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Hypoglycemic and antioxidant action of melatonin in alloxan diabetic rats

Działanie hipoglikemiczne i antyoksydacyjne melatoniny u szczurów z cukrzycą alloksanową

INTRODUCTION

Melatonin is a circulating hormone that is primarily released from the pineal gland. It is best known as a regulator of seasonal and circadian rhythms; its levels are high during the night and low during the day. Oral melatonin supplementation may be useful for known sedative and antioxidant properties. Interestingly, insulin levels also exhibit a nocturnal drop, which has previously been suggested to be controlled, at least in part, by melatonin. Increased oxidative stress and impaired anti-oxidant defense have been suggested as contributory factors for initiation and progression of complications in diabetes mellitus. Alloxan is a classical diabetogen which is used to achieve beta-cell destruction and type 1 diabetes due to its selective cytotoxic effect on pancreatic beta-cells. The present study was to determine the protective effects of melatonin in alloxan-induced diabetic rats, and to analyze the parameters related to diabetes and oxidative stress.

The object of this experimental research was to ascertain the influence of exogenous melatonin on the level of basal glycemia (BG), glycosylated hemoglobin (Hba1c), total antioxidant activity (TAOA), malonic dialdehyde (MDA) and glutathione (G-SH) in rats under conditions of alloxan diabetes.

MATERIAL AND METHODS

The experiments were carried out on 67 sexually mature male albino, not thoroughbred rats with the body mass – 0.18–0.20 kg. The animals were kept in a vivarium under conditions of natural lighting at a constant temperature, air humidity and free access to water and food. Alloxan diabetes was evoked via injecting the rats with a 5% solution of alloxan monohydrate intraperitoneally in a dose of 170 mg/kg following a 24 hour period of fasting. The melatonin preparation was used in the research (the manufacturer – "Sigma", USA). The animals were divided into three subgroups: 1) intact rats (control group); 2) alloxan diabetic rats; 3) alloxan diabetic animals which were introduced the melatonin preparation intraperitoneally in a dose of 10 mg/kg at 8 a. m. daily during 6 weeks

starting with a 5-th 24 hour period after the injection of alloxan. Blood was taken from the tail vein to evaluate the basal glycemia (BG) level with the use of One Touch Ultra (LifeScan, USA). On the third (critical) day the death of a part (50%) of the alloxan diabetic animals was observed. Determinations of the content of Hba1c were conducted by a biochemical analyzer D 10 ("Bio-Rad Laboratoria Inc.", France). TAOA, MDA and G-SH were determined with standard methods.

RESULTS

In accordance with the findings, an introduction of alloxan monohydrate caused a sharp rise of the level of basal glycemia (BG) on an empty stomach in a part of the rats (by 111% in comparison with the indices of control group of animals); such animals formed a group of rats with overt diabetes (BG ≥ 8.0 mmol/l). The level of BG did not reliably differ in the rest of the alloxan diabetic animals from the indices of the intact rats (BG ≤ 6.9 mmol/l); such animals were placed into a group of alloxan diabetic rats with occult diabetes. The introduction of melatonin during 6 weeks was conductive to normalization of the level of BG in the group of animals with overt diabetes and a decrease of the BG level (by 37% in comparison with intact rats) in the animals with occult diabetes, indicating a hypoglycemic action of the melatonin preparation.

The content of HbA1c in the blood of the rats with overt and occult diabetes increased by 221 and 122%, respectively, as compared with the indices of the control group of animals. The introduction of melatonin over a period of 6 weeks contributed to a decrease of the blood HbA1c content of the rats with overt diabetes by 45%, as compared with the values of untreated animals. On the other hand the HbA1c content in the group of animals with occult DM did not considerably differ from the values of intact control.

Table 1. Changes of the state of antioxidative defence on the background of alloxan diabetes in rats (M±m, n=6)

Indexes / Groups	BG on 4-th day, mmol/l	After 6 weeks of alloxan introduction				
		BG, mmol/l	HbA1c,%	TAOA,%	MDA, mkmol/g tissue	G-SH, mkmol/g tissue
1.Control group	5.5±0.49	5.5±0.40	4.7±0.77	83.2±2.30	30.0±1.58	7.2±0.41
2.Overt diabetes	11.5±2.15[a]	13.8±2.70[a]	15.1±1.13[a]	63.2±1.45[a]	48.1±1.21[b]	4.3±0.27[a]
3.Overt diabetes + insulin	12.0±2.49[a]	5.3±0.45[b,d]	7.8±1.58[b]	76.5±2.21[b]	27.3±1.56[b]	6.7±0.69[b]
4.Overt diabetes + melatonin	11.6±1.80[a]	5.8±1.41[b,d]	8.3±1.08[a,b]	72.7±2.24[a,b]	38.2±1.32[a,b]	6.8±0.38[b]
5.Occult diabetes	5.3±0.25[b]	6.1±0.39[b]	10.2±0.51[ab]	70.1±1.94[a,b]	40.4±1.23[a,b]	8.6±0.50[a,b]
6.Occult diabetes + melatonin	5.1±0.36[b]	3.7±0.36 [a,b,c,d]	6.2±0.28[b,c]	80.6±2.71[b,c]	28.7±1.15[b,c]	7.1±0.31[b,c]

The blood plasma total antioxidant activity (TAOA) in the animals with overt and occult DM increased by 24 and 17%, respectively, reliably lower than the values of the intact animals and that is, evidently, associated with a depletion of the system of the body's antioxidant defense in alloxan diabetic rats. The introduction of the melatonin preparation resulted in normalization of this particular index in the group of animals with occult DM and its reliable elevation by 15 % in the group in the group of animals with overt DM, as compared with the control indices.

The level of malonic dialdehyde (MDA) reliably increased in the groups of animals with overt and occult DM by 60 and 30%, respectively, compared with the indices of intact animals and that is indicative of intensification of free radical lipid peroxidation in the case of DM. The introduction of exogenous melatonin resulted in normalization of this particular index in the animals with occult diabetes DM and a considerable decrease of the MDA level in the group of animals with overt DM by 20%, as compared with the indices of untreated rats. A reliable decrease of the content of G-SH by 40% occurred in the liver of the rats with overt DM, whereas a reliable increase of this particular index by 20% was observed in the animals with occult DM in comparison with the indices of intact animals and that conforms to bibliographical findings. An increase of the G-SH content in the rats with occult DM is likely to take place at the expense of its intensified regeneration from its oxidative form. The administration of the melatonin preparation induced normalization of the index in question in the alloxan diabetic animals of both groups.

DISCUSSION

The introduction of melatonin during 6 weeks was conductive to normalization of the level of BG in the group of animals with overt diabetes and a decrease of the BG level in the animals with occult diabetes, indicating a hypoglycemic action of the melatonin preparation. The introduction of melatonin contributed to a decrease of the blood HbA1c content of the rats with overt diabetes, as compared with the values of untreated animals; while the HbA1c content in the group of animals with occult DM did not considerably differ from the values of intact control. The introduction of the melatonin preparation resulted in normalization of TAOA index in the group of animals with occult DM and its reliable elevation in the group of animals with overt DM, as compared with the control indices. The introduction of melatonin resulted in normalization of MDA level index in the animals with occult diabetes DM and a considerable decrease of the MDA level in the group of animals with overt DM, as compared with the indices of untreated rats. An increase of the G-SH content in the rats with occult DM is likely to take place at the expense of its intensified regeneration from its oxidative form. The administration of the melatonin preparation induced normalization of the index of G-SH content in question in the alloxan diabetic animals of both groups.

CONCLUSIONS

The introduction of melatonin during six weeks to alloxan diabetic rats is conducive to a decrease in them of the level of BG and HbA1c, as well as stabilization of the indices of the body's antioxidant defense disturbed under the conditions of an absolute deficit of insulin.

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SUMMARY

This study investigated the possible protective effects of melatonin as an antioxidant against alloxan-induced diabetic liver injury in rats. The introduction of melatonin to alloxan diabetic rats is conducive to a decrease in them of the level of basal glycemia BG and HbA1c, as well as stabilization of the indices of the body's antioxidant defense disturbed, namely total antioxidant activity (TAOA) of blood plasma, malonic dialdehyde (MDA) and glutathione (G-SH) in rats liver.

Keywords: melatonin, alloxan diabetes, carbohydrate metabolism, antioxidant protection, liver, rats.

STRESZCZENIE

W pracy ocenie poddano prawdopodobny antyoksydacyjny efekt ochronny melatoniny w przebiegu uszkodzenia wątroby szczurów z cukrzycą alloksanową. Podanie melatoniny u szczurów z cukrzycą prowadziło do spadku wartości glikemii podstawowej i HbA1c, jak również stabilizacji wskaźników systemu antyoksydacyjnego organizmu: całkowitej aktywności antyoksydacyjnej (TAOA) osocza krwi, dialdehydu malonowego (MDA) oraz glutationu (G-SH) w wątrobie szczurów.

Słowa kluczowe: melatonina, cukrzyca alloksanowa, metabolizm węglowodanów, ochrona antyoksydacyjna, wątroba, szczury