was registered in the R wave, which declined by 58.62 %. In contrast, the sizes of the other waves did not decrease statistically significantly compared to the control group. Against the background of castration, changes in the amplitudes of the P and T waves were insignificant compared to rats with normal testosterone levels. The values of the R and S waves tended to increase compared to rats in the ACI group. The amplitude of the S wave did not differ from the control, and the R wave was smaller by 25.2 % compared to the control group.

When analyzing and calculating the length of the main intervals on the ECG of male rats in the II standard lead, it was found that two of the four studied intervals lengthened against the background of castration. Still, their value did not exceed the standard error limits; we are talking about the QT and ST intervals, and the average values of these intervals lengthened by 26.6 % and 14.2 %, respectively, compared to the control. Against the background of an acute cold injury, all studied intervals lengthened, respectively: PQ – 50.0 %, QRS – 19.04 %, QT – 33.3 %, and ST – 28.5 % compared to the values of these intervals in the control group (Fig. 3).

This indicates a violation of conduction in the heart of rats after exposure to low temperatures. In addition, the trophic state of the myocardium is disturbed, and signs of ischemia appear. On the other hand, when the cardiograms of male rats with orchidectomy were examined, the signs mentioned above were half as pronounced.

The reaction of the cardiovascular system to the action of ultra-low temperatures depends not only on the work of the heart but also on blood pressure parameters. It is known that when exposed to cold, peripheral blood vessels react from peripheral vasospasm to vasodilatation in the terminal stages of cold injury. At this point, people develop a paradoxical response to cold; they feel heat all over their bodies and even try to remove their outer clothing. Therefore, studying blood pressure parameters against the background of different levels of androgens in male rats is necessary for understanding the mechanisms of involvement of sex hormones in the processes of vascular reactions against the background of cold injury. The study of blood pressure parameters in rats with different levels of sex hormone saturation showed that in the control group of animals, the average systolic pressure was 129.7±7.46 and diastolic 92.13±2.89 (p≤0.05) (Fig. 4).

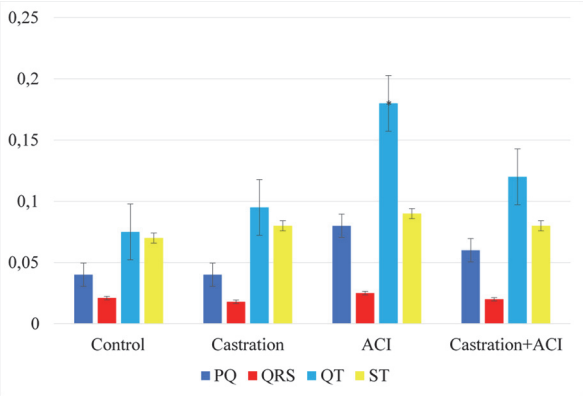

Fig. 3. ECG intervals in male rats with different hormonal backgrounds after acute cold injury.

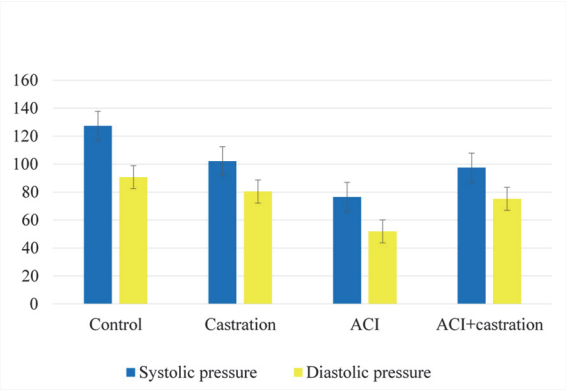

Fig. 4. The value of blood pressure parameters in male rats with different hormonal backgrounds against the background of ACI.

After gonadectomy, blood pressure parameters in male rats almost remained the same. Only the average systolic pressure decreased by 19.8 %. In contrast, after acute cold injury, blood pressure in hormonally normal male rats decreased dramatically: systolic by 39.95 % and diastolic by 43.46 %. In the background of castration of male rats, the decrease in blood pressure was slightly less than in the group of rats with a normal hormonal background and was 23.4 % and 20.06 % compared to the control group.

Humoral factors play an essential role in regulating the work of the cardiovascular system. Hormones, as biologically active substances, can regulate the work of many organs and systems. However, the effect of hormones on the heart's work is still being studied. Literary sources have described the ability of the adrenal cortex hormones to stimulate the adrenal system of the human body and animals many times. Still, the role of sex hormones has not been thoroughly studied. Therefore, determining the influence of male and female sex hormones on the work of the cardiovascular system will make it possible to expand the existing concepts of gender pharmacology. Data from the world literature convincingly testify to changes in the level of sex hormones when the pathology of the cardiovascular system occurs [11]. Many literary sources also testify that sex hormone levels depend on the production of vasoactive molecules. These molecules ensure the proper tone of both coronary and peripheral vessels, ensuring normal blood pressure indicators. It is known that a high level of testosterone is associated with vasospasm and a decrease in the production of vasorelaxing molecules, while estrogens, on the contrary, change this vector to the opposite.

According to the literature, gonadal hormones are important factors that determine the different sensitivity of the body of male and female animals to adverse environmental factors. Previously conducted studies of sexual dimorphism of the body's tolerance to extremely low and high temperatures showed greater endurance of the female body. Still, after removing the sex glands, the life expectancy of females decreased, while in males, on the contrary, it increased, and the sex difference was practically leveled [2, 6]. Our work involved researching changes in the functional parameters of the cardiovascular system in males with different hormonal statuses and against the background of acute cold injury. It was established that gonadectomy in male rats contributed to a decrease in systolic blood pressure and caused several changes on the electrocardiogram, namely, a reduction in the amplitude of the R wave, an increase in the amplitude of the S wave, and a prolongation of the QT and ST intervals. The results obtained regarding changes in hemodynamic parameters and electrical activity of the myocardium of male rats against the background of testosterone deficiency do not contradict the data of the literature [6, 7]. Acute cold injury caused disorders of cardiohemodynamics in males with different hormonal statuses, although the expressiveness of the changes was greater in animals with normal testosterone levels. Thus, in animals without changes in hormonal status, acute cold injury caused marked violations of myocardial contractility and conduction, as well as hemodynamic disorders: a probable decrease in heart rate, systolic and diastolic blood pressure, a reduction in the amplitude of the R wave, and a prolongation of the PQ, QRS, QT, and ST intervals was recorded (28.5 %) compared to animals in the control group. Similar changes in the functional parameters of cardiovascular activity against the background of the effect of the cold factor were recorded in earlier clinical studies, in which, in addition, the appearance of the J wave and Osborne waves on the ECG was recorded [9]. Against the background of gonadectomy, acute cold injury caused less pronounced disturbances in cardiovascular activity because the changes in the cardiohemodynamic parameters we studied were significantly more minor than in animals with normal testosterone levels.

Our results are evidence that male sex hormones potentiate the negative effect of the cold factor on the state of the cardiovascular system. There is a question about the possible mechanisms by which androgens influence the cardiovascular system's sensitivity to damage. According to the literature [4, 10, 12], it is known that testosterone causes an increase in the concentration of calcium ions in vascular myocytes, increases the expression of angiotensin receptors, decreases the synthesis of vasodilators, inhibits microcirculation, exhibits a pro-oxidant effect in the myocardium (causes a decrease in the activity of superoxide dismutase, an increase in the activity of NADPH-oxidase and strengthening of lipid peroxidation processes). It is accompanied by increased susceptibility of the heart and blood vessels in males to the action of damaging factors, including cold injury.

Conclusions

1. Acute cold injury causes a violation of contractility, conduction, electrical activity of the myocardium and disorders of hemodynamics in males without changes in hormonal status, which is probably evidenced by a decrease in heart rate (by 32.2 %), BP (systolic by 39.95 %, and diastolic by 43.46 %), decrease R wave amplitude (by 58.62 %) and prolongation of PQ (by 50.0 %), QRS (by 19.04 %), QT (by 33.3 %), ST (by 28.5 %) intervals compared to animals of the control group.

2. Castration of males reduces the negative impact of the acute cold injury on the functioning of the cardiovascular system, which is evidenced by less pronounced changes in cardio-hemodynamic parameters in animals with a reduced level of testosterone compared to controls: a decrease in heart rate and blood pressure is 20.06–25.9 %, a decrease wave amplitude – 25.2 %, prolongation of PQ, QRS, QT, and ST intervals – 14–25 %.

3. The level of testosterone is an important factor in modifying men's sensitivity to the action of the cold factor. This determines the need to control the serum content of male gonadal hormones in persons whose work is associated with extremely low temperatures.

4. Further research in this direction will deepen our understanding of how sex hormones influence acute cold injury's pathogenesis and optimize personalized pharmacotherapy approaches.

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