Regulation of Circadian Rhythm of Glycemic Reaction on Background of Physical and Glucose Loading

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Abstract: The review considers modern concept on role of physiological and biochemical properties of epiphysis and suprachiasmatic nuclei of hypothalamus in neuro-endocrine regulation of circadian rhythm of glycemic reactions and other functions of organism. Both in norm, and on background of glucose loading, short-term or long-term physical loading the level of glycemic reaction of circadian rhythm in the morning time (08.00-12.00 A.M.) is relatively minimal in comparison to afternoon and evening hours, while this value in the afternoon time (01.00-05.00 P.M.) is maximal relatively to the morning and evening time and this value in the evening time comes close to the original level. It was revealed that under glucose loading in the one-month-, three-month-, six-month- and one-year-old animals, levels of glycemic reactions of circadian rhythm upregulated accordingly to their original levels in the morning, afternoon and evening time. Particularly, after glucose loading level of glycemic reactions upregulated more sharply in the morning time at 08.00-10.00 A.M., in the afternoon at 01.00-03.00 P.M. and in the evening at 06.00-07.00 P.M. Towards 12.00 A.M., 05.00 P.M. and 10.00 P.M. the level of glycemic reactions of circadian rhythm downregulated and returns to the original level. Relatively to the normal values the level of glycemic reactions of circadian rhythm in the morning, afternoon and evening upregulated after short-term physical loading, whereas it downregulated after long-term physical loading. Upregulation and downregulation of glucose level in the blood under short-term and long-term physical loading on background of glucose loading throughout the day are related to upregulation and downregulation of epiphyseal hormone melatonin.
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1. Introduction

As famous neurobiologist G.M. Sheperd [17] has noticed, while the underlying mechanisms of circadian rhythms have been studying and surprising multidirectional impact of circadian rhythms on the organism got clear, they raise growing interest among researchers. K.Pitendrih wrote that circadian rhythm is being in constant phase relationship to its determining 24-hour rhythm of light and darkness. Circadian fluctuations of physiological processes related to rotation of the earth round its axis have tremendous importance for functioning of all living organisms. On the basis of this recognition of functional properties of regulatory apparatus of circadian biorhythms the leading role is referred to so called suprachiasmatic nuclei of hypothalamus (SChN). These nuclei carry out regulation over melatonin production via light information acquired through retino-hypothalamic tracts of hypothalamic SChN for upregulation and downregulation of tropic relasing factors of hypothalamic nuclei and tropic-related hormones production of hypophysis and as a result nervous signals through adrenergic sympathetic nerves and superior cervical ganglion reach epiphysis. Finally, changes functional activity of physicological systems of the organism, engaged into neuro-endocrine regulation of circadian rhythm of glycemic reactions following physical and glucose loading.

Disturbances of light regime as well exert modifying impact on development of spontaneous tumors in the rat females. So, in the group of rats kept under natural regime of illumination (NRI) incidence of tumor formation increased relatively to the control group, mostly due to two times increase of incidence of development of benign tumors of the mamma. It should be noticed that in the NRI group several cases of formation of adenocarcinoma of the uterus, wreas in the control group development of such tumors was not fixed. In contrast, keeping rats in conditions of light deprivation inhibited significantly development of all tumors, mostly tumors of the mamma in comparison to the control. So, as both natural regime of illumination and constant illumination has promoting effects on tumor development, light deprivation inhibits spontaneous carcinogenesis in rat females.

Analysis of the results indicates to negative impact of constant and natural regimes of illumination on indexes of homeostasis of rat females that adheres to the results of a number of researchers on relation of epiphysis to endocrine regulation of metabolic processes [19, 20]. Decrease tolerance to glucose, upregulation of total lipids, redistribution of fractions of free and bound insulin were observed in pinealectomized animals [19].

Biofeedback information on temporary organization of controlled internal milieu of the organism SChN get through receptors of different hormones, broadly presented on membranes and nuclear apparatus of cells. Among mostly involved in maintaining circadian rhythm undoubtedly are melatonin and corticosteroids. Besides, special importance in realizing regulation of the whole circadian system of the organism belongs to the effects of melatonin.

So, literature data [16, 28, 29, 30] enough convincingly indicate to age-dependent downregulation of epiphysis functional activity of animals and humans, particularly the most important disorder is decrease of amplitude of night upregulation of melatonin of circadian rhythm.

Circadian rhythms regulating changes of glycemic reactions in the organisms of healthy humans and animals subjected to physical loading always raise significant interest [1-7, 11-14, 25].

According to the literature data indicated above, in adaptive reactions of organisms as well as in glycemic and humoral and shifts in different time of a day happening both under heavy physical and emotional loading an important role belongs to hormones of epiphysis engaged in neuro-emdocrine regulation of circadian rhythm of glycemic reactions realized through epithalamo-hypophyseal-adrenal systems of the humans' and animals' organisms [2, 7, 10, 11, 15, 17, 18, 19, 21, 26, 27, 29].

However in ontogenetic aspect under physical and glucose loading this problem still remains opaque. In this relation, the goal of the present study was to analyze role of short-term and long-term physical loading on the changes of biorhythm of circadian glycemic reaction on background of glucose loading in postnatal ontogenesis.

2. Materials and Methods

In our studies we used the experimentally induced physical loading. For this purpose the mechanical device with freely moving drum was constructed in the laboratory. Rate of drum rotation fluctuated within limits of 40-50 rpm. Rabbits were subjected to physical loading in the form of forced movement and vibration effects for 5 and 40 min.

Glucose level was measured with application of express method by glucometer (manufacturer by "Bayer-Healthcare", USA and Canada). The studies were conducted over the one-month-, three-month-, six-month-old (sexually matured) and one-year-old rabbits (adult). These stages of development are clearly characterized by over pathomorphological and physiological parameters and reflect sequential formation of organism's functional systems.

In the 1st series of studies the dynamics of glycemic reactions of circadian rhythm was analyzed in the one-month-, three-month-, six-month- and one-year-old animals throughout the day (morning, afternoon and evening time).

In the 2nd series the dynamics of the level of glycemic reactions of circadian rhythm of animals of different ages under glucose loading throughout a day – in the morning (08.00-12.00 A.M.), afternoon (01.00-05.00 P.M.) and evening (06-10.00 P.M.) was studied.

In the 3rd series effects of short-term and long-term physical loading on the level and changes of glycemic reactions of circadian rhythm was studied.

In the 4th series in different time of a day effects of short-term and long-term physical loading in the animals subjected to glucose loading (3 g per 1 kg of body mass) on glucose levels in the blood were evaluated. The experiments were conducted on in the one-month-, three-month-, six-month- and one-year-old animals. Blood samples were taken from the rabbit's ear edge vena in the morning at 8.00-12.00 A.M., in the afternoon at 01.00-05.00 P.M. and in the evening at 06.00-10.00 P.M. prior to and after sugar loading.

The data were subjected to statistical analysis with method of Fisher-Student and other methods with application of packet of statistical research program Excell 7.0 on the personal computer Pentium-4.

3. Results and Discussion

As it issues from Fig. 1, the level of glycemic reaction of circadian rhythm in the animals of all ages in the morning time (08.00-12.00 A.M.) is relatively minimal in comparison to afternoon and evening hours, while this value in the afternoon time (01.00-05.00 P.M.) is significantly upregulated and this value in the evening time goes down.

It issues from the obtained data, depending on the animals' age glucose level in the blood upregulates and is related to the status and rate of development of central nervous system. On the basis of the studies one can come to a conclusion that in different ages in the control groups of animals the level of glycemic reactions of circadian rhythm depends on functional state of the central nervous system.

The data presented in Fig. 1-4, show that after glucose loading (3 g per 1 kg of body mass) the level of glycemic reactions of circadian rhythm in the morning, afternoon and evening time in the all age groups significantly upregulated. In this case in the one-month-old rabbit pups subjected to glucose loading the level of glycemic reactions was lower in 08.00 A.M. and significantly upregulated to 09.00 A.M., 02.00 P.M., 07.00 P.M. reaching their maximum in 10.00 A.M., 03.00 P.M., and 08.00 P.M., thereafter going down to 12.00 A.M., 05.00 P.M. and 10.00 P.M. and reaching original 08.00 A.M., 01.00 P.M., and 06.00 P.M. levels. Similar pattern was observed in the three-month-, six-month- and one-year-old animals. In the one-month-old rabbit pups subjected to glucose loading the level of glycemic reactions relatively to 08.00 A.M., 01.00 P.M., 04.00 P.M. throughout a day upregulated significantly and reached its maximum at 10.00 A.M., 03.00 P.M. and 08.00 P.M., thereafter going down to 12.00 A.M., 05.00 P.M. and 10.00 P.M. corresponding to the 08.00 A.M. level, but at 10.00 P.M. this downregulation was more noticeable in comparison to the 08.00 A.M. level. In the one-year-old animals after glucose loading the level of glycemic reactions upregulated more sharply in the morning time at 08.15-10.00 A.M., in the afternoon time at 01.15-03.00 P.M., in the evening time at 06.15-07.00 P.M. and the level of glycemic reactions downregulating to 12.00 A.M., 05.00 P.M. and 10.00 P.M., returned to the 08.00 A.M. level.

As a result of conducted studies it became clear that in the control animals the level of glucose in the blood in the afternoon time is higher than in the morning time, while in the evening time is lower than in the morning and afternoon time. In the experimental animals after glucose loading the level of glucose in the blood remains upregulated significantly for nearly 3-4 hours relatively to the control level.

In the different age groups of animals glycemia observed after glucose loading, after 4 h the level of glucose in the blood got back to the original values.

So, as a result of conducted studies it was revealed that in the animals with glucose loading relatively to intact animals the level of glycemic reaction of circadian rhythm deviates towards hyperglycemia.

Fig. 1-4 present changes occurring in glycemic reactions of circadian rhythm in 5-minute (short-term) and 40-minute (long-term) physical loading in the one-month-, three-month-, six-month- and one-year-old rabbits under glucose loading. As one can see from the data presented, normal glucose levels in the blood of the one-month-, three-month-, six-month- and one-year-old rabbits were different and hence the values of glucose level in the blood of these animals after short-term and long-term physical loading were different too. The data presented in the figures show that after 5-minute physical loading the levels of glycemic reactions of circadian rhythm in the morning, afternoon and evening time in the one-month-, three-month-, six-month- and one-year-old upregulated signifycantly and in the morning time prior to physical loading they varied within 82-125 mg%, while after short-term physical loading it was within 93-147 mg%, and after long-term physical loading it was within 68-102 mg% (Fig. 1).

In the afternoon time these changes prior to physical loading varied within 85-132 mg%, after short-term physical loading they were within 103-152 mg%, and after long-term physical loading they were within 72-116 mg%. These values in the evening time prior to physical loading varied within 75-114 mg%, while short-term physical loading brings to significant upregulation of glucose level in the blood, i.e. to hyperglycemia, and long-term physical loading, in contrast, leads to inhibition glycemic reaction, i.e. is the reason of hypoglycemia.

The data presented in Fig. 1 after glucose loading the level of glycemic reactions of circadian rhythm upregulated significantly in the morning, afternoon and evening time in the all age groups.

Analysis of glycemic reactions in the rabbits of different ages demonstrated that after glucose loading plus short-term physical loading glucose level in the blood upregulated, whereas under impact of glucose loading plus long-term physical loading its level downregulated significantly.

Analysis of glycemic reactions in the one-month-, three-month-, six-month- and one-year-old rabbits (Fig. 1-4) showed that under short-term physical loading (5 min) in the morning, afternoon and evening time the level glycemic reactions of circadian rhythm upregulated significantly, while under long-term physical loading (40 min) it downregulated. In the all age groups of animals the maximal changes of glycemic reactions under both separate glucose loading, short-term and long-term physical loadings, and simultaneous effects of these factors (glucose loading plus short-term physical loading and glucose loading plus long-term physical loading) were revealed in the morning at 10.00 A.M., afternoon at 02.00-03.00 P.M. and evening time at 07.00-08.00 P.M.

So, comparative study of glycemic reactions in the rabbits subjected to glucose loading showed that the level of glycemic reactions of circadian rhythm prior to and after both short-term and long-term physical loadings deviates in different manner dependently on animals' ages that is related to cortical regulations of glycemic reactions of circadian rhythm in the organism [7, 8, 10, 13]. Changes of level of glycemic reactions prior to and after glucose loading, short-term and long-term physical loadings in the six-month- and one-year-old animals relatively to the one-month-, three-month-old animals were manifested more prominently. In animals of different age groups after glucose loading the level of glucose in the blood for 4 h gets back to the original level.

Physical loading accelerates adrenaline delivery from adrenal glands into the blood, thereafter into peripheral tissues and central nervous system, i.e. 5-minute physical loading induces hyperglycemia, while 40-minute – hypoglycemia in peripheral blood of the intact animals [4].

In normal conditions light stimuli which through the eye by retino-hypothalamic pathway reach epiphysis, upregulate glucose level in the blood. It is known from the literature that in sportsmen after running long distances and during coaching and playing in hockey players and footballers melatonin level in the blood serum doubles relatively to its level prior to running and play [8, 10].

Coaching does not bring to chronic changes in melatonin secretion; besides, its upregulation is controlled and under physical loading its level remains the night values. What is epiphysis activation in night time is related to? This is related to upregulation of melatonin-synthesizing enzyme in the night time, due to inhibition of glucose-regulatory systems, which is responsible for downregulation of glucose in the blood [2, 4, 6]. The indicated physic-ological and biochemical processes were realized through following pathways. Presentation of bright light leads to blocking immediately the melatonin synthesis, whereas staying under constant darkness maintains circadian rhythm of melatonin release supporting by periodic activity [6].

Melatonin is synthesized from essential aminoacid tryptophan coming to the organism with food. Reaching epiphysis with blood flow tryptophan turns into serotonin in two stages which are catalyzed with tryptophan-hydroxylase and 5-oxytryptophan-decarboxylase. Thereafter serotonin turns into melatonin also in two stages, which are catalyzed with enzymes N-acethyltransferase and hydroxyl-indol-o-methyltransferase.

Melatonin is not accumulated in the epiphysis, but released immediately into the blood flow and liquor [6, 8, 11]. Most part of released melatonin is bound to serum albumin. This way systemic melatonin is protected from quick decomposition and transported to the cells-targets [2-9, 12].

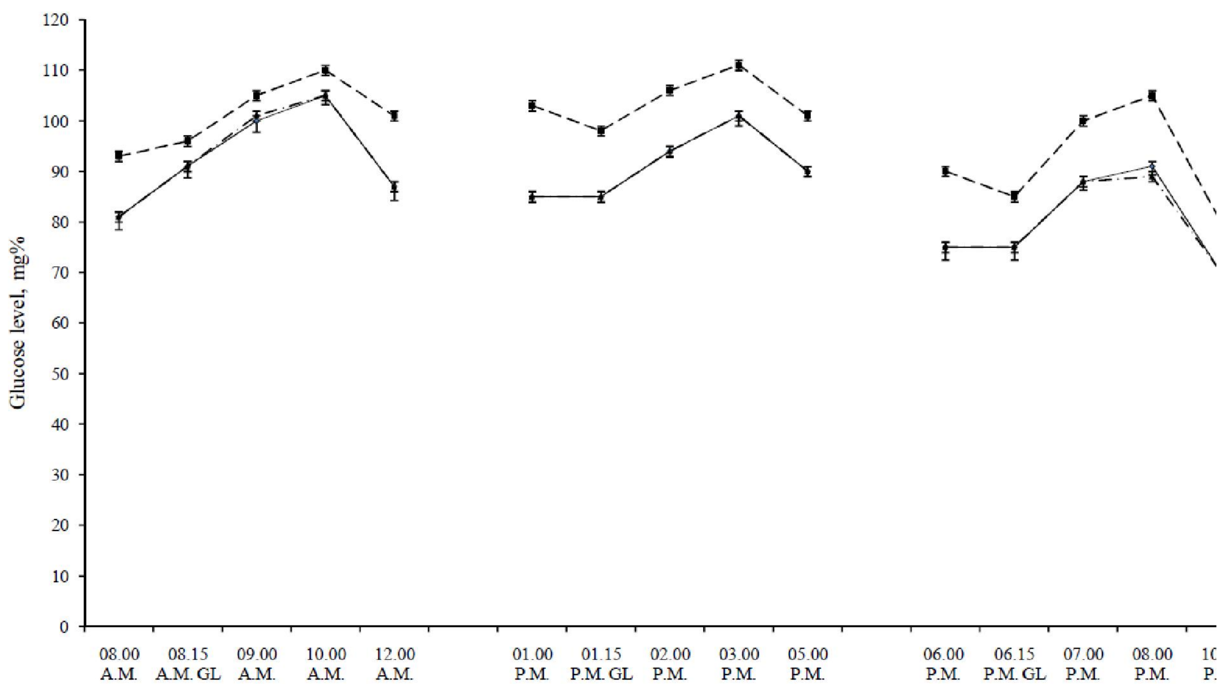

Figure 1. Role of short-term (ShTPhL) and long-term (LTPhL) physical loading in regulation of glycemic reactions on background of glucose loading. (GL) in the one-month-old rabbits.

GL   GL+ShPhL   GL+LPhL

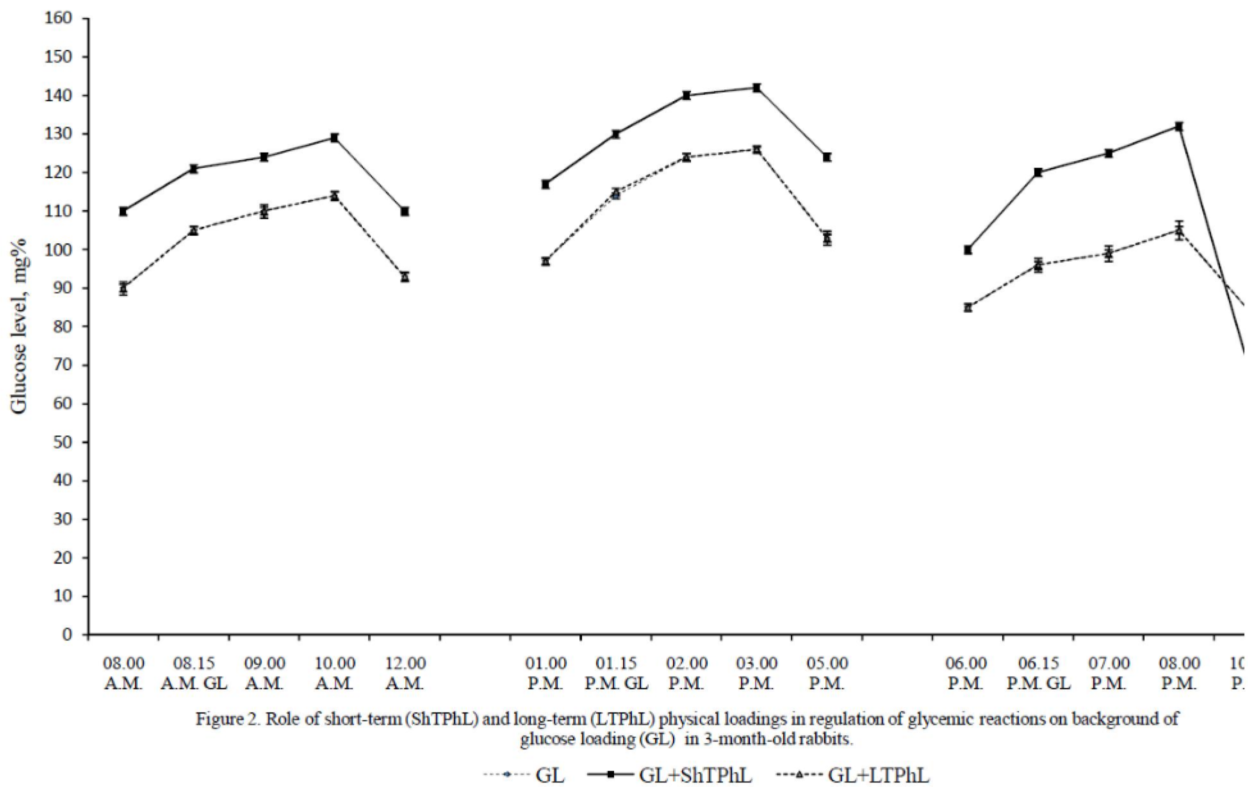

Figure 2. Role of short-term (ShTPhL) and long-term (LTPhL) physical loadings in regulation of glycemic reactions on background of glucose loading (GL) in 3-month-old rabbits.

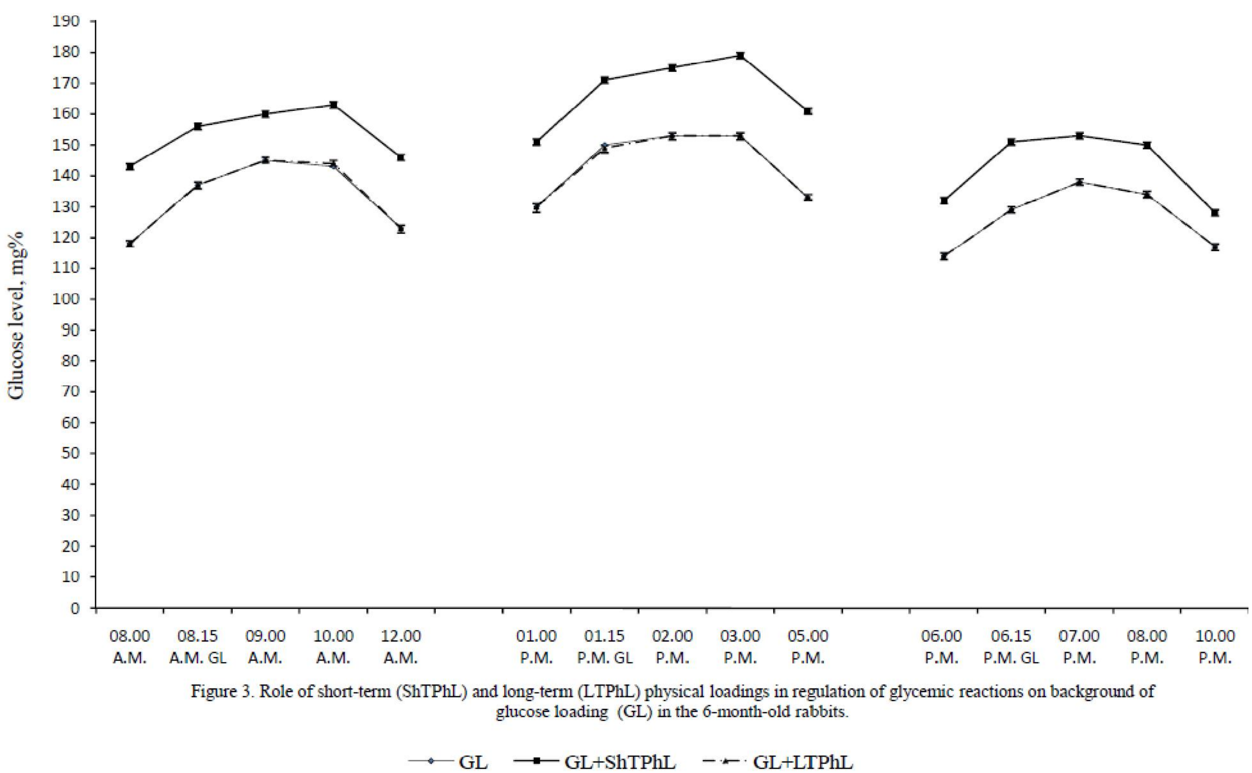

Figure 3. Role of short-term (ShTPhL) and long-term (LTPhL) physical loadings in regulation of glycemic reactions on background of glucose loading (GL) in the 6-month-old rabbits.

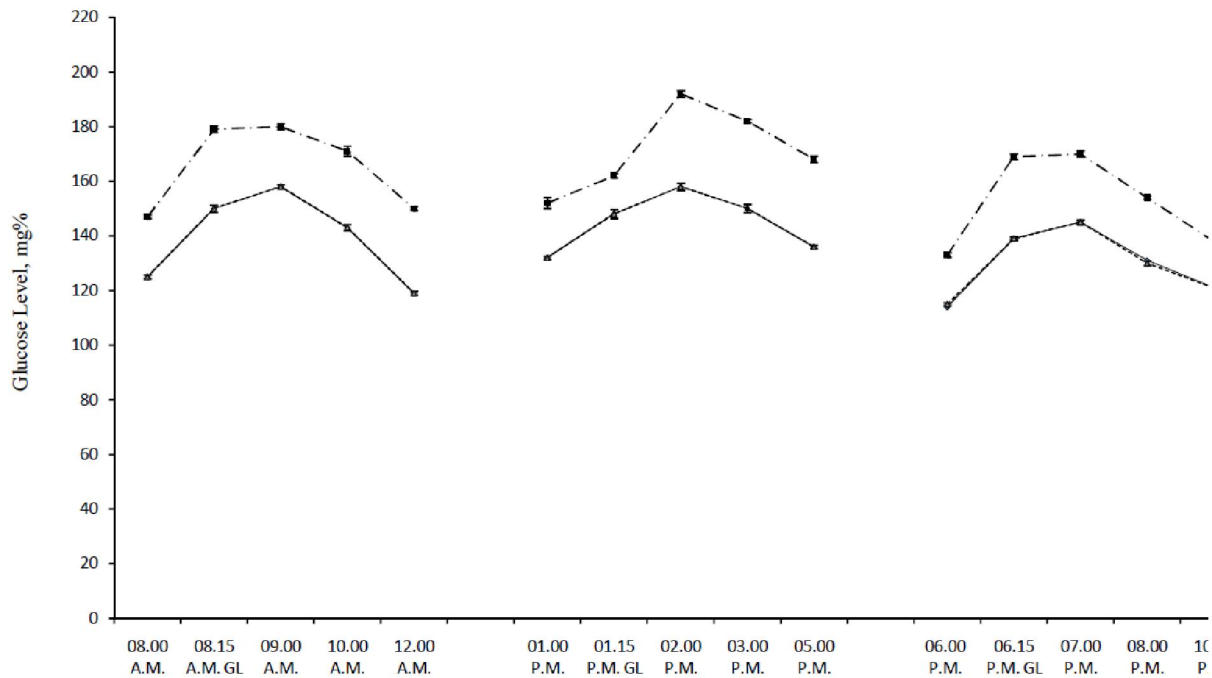

Figure 4. Role of short-term (ShTPhL) and long-term (LTPhL) physical loading in regulation of glycemic reactions o background of glucose loading (GL) in the one-year-old rabbits.

GL GL+ShTPhL GL+LTPhL

Issuing from the said above, one may conclude that presently there are enough convincing data, pointing to the role of the epiphysis in regulation of glycemic reactions realized through mediation of central nervous system, especially through hypothalamo-hypophyseal-adrenal systems [1, 2, 5]. Prolonged biorhythmiological studies give grounds to us and other searchers to come to a conclusion that age has an important role in circadian organization of animals and that incidence of different oscillators may change with aging [1, 2].
Taking into account the above said, one may come to a conclusion that glucose level upregulation or downregulation in the blood under short-term (5 min) or long-term (40 min) physical loading is related to inhibition in light regime or activation in darkness regime either the adrenal system via epiphysis or inhibition of hypothalamic releasing factors and hypophyseal hormones' production [2, 10, 12].

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