Biological Chemistry and Physiopathology of Metabolism During Fever

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Physiopathology determines the causes and conditions of pathological processes, in other words, of aetiology, as well as the mechanisms of their production, namely pathogenesis; this discipline studies the general reactions of the organism, regardless of the form of the disease by which they would manifest themselves; it also studies the general rules for the occurrence and evolution of the disorders of the functions of different systems which depend on the properties of the whole organism. The tasks of physiopathology become clearer when we compare it with the tasks of the clinical investigation. Physiopathology clarifies the causes and the mechanism of the onset of a thermal reaction of the body, such as fever; the clinical part, in this case, deals with certain well-defined forms of febrile disorders, especially of infectious origin. Physiopathology studies the general rules of occurrence and development of the inflammatory process, while the clinical disciplines investigate a number of diseases caused by different forms of inflammation. Physiopathology is closely related to biology. The personal clinical study was carried out during the period 2016-2018 on a sample of 362 patients, who showed changes in the functions of different systems and organs during fever. The problem of the influence of fever, seen as a general reaction of the organism to the action of infectious agents, is of major importance in clarifying the role of fever as a reaction of adaptation in the fight of the body against infection, and it largely determines its treatment. Excessive temperature increase, as well as a sudden drop, can exert a harmful effect on the body.

Keywords: physiopathology, functional changes, pathological processes, occurrence mechanism

The ability of the body to maintain its temperature at a certain level (within certain limits), independent of the external environmental temperature variations, is called thermoregulation.

Chemical thermoregulation (heat production) and physical thermoregulation (heat release) are the mechanisms by which the thermal balance and the temperature of the internal environment of the organism are established.

Thermal balance disorders increase in hypothermia (cooling), hyperthermia (overheating) and fever (general reaction of the homeothermic organism to the action of a pathogen, mainly of infectious nature). All these changes of the thermal balance occur as a result of a thermoregulation disorder and are characterized by the change in body temperature.

The mechanisms regulating thermal balance in the body are physical and chemical thermoregulation. The enlargement of the peripheral vascular bed increases the amount of heat released by the skin. The vascular mechanism of heat release is usually a reflex one. The physical regulation of the heat is achieved by means of sweat secretion that is achieved through the nerve centres situated in the diencephalon and the bulb, by reflex path following the action of the heat or directly by means of the heated blood. The activity of these centres is subordinated to the cerebral cortex, a fact proven by the psychic emotions influence sweating. The impulses from the central nervous system are directed through the intermediate neurons along the sympathetic nerves that innervate the sweat glands.

Breathing is the third way of physical regulation of the heat. In the physical regulation of heat with the help of breathing, the cerebral cortex is of particular importance.

The main devices for the physical regulation of heat are in a continuous interaction. This is because in the general thermal balance they are able to replace each other.

The chemical regulation of heat, and by this we mean the regulation of metabolism, is of great importance in the thermal balance. In response to the decrease of the temperature of the environment, the thermogenesis processes in the body intensify and, on the contrary, in response to the increase of the ambient temperature, these processes decrease in intensity. Thermogenesis disorders occur due to impairments in nervous regulation.

From the central region of chemical regulation of heat, the nerve conductors go into the spinal cord and, continuing on new neurons, leave it approximately at the level of the last cervical segment and of the first thoracic segment.

The vegetative segment of the nervous system constitutes an intermediate link in the central regulation of thermogenesis; particular importance is attributed to the sympathetic nerves.

The physical and chemical regulation of heat are also brought together by means of the function of the upper segments of the brain. A very important role in this regard is assigned to the cerebral cortex.

In the process of phylogeny and ontogeny, the role of the chemical regulation of heat is reduced, the physical regulation gaining greater importance.

The peripheral organs participating in the processes of chemical regulation of heat consist of all the tissues of our organism in which the metabolism of the substances and the energetic one take place, the most important organs of thermal metabolism are the muscles and the liver, where the greatest amount of heat is developed. These organs

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participate more than the others in the disorders of thermal metabolism.

In fever, the processes of protein degradation are energetically carried out in the liver and metabolic processes are increased, the temperature of the liver being in such cases higher than the temperature of blood and other organs. The denervation of the liver leads to a certain disorder of the heat balance, due to the interruption of those nerve pathways that connect this organ with the central area of †thermoregulation.

Talking about muscles as one of the main areas of heat exchange we usually consider their participation in the chemical regulation of heat even in the absence of visible muscle contractions. Not only the liver and muscles, but also all organs and tissues participate in the processes of heat exchange; the liver and muscles are given special attention due to the fact that, especially at their level, the chemical regulation of heat is achieved.

The thyroid gland is part of the chemical heat regulation system; the function of the thyroid gland changes due to variations in the surrounding temperature. Clinical observations show that in the hyperfunction of the thyroid gland, the temperature is higher than in cases of its hypofunction. The adrenal glands and pituitary gland also participate in the chemical regulation of heat.

Fever is a general reaction of the body's adaptation to the action of a harmful agent, but most often of an infectious nature, a reaction that occurs during evolution and represents a disorder of thermoregulation; due to this disorder, heat accumulation and temperature rise occur of the body, regardless of the temperature variations of the external environment.

Unlike hyperthermia, which occurs exclusively under the influence of the increase in external temperature, fever may occur under ordinary thermal conditions. As a result of the central thermoregulation disorder, the normal correlation between heat release and production changes, which eventually causes the body temperature to rise. The pathogen agent first causes the modification of the physical thermoregulation.

The febrile organism retains its ability to regulate the temperature, but the character of this adjustment is qualitatively modified: the correlations between various control systems are disturbed, the body's resistance to changes in the external environment temperature decreases, the heat regulation limits are reduced; often, the febrile organism may be more easily subjected to cooling or overheating.

In the pathogenesis of fever, the main importance belongs to the disturbance of the function of the central nervous system, which regulates the thermal balance. In the mechanism of the appearance of fever, a direct humoral action of the pyrogenic substances is suspected to appear on the central nervous system (automatic action).

In the evolution of most fevers we can distinguish three stages: the temperature rise stage, usually of short duration, is characterized by the increase of the body temperature. It occurs right at the beginning of its development, by decreasing the release of heat following peripheral vasoconstriction. The ratio between heat production and release is increased. This discrepancy between heat production and release is often accompanied by chills. In these cases, due to muscle contractions, thermogenesis increases even more.

The faster the fever progresses, the greater the discrepancy between the chemical and physical regulation of the heat, and the more pronounced the chill is; in such cases, thermogenesis almost always exceeds the heat release.

The second stage is characterized by an increase in both thermolysis and thermogenesis established at a certain level. The balance between the production and the release of heat is set at a higher level than in a healthy man.

The body does not lose its ability to adjust the temperature set to another level. It also retains the peculiarities of a febrile organism. The release of heat occurs on the same paths as in the normal condition, with the only difference that the role of perspiration is relatively low.

The decrease stage is characterized by a decrease in thermogenesis and an increase in thermolysis. Increased heat release can occur as a result of increased sweating (sometimes very abundant) and by peripheral vasodilation. The relationship between thermogenesis and thermolysis is reversed as compared to the first period of fever. Then thermogenesis and thermolysis as well as body temperature, return to normal. At this stage, temperature is often unstable.

In all the described phenomena, both physical and chemical thermoregulation participate. The disorder of physical thermoregulation is of predominant importance. In the various stages of febrile reaction, in the thermal balance we can find oscillations explained by compensation of disturbed functions, which is in turn related to the physiological role of defence of the central nervous system. The evolution of the different periods of the febrile process is determined, not only by etiological factors, but also by the state of the organism, by the reactivity of its nervous system, by metabolism and by the intensity of the oxidative processes.

Metabolism in fever is disturbed by several factors. Firstly, the increase of body temperature, secondly most often the infectious agent influences the etiological factor.

Metabolism disorders are not identical in fevers of different origins. However, there are certain metabolic disorders typical of most fevers. These disorders are explained by changes in thermoregulation, common to all fevers.

The hyperglycaemia that occurs in fever following increased glycogenolysis in the liver shows a change in carbohydrate metabolism. Occasionally, a transient glycosuria is also observed.

Lipid metabolism is also increased during fevers, especially those of infectious nature, with a chronic evolution. Increased lipid consumption does not depend only on fever, but also on associated starvation, and to some extent, perhaps, intoxication; sometimes there is the case of ketonemia. Some researchers consider that the disorder of lipid metabolism in fever is related to the change in the function of the lipid metabolism centre in tuber cinereum.

Particularly pronounced are the changes found in protein metabolism. During the fever, the amount of nitrogen eliminated through the urine increases, except for some aseptic fevers where there is no increase in the protein metabolism. In people with moderate fever, the participation of proteins in the general energy metabolism is about 15-20% and in fever with relatively high temperature, of over 30%; In infectious fevers, this participation of proteins increases significantly (by 50-100%, even more). Thus, a greater part of the thermogenesis is due to the oxidation of proteins.

An important issue is whether the increase in protective metabolism is due to the increase in body temperature or is only a result of the toxic action of the infectious agent.

Protein loss by an organism affected by fever can be compensated, according to the laws of isodynamics, by other proteins or lipids and carbohydrates introduced from outside. In reality, however, protein degradation cannot always be compensated for, since in severe febrile processes, protein degradation is much greater than their intake through food; the loss of nitrogen through the urine is much greater than the intake through food proteins.

The modification of carbohydrate, lipid, hydro-saline metabolism during febrile conditions also depends on the disturbance of the central portions of the tuber cinereum, which regulates the metabolism. Centrogenic thermoregulation is related to the entire central-vegetative area of metabolism regulation.

The concepts regarding the autonomy of all these centres of protein, lipid and carbohydrate metabolism and their connection to central thermoregulation should not have a dogmatic character. Based on all probabilities, the central areas of metabolism regulation are coordinated between them; this coordination is disturbed during fever.

The problem of protein metabolism during fever is of particular importance in the diet of patients affected by fever. During severe febrile conditions it is difficult to completely eliminate the loss of tissue proteins. In the case of serious infectious diseases, however, we must seek to limit protein losses by abundant carbohydrate administration in the most easily assimilable form.

In case of fevers of an infectious nature, intravenous administration of glucose is used, which is more easily oxidized and can cover to a certain extent the caloric deficit and the excessive losses of proteins, dangerous to a feverish organism, which fights against the pathogen.

The hydro-saline metabolism is also modified during the febrile processes. Following the increase of the metabolism and the accumulation of the products of lipid and protein metabolism, the water retention occurs in the tissues.

The disturbance of the filter function of the kidney is of particular importance in this regard, due to the intoxication and the temperature increase, especially in the second period of the fever. This period is accompanied by a decrease of diuresis. Water retention is already noticed towards the end of the period of temperature increase. In the third period, however, due to the pronounced increase of thermolysis, the intensification of perspiration and diuresis, it is noticed an intensification of the water elimination process.

With regard to mineral metabolism, it is known that during fever, in connection with the disturbance of the water metabolism, the retention of chlorides can be observed, which are eliminated in an increased amount during the third period, when diuresis begins to increase. Tissue degradation increases the elimination of phosphorus and potassium salts. The changes in the hydro-saline metabolism found in febrile processes are related to the changes in the entire metabolism in febrile states.

Experimental part

Material and method

The personal clinical study was carried out in the period 2016-2018 on a sample of 362 patients, who presented changes in the functions of different systems and organs during fever.

The clinical-statistical study – variables such as gender, age, country of origin, medical history were correlated with the incidence of the disease.

Results and discussions

Fever is characterized by the alteration of the functions of the nervous system, of the cardiovascular system, of the respiratory system, of the gastrointestinal tract and of the kidneys.

At the level of the *nervous system*, thermoregulation disorders occur during fever.

Of the 362 cases, in 64 cases (17.67%) we found phenomena that depend on the change of body temperature and on the state of intoxication. Hyperthermia as such (in aseptic fevers) causes, depending on its intensity, consecutive arousal and inhibition of the central nervous system. In the course of fevers of an infectious nature, there is often a feeling of weight in the head, general malaise or mental confusion, delirium, hallucinations, etc. In the exhausted patients, fever usually develops with phenomena of inhibition of the nervous system.

From the vegetative nervous system, we can see the predominance of the function of its sympathetic segment.

Heart rate, in fever, accelerates due to the reflex excitation of the sympathetic nervous system; our case study comprises 53 cases (14.64%).

The etiological factor that causes fever - especially the infectious agents and their toxins, as well as the metabolic products with toxic action - excites the activity of the heart.

The degree of functional change of the myocardium and of the governing system of the heart depends on the character of the infection and intoxication. The change of the condition of the vessels, during the fever, is related to the disturbance of the physical thermoregulation; for example, the stage of the shiver is accompanied by a spasm of the peripheral vessels and by a blood flow towards the internal organs.

Blood pressure during fever is characterized in the 119 cases (32.87%) at the beginning by a certain increase, due to the intensification of the activity of the heart and the excitation of the vasomotor centres; in the last stage, however, blood pressure decreases as a result of a weakened heart activity and vessel dilation. Blood pressure lowering can sometimes cause collapse.

Breathing is accelerated during fever in all 69 cases (19.06%) Acceleration of breathing goes in parallel with the acceleration of the pulse and the increase in body temperature. The function of the respiratory centre is also intensified in relation to the increase of blood temperature and the occurrence of acidosis, due to the accumulation of acid metabolic products. Respiration participates in the physical thermoregulation along with the vascular system and the sweat glands. Therefore, the change of respiration during fever is one of the mechanisms of physical thermoregulation.

The function of the *gastrointestinal tract* is altered in the 71 cases (19.61%) especially after the disturbance of the activity of the nervous system: the secretion of saliva, of gastric and intestinal juice, of bile decreases, dryness of the oral mucosa and tongue appears; intestinal peristalsis is changed in the sense of constipation, which leads to the intensification of the putrefaction processes, accumulation of gases and the appearance of meteorism. Insufficient digestion and diminished resorption lead to a marked decrease in the assimilation of food products, to phenomena of anorexia, intoxication etc. Digestion and insufficient assimilation of food prevents isodynamic compensation of proteins lost during fever.

The renal function presents in 55 cases (15.19%) pathological changes during fever. A particularly intense action is exerted by toxins on the renal filter during infectious fevers. At the beginning of the febrile process, the amount of urine decreases significantly; water is retained by tissues. The concentration of nitrogenous substances increases in the urine. The various febrile conditions, depending on the

etiological factors, have in this respect certain peculiarities in accordance with the degree of protein disintegration. The amount of urine increases markedly during the third period of fever, when the body temperature begins to decrease.

Urine, albumin, peptone and albumen are sometimes found in urine. The amount of albumin eliminated depends largely on the character and intensity of the kidney injury. A special role has, not so much the hyperthermia, but the infection and intoxication that caused the fever process.

Regarding the *anatomopathological changes* during fever, dystrophic phenomena are observed in most cases, especially in the parenchymal organs. Changes in internal organs usually have a turbid intumescence character, sometimes of waxy degeneration, of fatty infiltration, etc.

The dystrophic phenomena in the internal organs cause the disturbance of their function, which in turn reflects on the evolution of the febrile process.

Conclusions

To the extent that temperature reflects the degree of reactivity of the diseased organism, it may be a valuable index of the condition of the body fighting the infection.

In each case, the character of the fever evolution and its importance to the body must be particularly appreciated.

Fever considered as an adaptation of the organism, which appeared in the process of evolutionary development, in cases of moderate temperature increase can be useful in the fight of the organism against the infectious agent causing it.

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Manuscript received:10.05.2019