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ENDOTHELIAL DYSFUNCTION AND MELATONIN

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ЭНДОТЕЛИАЛЬНАЯ ДИСФУНКЦИЯ И МЕЛАТОНИН

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The item offers independent and referential data on the role that melatonin plays in the regulation of endothelial function. There is also an analysis of the impact that melatonin has on cardiovascular system activity, which is related to restriction of arterial hypertension, atherosclerosis, metabolic syndrome with hyperlipidemia and diabetes mellitus, and enhanced platelet hemostasis. There is a discussion of a set of mechanisms on the cellular level (counteraction to oxidative stress) as well as on the systemic level – psychotropic and chronotropic effects of melatonin.

Key words: melatonin, endothelial dysfunction

Рассматривается влияние мелатонина на деятельность сердечно-сосудистой системы, связанное с ограничением артериальной гипертензии, атеросклероза, проявлений метаболического синдрома с гиперлипидемией и сахарным диабетом, усиленным тромбоцитарным гемостазом. Приводятся собственные и литературные данные о роли мелатонина в регуляции функции эндотелия. Обсуждается комплекс механизмов на клеточном (противодействие оксидантному стрессу) и на системном уровнях – психотропный и хронотропный эффекты мелатонина.

Ключевые слова: мелатонин, дисфункция эндотелия

The current knowledge is that disturbed vascular endothelium or its dysfunction is in the core of various pathological processes while cardiovascular disorders top the list of the pathologies. These include hypertension, atherosclerosis, hypercholesterolemia, cardiac weakness, diabetes mellitus, etc., which makes the search for a way to counteract the pathology in question rather urgent. In the recent years, researchers and clinicians have been focusing on treatment capacity of melatonin (MT) – the major hormone of the pineal gland.

Central MT – main hormone of the pineal gland, which secreted with a clear diurnal periodicity (only in the dark part of the day) and gets into the bloodstream to be circulated round the entire body. Account high lipophilicity, it will be quickly distributed through various organs. Here its activity is enforced with the peripheral MT produced by the cells of some tissues (retina, gastrointestinal tract mucosa, blood cells, etc.). The different pools of MT, combined, interfere into the activity of the central nervous system and internal organs serving a large-scale adaptogenic mission [1].

According to a number of investigations, apart from its specific biological activity, MT holds a range of protective pharmacological properties. They may be used to day for therapy of different kind of pathology [6]. Besides, MT has proven effective for treating numerous cardiovascular system diseases, while its protective role in such cases has been documented in a number of reviews [9, 10, 13, 31, 79].

A brief overview of the works above-mentioned, with certain reservations though, makes it possible to say that the protective effects of MT towards the cardiovascular system can be appeared in different form. This hormone's effect is vasodilation and decrease of systemic arterial blood pressure; optimization of its circadian variation; restriction of the atherosclerotic process; reduction of left ventricular hypertrophy; decreased circulating blood mass and improved aggregation properties in blood, etc. No doubt, each of the effects is of therapeutic value, which allows now talking of further investigation into the pharmacology of MT towards wider introduction of its drug into clinical practice for treating cardiovascular diseases. One of the concrete determining factors is a study of MT's capacity to limit the manifestations of endothelial dysfunction.

Vasodilatory Effect. *In vitro* and *in vivo* experiments mainly performed on rat have revealed vasodilatory property of MT. Evidence to this could be seen in the increase of the inner diameter of the abdominal aorta, as well as femoral and mesenteric arteries in case of vascular perfusion with a liquid containing different volumes of the MT (50–300 pg/ml). When taken in dosages of 5 or 10 mg/kg it also demonstrates moderate antihypertensive action, which was obvious from the systemic arterial blood pressure registered in healthy animals. Contrary to that, surgical removal of their pineal gland was followed, for some time, with disposition to hypotension [46, 48, 61].

This effect, even at the level of vessels only, could be achieved with MT employing various mechanisms including a possible impact on the vasoconstrictor and vasodilator compounds production either by the endothelium of the vessels themselves or at the systemic level; reduction in the smooth muscle tone of the vascular wall; improved blood flow through more condacted vessels due to a limited infiltration of the endothelium with atherosclerotic plaques; optimization of blood rheological properties.

Endothelial cells are known to play a crucial role in maintaining blood pressure. Among other mechanisms, this is done due to expression of biologically active compounds having opposite effects on the vascular diameter [12].

Potent vasoconstrictor factors include endothelin-1, which is secreted by endothelial cells, and this process is especially intensive under hypoxia, ischemia, and acute stress. In addition to vasomotor reactions, endothelin-1 stimulates platelet aggregation, while enhancing the proliferation of smooth muscle elements of the vascular cover predisposed the development of atherosclerosis. Hence, the interaction of MT with this factor, which is antagonistic nature, takes on a specific role when applied to the issue of endothelial dysfunction. Such interaction can be indicated that pre-treatment of rats with MT (10 mg/kg) prior to the ischemia/reperfusion in rats prevents increased expression of endothelin-1 and its receptor ET(B) mRNA. There is also a reduction in the synthesis of endothelium-derived contractile factor (EDCF) with an increase in diameter of isolated arteries. On the contrary, pinealectomized animals show a significantly higher level of endothelin-1 in the thoracic aorta [48, 55, 56].

Another condition explaining vasodilatation under the effect of MT could be it potentiated influ-

ence on the secretion of vasodilatory compounds in endothelial cells. These include nitric oxide (NO), which relaxing vascular smooth muscle, prevents hypertension which easily developing after suppression activity of the endothelial synthase (eNOS) enzyme involved in NO production. This indicates why continuous administration of MT (10 mg/kg) into animals background high blood pressure caused by the eNOS inhibitor L-NAME, facilitates NO accumulation also resulting in vessels relaxation and hypotension. Apart from that, while ensuring the accumulation of calcium ions in the endothelial cells, MT initiates the release of another vasodilator bradykinin from them into the bloodstream, and prostacyclin – from platelet cells [56, 60].

Improved vascular condaction is partially due to anti-inflammatory activity of MT, the manifestations and mechanisms of which have already been rewieved in detail before [14]. In particular, its local injection into rats restricted the increased vascular permeability caused by the leukotriene B4. There was a decrease in the wall infiltration with neutrophils and its lesion with pro-inflammatory cytokines; during that, however, insufficient MT due to pinealectomy coincided with opposite shifts [50, 83].

The vascular effects of MT are clearly seen under conditions imitating various pathologies. Simulation of intermittent hypoxia in rats, for instance, comes associated by hypertension with severe deficiencies in the oxidant status, a decline in the NO level, and a disturbed expression of endothelial NOS. These changes were not observed when the animals had been initially administrated (for 2-3 weeks) MT (5 mg/kg) [42]. In a strain of mice with apolipoprotein E deficiency that simulated age-associated hypertension, a repeated use of MT eliminated adverse hemodynamic changes, the metabolic dysfunction and other associated aberrations in the vessel cytoarchitectonics [69].

A similar MT protection was seen in case of nicotinic vasculopathy. If, for a longer period of time, the rats had been given nicotine (100 μg/ml) in their drinking then, just like chronic tobacco abusers, they developed vascular disorders. This, judging by the investigation of the aorta from such animals, usually had come along with an increased expression of various stress proteins, fibrosis of the vascular wall with leukocyte infiltration, and enhanced platelet adhesion. In other words, there had been preconditions typical of chronic nicotine intoxication, which lead to hypertension and atherosclerosis. A long-term (28 days) combined of MT (5 mg/kg) along with nicotine, however, prevented the side effects of smoking [71].

Therefore, even if limiting the endothelial dysfunction locally and through various ways, MT is able to dilate the peripheral arteries and predispose them to hypotension. Its extra capacity to enlarge vessels is due to the ability to relax their smooth muscles, which, however, takes place in other organs as well [61]. Besides, the reduction of systemic arterial blood pressure is part of the inhibitory effect MT on the activity of the individual components of the renin-angiotensin-aldosterone system (RAAS).

Many investigated today admit that at the cell level almost all of the MT effects are based on the same universal mechanism linked to its strong antioxidant properties. Like in other cases, they can be reduced to without receptor pathway neutralization of oxygen and nitrogen free radicals, and an increased activity of antioxidant enzymes (superoxide dismutase, catalase, etc.), accumulation of glutathione and so on. [38, 58, 70]. Actually, the limitation of oxidative stress that takes place actually under any cerebral and visceral pathology is viewed as the leading mechanism that lays the basis for both common and unique protective effects of MT [3, 65].

Suggesting of the MT vascular changes, necessary to say that the large part of their triggered by activation specific receptors. Their membrane and nuclear varieties have been identified. The most common ones prevailing in the peripheral organs and in the central nervous system include G protein-coupled membrane receptors types 1 (MT1) and 2 (MT2), the less prevalent being orphan nuclear receptors of RORa/RZR family and membrane MT3 receptors. The endothelium and vascular intima contain membrane receptors of both types, which are not equally represented in various parts of the vascular system. For instance, the isolated aorta in rats have shown mRNA expression primarily for MT1, but not MT2 receptors. Moreover, some views hold that it is only MT1 receptors that are related to vasodilation, while MT2 receptors triggering may be involved in developing vasopressor response seen in a number of cases similar to the situation below [74, 77].

Most of the evidences presented can be regarded as proof to the MT capacity to attenuate the endothelial dysfunction due to the direct vasodilatory action. However, there is an opposite viewpoint based on the data obtained from studies on isolated coronary arteries from porcine hearts. Parts of the vessels with intact endothelium, when placed in a chamber to register the isometric tension of the smooth muscle, would predictably relax with an increase of the NO levels after sodium nitroprusside and other nitrates in the medium; nevertheless, this relaxation was somehow blocked when supplemented MT. It also weakened the tolerance to the vasodilatatory effect of nitroglycerin [54, 82]. The source of such contradiction could be due to the specific and regional features of coronary arteries (at least they have some difference if compared to the major arteries in terms of their response to neurohumoral stimuli). Another explanation could be seen through the fact that their walls have been found to contain not MT1 but previously MT2 receptors [82].

Antiatherosclerotic Effect. Apart from vasodilation, MT is capable of resisting the endo-

thelial dysfunction in another way – through involvement into the process of atherosclerotic vascular lesions, which leads to limitation vessels conduction, an increase in peripheral vascular resistance, and also provokes and aggravates hypertension.

The commonly shared idea is that atherosclerosis is a consequence of the vascular wall damage, endothelium first of all, and it is largely determined by the concomitant hypercholesterolemia. The latter is a source of structural change in the endothelium, a serous reason behind its disturbed barrier function with excessive infiltration of the intima by low-density lipoproteins (LDL). Their peroxide modified form, which is the most atherogenic, is the important reason of endothelial function disturbance. Along with reduced NO production, there is also a change in the adhesiveness of its surface for monocytes and platelet cells, which facilitates thrombus formation and development of fibrous atherosclerosis plaques in the vessel wall. Another extremely typical phenomenon here is enhanced inflammation in the vascular wall. All these acting together restrict the vascular permeability thus contributing to the risk of myocardial infarction and stroke [19, 81].

As show numerous experimental data, MT interferes into the atherosclerotic process through various mechanisms. Its atheroprotective effect is due to its impact on pathogenic signaling processes and, first of all, on the oxidative stress. Moreover, as mentioned before, oxygen free radicals get neutralized, the activity of antioxidant enzymes and glutathione levels go up, and disturbances in the respiratory function of mitochondria prevented, etc. [22, 36].

An improved antioxidant status of the organism at whole and of the vessels in particular coincides with anti-inflammatory action of MT. Experiments involving rabbits fed with high cholesterol diet have shown that long-term (12 weeks) administration of MT (10 mg/kg) inhibited the formation of atherosclerotic plaques in the aortic wall, which came parallel to restricted expression of pro-inflammatory factors – TNFα, Il – 6, NF-kB, as well as Toll-like receptors. This coincides with a decrease in the plasma content of a standard inflammation marker C-reactive protein [41, 75, 83].

The antiatherosclerotic activity of MT reveals itself through interaction with other drugs. For instance, in the initial phase of the development of atherosclerosis in genetically early aging mice deprived of apolipoprotein E, cyclophilin A enhanced the expression of interleukin-6 as well as other markers of inflammation in the vascular wall, and monocyte migration into it. In such animals, continuous use of MT introduced in wide dosage range (0.1–10 mg/kg) was successful in preventing the development of atherosclerotic lesions [67]. Opposite to this kind of antagonism MT increased the specific effect of atorvastatin – one of the antiatherosclerotic drugs belonging to the statin family. In the human umbilical vein endothelial cells culture, atorvastatin was able to prevent lipopolysaccharide-induced inhibition of eNOS mRNA expression, and this activity was potentiated by MT. Besides, MT, unlike statin, additional weakened the manifestations of oxidative stress and inhibited the increased production of interleukin-6 [29].

Limitation of the severity of the atherosclerotic process demonstrated by MT is also due to elimination of dyslipidemia. In animals with hypercholesterolemia caused by a respective diet or hypothyroidism, a repeated long-term (12 weeks) administration of MT introduced with drinking liquid or through parenteral injections (10–12 mg/kg/day) resulted in a decrease in plasma levels of total cholesterol and LDL. At the same time there was prevention to a drop of high-density lipoproteins (HDL) blood concentration with an increase in the HDL/LDL ratio; besides, there was a significant suppression of lipid peroxidation in the tissues of the internal organs. Among other mechanisms, this protected cell membranes, including those of vascular endothelium, against oxidative damage [23, 26, 40].

Limitation of Metabolic Syndrome. The normalizing effect that MT has on lipid metabolism is only part of a much larger interference into the metabolic processes performed in the whole organism. This has been shown through study its role in the development of the so-called metabolic syndrome, which is a set of severe metabolic disorders. The major parts of the syndrome including hypertension, early atherosclerosis and dyslipidemia. All these are indicators of endothelial dysfunction, and obvious risk factors for cardiovascular disorders, and at the same time they are direct targets for the protective action of MT. However, the metabolic syndrome has another important component in the form of insulin resistance and hyperglycemia, which allows talking about diabetes mellitus type II, which often comes accompanied with obesity. Their dependence on the MT activity is a priori possible based on the facts demonstrating its involvement in human and animal energy metabolism regulation in general, as well as its role in body weight control.

Meanwhile, in the recent years presented many of experimental evidences that MT able exert of the direct influence on the processes associated with diabetes mellitus. Earlier they have already been summarized in a quite detailed fashion [4]. In view of that, as well as taking into account the obvious clinical significance of the problem, this point requires some consideration with limitation of details and references.

Most of the data on MT interaction with insulin is derived from various experimental models of diabetes mellitus (primarily rodents) and from *in vitro* experiments. One of such models is streptozotocin diabetes in rats associated with reduced carbohydrate tolerance, a decrease in the activity of glucokinase and glucose-phosphate-dehydro-

genase in the liver, and a reduced total antioxidant status. Previous regularly administration of MT dosage (5 mg/kg, 2 weeks) reduced the severity of violations described. In Goto-Kakizaki rats with diabetes similar to that of human diabetes mellitus type II, there were issues observed like hyperinsulinemia and hyperlipidemia, reduced concentration of glucagon and the insulin receptor tyrosine kinase activity. It should be note that in analogous situations, long-term prophylactic use of MT also resulted in a evident anti-diabetic effect.

These facts are very much in line with data of *in vitro* experiments. For instance, the islets of Langerhans located within the pancreas of mice with alloxan diabetes there were degenerative changes registered. If such animals had been injected with MT (0.15 mg/kg, 15 days) then neither the number nor the structure of their isolated beta cells were different from the control indices. Introduction of MT into incubation medium of hepatocytes isolated from mice with alimentary diabetes increased their glycogen synthesis; moreover, the protective effect of MT was eliminated with its antagonist luzindole. It is also of interest that MT facilitated graft retention of islets of Langerhans in diabetes-affected mice. On the other hand, pinealectomized rats showed a reduction in the density of the islets and loss of their cellular elements.

The results of not numerous observations on humans basically coincide with the experimental findings and confirm the antidiabetic properties of MT. Insulin resistance is known to be of key importance in the development of metabolic syndrome associated with diabetes mellitus type II and cardiovascular disorders. At the same time patients with this pathology often demonstrate a disrupted ratio between the plasma levels of MT and insulin, which, as many researchers suggest, is evidence to a role pineal gland deficiency in the pathogenesis of metabolic syndrome. Regular (during 1 month) administration of MT (5 mg/day) to elderly patients with insulin independent diabetes had a positive effect on their clinical condition and reduced manifestations of oxidative stress with an increased activity of erythrocyte superoxide dismutase and a reduction in the level of malone dialdehyde.

MT involvement in the regulation of carbohydrate metabolism and its contribution into the pathogenesis of diabetes mellitus may be through different ways. A leading one is obviously direct involvement into the function of islets of Langerhans cell elements via specific receptors. Both in human and in rodents alpha and beta cells membranes express mRNAs of the main types of MT receptors (MT1 and MT2), while MT1 were found in alpha-, and MT2 – mostly in beta cells. In particular, MT may have a direct impact on insulin production due to activating the cGMP-signaling pathway through MT2 receptors. MT can overcome the insulin resistance, which is peculiar to diabetes, in a different way as well – through increasing the tissue sensitivity to hormone as a result of direct stimulation of cellular insulin receptors, and, at the same time, an easier glucose involvement in metabolism.

All the facts mentioned make it possible to join some researchers viewing the changes in the integrated MT-ergic system as one of the serious diabetes mellitus risk factors, and pineal gland disorders – as an extra source of phenotypic variations in the metabolic syndrome [28, 52, 68].

A common component of the metabolic syndrome is, as we know it, weight gain, which is another source of cardiovascular disorders as an indicator of endothelial dysfunction. Obesity is a clear evidence of some gross disorganization in the metabolic homeostasis as a whole with the heart and vascular system involved undoubtedly. Therefore the efforts aiming at its restriction should, in the long run contribute to the normalization of the vascular endothelium function [19]. Obviously, MT should have its prominent place in the combat against the disease.

Indeed, continuous (4–6 weeks) administration of MT (1–10 mg/kg) accompanied with decreasing in the weight in rats whose diet included a high share of fructose or cholesterol. This came together with a reduced oxidative status of blood and tissues, and normalized plasma insulin/glucose ratio. The effect proved stronger when a higher dosage of MT was used [43, 75, 85].

Quite expressive were the results obtained in the ob/ob obese mice. After continuous administration of MT (8–12 weeks, introduced with drink) there was a significant body weight loss observed along with their antioxidant status recovery, limited dyslipidemia, and a rather substantial change in the state of blood vessels. In particular, its impact reduced the symptoms of inflammation in the perivascular adipose tissue that are typically correlated with vascular dysfunction. The aortic walls in such rats had a typical damage to the elastic fibers and collagen accumulation. Such histopathological changes were avoided with preventive use of MT [15, 35].

Obviously, MT can not only limit obesity with its concomitant endothelial dysfunction and subsequent cardiovascular disease, but also, to a certain extent, prevent the development of various types of obesity, alimentary in particular. This must be based on its capacity to interfere with the mechanisms of eating behavior regulation, through modulating appetite and leptin production in adipocytes, which controls the mass of adipose tissue [14, 16, 18, 59]. Interesting to note that leptin through its feedback mechanism can restrict MT production by the pineal gland [57].

In conclusion, to the data provided we can state that along with aging in humans and animals, due to involution of the pineal gland the MT secretion is getting decreased. Therefore, a whole set of age-related disorders including the metabolic syndrome together with obesity, hypertension, atherosclerosis, cardiac disorders, diabetes mellitus

etc. could be attributed, to a certain degree, to MT deficiency. Based on that some authors logically recommend to the elderly people use MT drugs for preventive purposes and that it be a part of conventional set of geriatric medicine. This idea is also justified with other therapeutic opportunities that MT offers for age-related pathology, which is the subject below.

Limitation of Renin-Angiotensin System Activity. Endothelial dysfunction is closely related to RAAS excessive activity. It is a well-known fact that its effector is angiotensin II (Ang II), which is produced with the participation of angiotensin-converting enzyme (ACE), the major part of which is localized on the membranes of vascular endothelial cells. Ang II is a powerful vasoconstrictor whose action is primarily due to direct stimulation of Ang I receptors of the vascular smooth muscle, as well as to enhanced expression of endothelin-1. Another source of vasoconstriction is related to the increased degradation of vasodilator bradykinin influenced by ACE. Simultaneously, there takes place a start of processes of oxidative stress and synthesis of a number of growth factors (fibroblasts, platelets, etc.), which worsen the morphology of the vascular wall. These shifts are complemented with an increase in the circulating blood mass and remodeling of the vascular wall and heart muscle with left ventricular hypertrophy. All these combined explain the important role that RAAS plays in the development of hypertension, and ACE inhibitors – in its treatment in clinic.

Pineal MT can counteract the effects related to RAAS activation. This fact has been demonstrated both in evaluating the performance of the cardiovascular system as a whole, and through studying of its parts. The mechanisms in the core of the protective capabilities of MT was detailed studied on the cellular and systemic levels.

The hypotensive effect of MT has been detected, for instance, in experiments involving spontaneously hypertensive rats and in case of renovascular hypertension when cross-clamping of one of the renal arteries – the model that offers the most appropriate simulation of RAAS activation. This Ang II-dependent hypertension is accompanied with enhanced expression of its receptors in the vascular wall and complex biochemical abnormalities manifested as accumulation of malon dialdehyde in the plasma and tissues of peripheral organs (kidneys, heart) along with a simultaneous decrease in the activity of superoxide dismutase and catalase. The changes described above coincided with a fall in the plasma glutathione content, all these together demonstrating a reduction in the animals' antioxidant status. A phenomenon concomitant to this was a decrease in the blood levels of endothelium-derived relaxing factor – NO. When the animals, prior to the artery ligation, were injected MT (10 mg/kg) with its further administration for 3 weeks, this limited the renovascular hypertension, also reducing the humoral and tissue manifestations of oxidative stress and endothelial dysfunction [24, 33].

In the case of persistent increase in systolic blood pressure after a long-term exposure of rats to light, MT just like ACE inhibitor captopril would provoke clear hypotension, but unlike the latter, it also limited fibrotic lesion of the aortic wall, reducing contents of collagen I and III. During that, in spontaneously hypertensive animals, the hypotensive effect of MT, if compared to captopril, showed a higher level of stability with more expressed limitation of the left ventricular myocardial remodeling [66, 76].

The results of *in vivo* experiments coincide with those obtained *in vitro*. The findings of experiments involving the culture of vascular endothelial cells showed that adding of Ang II in the medium led to their damage and increased generation of free radicals at the same time inhibiting the NO synthesis. Free radical aggression and endothelial dysfunction were clearly prevented by preliminary MT administration. Likewise, there was observed limited evidence of oxidative stress in the aortic walls of rats, caused by Ang II, when its infusion was combined with MT [53].

The antagonistic capacity of MT towards the RAAS effects can be also seen from the cardiac activity studies. The model of heart ischemia/reperfusion in healthy hamsters, as well as models with deliberately induced cardiomyopathy demonstrated that MT (10 mg/kg, intravenous) would clearly attenuate the functional and biochemical abnormalities in the heart muscle. Along with the recovery of myocardial contractility and reduced fibrosis in it, there was also a significant reduction in the post-ischemic ventricular tachycardia and full suppression of fibrillation. The data obtained through intravital microscopy suggest that MT eliminated vascular spasms caused by Ang II and noradrenaline, relieved capillary perfusion, as well as prevented microvascular damage. These shifts correlated with reduced oxidative stress in the myocardium and vessels, and the accumulation of NO [21, 64].

Steady light exposition (a physiological way to simulate MT deficiency) combined with inhibitor of endothelial NO synthase L-NAME provokes in rats, together with arterial hypertension, myocardial hypertrophy of the left ventricle. Along with that also comes increased tissue expression of ACE. MT (10 mg/kg, each day, for 1 week), like captopril, graded down the intensity of these disturbances, again demonstrating its antagonism to RAAS [76].

If, on the cellular level, MT impedes the RAAS effects mostly through limiting processes of oxidative stress and increased NO production in the endothelium, then on the systemic level it reaches the aim via more various mechanisms. These include MT interaction with peripheral endocrine glands, involvement in the control of emotiogenic structures of the brain, and organization of circadian periodism.

RAAS activation, among other processes, is accompanied with disturbances of carbohydrate homeostasis and dyslipidemia, causing a predisposition for hypertension under metabolic syndrome. One of the reasons is the capacity of Ang II to bring about insulin resistance through triggering Ang I receptors and increased secretion of mineralocorticoids [62]. Meanwhile, MT, as mentioned before, interferes with the endocrine function of the pancreas thus revealing antidiabetic properties, and, therefore, a capacity for secondary restriction of concomitant hypertension.

Another indirect endocrine effect comes through well-studied pineal-adrenocortical relationship that become of restricting nature under certain conditions. At the same time, RAAS mobilization will accompanied with increased secretion of aldosterone, which makes a significant contribution into the development of cardiovascular disorders. MT may influence on hyperactivity of the hypothalamic-pituitary-adrenocortical system thus limiting the secretion of corticosteroids due to inhibiting the function of its individual components, also suppressing the synthesis of aldosterone directly in the adrenal cortex [8, 37].

Another reason behind MT's ability to counteract the RAAS effects on the systemic level is their different impacts on the psychoemotional status in animals and humans. Ang II, both humoral and produced in the brain locally, can interfere directly in the activities of the emotiogenic limbic brain structures, which is done through specific Ang receptors found there [17]. Obviously, their mobilization, among other reasons, is responsible for limitation of the investigate activity and increased anxiety in hypertensive rats in the open field and elevated X-maze labyrinth tests. Interesting to mention that behavioral disorders coincide with high plasma levels of Ang II. This, perhaps, could be the explanation for clear disturbances in the spatial orientation that the animals showed in the Morris water maze after its intravenous injections.

The psychoemotional changes in animals correlating with arterial hypertension can be limit with a long-term (about 3 weeks) administration of MT (40 μg/ml) consumed with water. This coincides with a similar effect found under the same conditions in candesartan – the selective blocker of Ang I and Ang II receptors [47, 80]. MT has a capacity to grade the behavioral deviations that are induced through RAAS activation. The findings of numerous experimental data summarized before [2] show that the pineal hormone has a wide spectrum of psychotropic activities including anxiolytic effect due to modulation of the limbic brain structures' function and enhancing their inhibitory processes.

Indeed, when stressed rats with a significant level of anxiety, high blood pressure and increased blood levels of Ang II, were preliminary administered with MT (1 mg/kg) this eliminated their behavioral and cardiovascular disturbances. The protective effect of the hormonal drug did not reveal itself against injected GABA A receptor inhibitor bicuculline. Therefore, there is every reason to believe that GABA-benzodiazepine receptor complexes do have a role in MT's capacity to decrease the central manifestations of the RAAS activity [49].

Platelet Hemostasis Restriction. There is no need today to search for new evidence proving the idea of a connection between any kind of damage to the heart and blood vessels and thrombosis-type complications. Also, thrombosis and thromboembolism are frequent phenomena accompanying any manifestations of endothelial dysfunction viewed above [30, 45, 51]. The formation of blood thrombus participated numerous vascular factors involved in coagulation and fibrinolysis; however platelet aggregation is assigned a special role here [12]. Meanwhile, MT can be actively involved in platelet hemostasis and its circadian organization. This was the reason for discussing the issue earlier [7], sparing this work the need of being loaded with references to some particular literature sources.

The question about of the influence central (pineal) and local MT has on platelet hemostasis should be obviously viewed as one regarding its important functional properties. In experiments involving both animals and humans it has repeatedly been the focus of the closest attention though some aspects of problem remain questionable.

Among those statements that raise no doubt should be the very fact that MT has a role in the platelet activity. These relationships are of complex nature. On one hand, it has already been shown that platelets obtained from the blood of animals and humans demonstrate high density of specific binding sites for labeled MT on their surface. Therefore, platelet cells well deserve to be considered most meaningful transport factors in the blood responsible for its delivery to the tissues.

On the other hand, these cells do not just perform a passive transport mission yet they are directly involved in the formation of extrapineal MT. Already in the early 80s of the last century platelets isolated from the blood of rabbits were used to show (and to be confirm later) that they are important sources of peripheral MT. They contain a whole set of enzymes necessary for its synthesis (including the key enzymes N-acetyltransferase and hydroxyindole-O-methyltransferase), as well as a significant amount of serotonin – the main precursor of MT.

Finally, both platelet and plasma (pineal) MT has a direct interest in regulating the platelet activity during the circadian cycle. In healthy people, MT of any origin seems to have the same protective mission, among other functions, also being able to prevent the formation of thrombosis in the night time. And the major role here could be played by restriction of the blood aggregation properties via MT.

In vitro experiments involving platelets isolated from donor human blood have shown that micromolar concentrations of MT inhibited their aggregation with circadian rhythm in a dose dependent manner. The effect was clearest in the evening hours, while a similar result could be reached in the morning but would take much higher concentration of the drug. The antiaggregant effect of MT embraced both spontaneous and induced (with collagen, ADP) platelet activity. The inhibition of aggregation is related to disturbance in the arachidonic acid cascade, largely due to inhibiting of thromboxane production yet without disturbed prostacyclin system activity. *In vivo* such changes clearly correlated with circadian variation of the hormone levels in blood plasma, while the peak sensitivity of platelet receptors to MT preceded an increase in the hormone plasma level. This well allows regarding the natural restriction in the secretory activity of the pineal gland with reduced MT expression in the daytime, as one of the reasons behind a higher risk of thrombotic complications in patients with cardiovascular disease run in the morning time.

The list of the most possible mechanisms of MT interaction with platelets should include its suppressing effect on serotonin absorption from the blood, and release of the substance by platelet cells. Inhibited serotonin secretion, among other, inhibits vasoconstriction, which is peculiar to it. Interesting to note that and this capacity of MT also find on animal models, also follows circadian periodism and has a minimum manifestation at the beginning of the light part of the day. As for the circadian rhythm disturbance, which can be observed in people working in shifts, it results in a drop of the serotonin level and of its major metabolite 5-oxyindoleacetic acid in platelets.

The antiaggregant effects of MT are obviously complemented with it influence on coagulation and fibrinolysis. Experimental findings suggest that thermal injury in rats leads to blood-clotting disorders with an increase in the prothrombin index, higher levels of fibrinogen, and a simultaneous disturbance in the platelet morphology. Parenteral administration of MT (10 mg/kg) done straight after the injury, diminishes the changes also preventing disseminated intravascular coagulation of blood. Similarly, even a single intake of MT (3 mg) by healthy people reduced the level of plasma fibrinogen and VIII factor of coagulation, while the degree of coagulant activity clearly correlated with its content in the blood. Besides, MT administered in the same mode to healthy volunteers prevented the development of hypercoagulation provoked by acute psychosocial stress.

At the same time it must be mentioned that while maintaining a certain level of liquid consistency of blood, MT also reveals some protective effect on the bone marrow hemopoiesis in general and, in particular, a capacity to have a stimulating effect on thrombocytopoiesis. This fact stays in conformity to the understanding of peculiar modulator (adaptogenic) properties found in MT. They come down to corrective regulation of any physiological processes that it enhances on the background of initial weakness, but restricts them in case they get too much prominent.

Indeed, as a rat model of traumatic disease shows, pre-treatment with MT (10 mg/kg) limited thrombocytopenia, also reducing the degree and duration of the disturbances in the platelet hemostasis. Just similarly, a repeated use of MT for oncology patients in a rather high daily dose (20 mg) combined with methoxytryptamine weakened the hematologic disorders caused by cytostatics-based therapy. The patients got a significant increase in the blood platelet count with a parallel protection against damage to lymphoid tissue. A similar protective effect revealed as thrombocytopoiesis activation was seen after regular use of MT (30 mg, daily) for thrombocytopenia in people with concomitant lead intoxication. Interesting to note that there is a description available concerning several clinical cases of idiopathic thrombocytopenic purpura where the intended therapeutic effect could be reached only through long-term (3 months) MT use.

Chronotropic Properties. Apart from endocrine and psycho-emotional factors, other MT-based systemic mechanisms for restricting the consequences of endothelial dysfunction should include its impact on the rhythmic organization of the cardiovascular system activity. This capacity of MT, which is considered as natural chronotropic agent, plays a crucial role in all its effects and thus deserves a special focus.

The activity of the cardiovascular system components, just like any physiological phenomena, have of fluctuations in time, including the basal circadian rhythm. At the same time, the peak of the basic indicators (blood pressure, heart rate, cardiac output, etc.) is observed through the active phase of the circadian cycle. On the other hand, any form of pathology including cardiovascular disorders, is accompanied with disruption of normal rhythmic processes – dysrhythmia. Being a result of some pathological process, it joins its structure further on, and thus exacerbates the pathology. Hence, dysrhythmia control turns into an additional tool for pathogenetic therapy.

Obviously, MT performs its capacity to counteract cardiovascular disorders accompanying endothelial dysfunction, as long as the pineal hormone is a typical natural chronobiotic. Shaping clear biorhythms, including those with a daily (circadian) period, elimination of various dysrhythmias – this is an important part of its biological role in complex organisms [1].

In particular, human and animal experimental models offer extensive evidence of MT's capacity to restrict disturbances in time organizations of metabolic disorders in cardiovascular system diseases. These findings have already been dis-

cussed in a series of reviews [25, 27, 44] now allowing just mentioning them briefly.

For instance, in a rodent model of diabetes mellitus type 2, arterial hypertension and obesity, just like in people with a clinically apparent similar pathology, there could be seen a reorganization of the conventional MT circadian secretion by the pineal gland with a change in its curve (phase shift, flattening, inversion). This coincides with inadequate fluctuations in the plasma levels of insulin, glucose, and leptin. Against such background, replacement therapy for people done with MT itself or through melatoninergic drugs (ramelteon, agomelatine, tazimelteon) offers clinical improvement with a limited severity of cardiovascular and metabolic disorders.

Weak or irregular production of MT coincides, to a certain degree, with changes in the normal circadian dynamics of blood pressure; moreover, it can even determine them. In most people, systolic blood pressure tends to slow down in the night hours (so-called dippers). Fewer are cases where it remains at the same level (non-dippers) or even goes up at night (night-peakers). It has been proven todys that those belonging to the two latter types run risk of developing vascular hypertension, renal disease, cardiac ischemic events, left ventricular hypertrophy, etc. The same people often fall prey to myocardial infarction or stroke. These findings lay the basis for the current chronotherapy of hypertension, which relies on antihypertensive agents used mostly in the evening [39].

Low plasma levels of MT, deformation of its circadian production curve and aberrant dynamics in the blood concentrations of some other metabolites involved in regulation of the cardiovascular system, develop a predisposition to this chronopathology [34]. Therefore, MT in its low, physiological doses can be used before sleep not only as a mild hypnotic, yet also as a remedy for preventing cardiovascular incidents. Also, this use of the substance could obviously help reduce the number of nondippers in the population. Indeed, as Rechinski et al. observed [63], long-term (30 days) evening use of MT (5 mg/day) helped bring down the number of nondippers in the group by 30%, all of them being transformed into stable dippers.

Another serious issue of practical value is maintaining the health in those who are employed working by shifts. They are known to be among the most often vulnerable to endothelial dysfunction with cardiovascular and metabolic disorders, which are typical of it; the same group of people inevitably reveal severe defects in the secretory activity of the pineal gland. The reason behind the latter is that it cannot be strictly bound to a regular change of light and dark, which is typical of normal conditions and which is responsible for MT synthesis [72, 84]. Therefore, systemic administration of MT for those involved in work on shifts (nurses, police, etc.) should be aiming at developing a clearer circadian periodism of the basic physiological functions on the one hand, and at preventing numerous pathologies, cardiovascular among them, on the other.

MT involvement in the circadian fluctuations of the cardiovascular system activity depends, first of all, on close functional ties between the pineal gland and the circadian biorhythms pacemaker – suprachiasmatic nuclei (SCN) of the hypothalamus. These, in circadian mode, develop signals to manage the endocrine gland activity, which, in turn, uses MT to transfer information on external photoperiodism to the effector organs.

We have already offered some contemporary views on the mechanisms of SCN and their endocrine mediator involvement in circadian rhythmic of the cardiovascular structures [5]. Compared to the previous data, the new approach to understanding these mechanisms is due to decoding the nature of interaction between the central oscillator of circadian rhythm (SCN) and the oscillators of peripheral tissues as clock-genes. MT, via specific receptors identified not in vascular and cardiac tissues alone but on SCN neuronal membranes as well, acts as an endogenous synchronizer, coordinating in time central and peripheral signals. And the impact MT has on the expression of clock-genes could be a real way to ensure such coordination [32, 78, 86].

In case of MT deficiency, including for reason of abnormal pineal activity, there are premises for phase mismatch of biorhythms and desynchronosis development. This favors more factors for cardiovascular disorders, which are «regulars» in terms of accompanying endothelial dysfunction. On the other hand, while synchronizing the circadian rhythmic both in the central and the peripheral structures, the MT introduced from the outside shall harmonize the cardiovascular system functioning in general. And such chronotropic effect of the hormone, of course, contributes seriously to its therapeutic benefits in various forms of cardiovascular disease.

Melatonin of central (pineal) and peripheral origin has a wide effect on the cardiovascular system activity preventing its organs from developing pathologies, which accompany endothelial dysfunction. Both experimental and clinical data show that, via specific receptors, it can inhibit hypertension, atherosclerosis, metabolic syndrome with hyperlipidemia, diabetes mellitus, and enhanced platelet hemostasis.

The protective properties of MT are determined by complex of mechanisms, and on the cellular level the universal role here belongs to its capacity to counteract oxidative stress, while on the systemic level these mechanisms include its psychotropic and chronotropic effects. The first successful experience in studying MT's capacity in a clinical setting makes it possible to recommend this low toxic natural adaptogen be part of comprehensive treatment for many cardiovascular disorders. However, this could be done only after some additional multicenter and placebo-controlled studies.

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