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The effect of systemic melatonin administration on the intensity of free radical damage to lipids and proteins in the burn wound in the dynamics of experimental thermal injury

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ABSTRACT

Aim. To assess the effect of melatonin (MT) on the content of lipid peroxidation (LPO) and protein oxidation (PO) products in the tissue homogenate from the burn wound in experimental thermal injury (TI).

Materials and methods. Third-degree (IIIA) TI with a relative area of 3.5% was modeled on male Wistar rats via contact of the skin with boiling water. Intraperitoneal administration of MT (10 mg / kg) was performed once a day for 5 days. On days 5, 10, and 20, LPO products in the heptane and isopropanol phases of lipid extraction and PO products were determined in the tissue homogenate from the burn wound.

Results. The content of secondary and end products of LPO in the heptane phase and end products in the isopropanol phase increased in the wound. The content of primary and secondary PO products of neutral nature increased on days 5, 10, and 20, and the level of secondary PO products of neutral nature elevated on days 10 and 20. Administration of MT reduced the content of LPO end products in the heptane phase, secondary and end products of LPO in the isopropanol phase, and the total amount of PO products due to primary and secondary products of neutral nature.

Conclusion. In the 20-day follow-up, LPO and PO products accumulated in the burn wound. The administration of MT at a total dose of 50 mg / kg led to reduction and partial restoration of the content of LPO and POM products, which can limit secondary alterations and accelerate healing of the burn wound.

Keywords: melatonin, thermal injury, lipid peroxidation, protein oxidative modification

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Влияние системного применения мелатонина на интенсивность свободно-радикальной деструкции липидов и белков ожоговой раны в динамике экспериментальной термической травмы

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РЕЗЮМЕ

Цель работы – исследовать влияние мелатонина (МТ) на содержание продуктов перекисного окисления липидов (ПОЛ) и окислительной модификации белков (ОМБ) в гомогенате ожоговой раны при экспериментальной термической травме (ТТ).

Материалы и методы. На самцах крыс линии Wistar моделировали ТТ степени IIIА площадью 3,5% контактом кожи с кипящей водой в течение 12 с. МТ применяли внутрибрюшинно (10 мг/кг), 1 раз/сут в течение 5 сут. В гомогенате ожоговой раны на 5, 10 и 20-е сут определяли содержание продуктов ПОЛ в гептановой и изопропанольной фазах липидного экстракта, продуктов ОМБ.

Результаты. В ожоговой ране увеличивалось содержание вторичных и конечных продуктов ПОЛ в гептановой фазе, конечных продуктов в изопропанольной фазе липидного экстракта; увеличивалось содержание первичных и вторичных продуктов ОМБ нейтрального характера на 5, 10 и 20-е сут, вторичных продуктов нейтрального характера – на 10-е и 20-е сут. Применение МТ снижает содержание конечных продуктов ПОЛ в гептановой фазе, вторичных и конечных продуктов ПОЛ в изопропанольной фазе липидного экстракта; суммарное количество продуктов ОМБ за счет первичных и вторичных продуктов нейтрального характера.

Заключение. В динамике 20-суточного наблюдения при ТТ кожи в ожоговой ране накапливаются продукты ПОЛ и ОМБ, применение МТ в суммарной дозе 50 мг/кг приводит к снижению и частичному восстановлению содержания продуктов ПОЛ и ОМБ, что может ограничивать вторичную альтерацию, ускорять заживление ожоговой раны.

Ключевые слова: мелатонин, термическая травма, перекисное окисление липидов, окислительная модификация белков.

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INTRODUCTION

Despite a wide range of drugs used to treat thermal injury (TI), their efficacy in the clinical setting does not always satisfy burn specialists, and side effects of the drugs often limit their use. When searching for new drugs, special attention is paid to endogenous regulators of homeostasis with pleiotropic effects [1–4]. The effectiveness of oxytocin, growth hormone, insulin, testosterone, and others has been proven in TI, and additional data are required to substantiate their use [5]. The skin is the largest organ with intense free radical oxidation (FRO), products of FRO formed in the skin have local and distant effects [6].

Oxidative stress is registered not only in the lesion, but also in the heart, lungs, kidneys, muscles, and

other organs [7, 8]. It is of particular interest to study aldehyde- and ketone-containing protein carbonyl derivatives in the TI focus – protein oxidation (PO) and lipid peroxidation (LPO) products as markers of FRO and the effectiveness of antioxidants [9]. Most data on the content of LPO and PO products in TI were obtained for plasma and internal organs, but not for a burn wound [7, 8, 10].

Melatonin (MT) is evolutionally one of the most ancient molecules with the original function of an antioxidant; its sources are the pineal gland, retinal ganglion cells, and the gastrointestinal tract [11]. Skin cells synthesize MT; its metabolites are found in keratinocytes, melanocytes, and dermal fibroblasts [12]. In the experiment, when the skin is damaged, MT accumulates in the epidermis, protecting the mitochondria [13]. MT receptors, including MT1 (Mel1a), MT2 (Mel1b), and RORα are found in keratinocytes, dermal fibroblasts, hair follicle cells, and melanocytes [14]. MT participates in the regulation of sleep – wake rhythms, has antioxidant, pro- and anti-inflammatory, and anti-apoptogenic effects, and regulates cell proliferation and differentiation [15]. These and other MT effects attract attention in terms of fundamental research due to homeostasis regulation and participation in the disease pathogenesis and in terms of applied research – due to potential use for prevention and treatment of diseases.

The aim of this study was to assess the effect of MT on the content of LPO and PO products in the tissue homogenate from the burn wound in experimental TI.

MATERIALS AND METHODS

The study involved 120 male Wistar rats weighing 200–240 g in the experimental biological clinic (vivarium) of the South Ural State Medical University. The experiment was carried out in strict compliance with the requirements for the care and maintenance of animals in accordance with the conclusion of the Ethics Committee (Protocol No. 10 of 15.11.2019). The animals were randomly divided into groups: group 1 ($n = 20$) – intact; group 2 ($n = 36$) – with TI; group 3 ($n = 32$) – with TI exposed to MT.

To simulate third-degree (type A) TI with a relative area of 3.5%, the interscapular area was immersed in water at 98–99 °C for 12 s. The burn depth was verified by morphological methods. Zoletil-100 (international nonproprietary name: tiletamine hydrochloride; Virbac Sante Animale, France) at a dose of 20 mg / kg was used for anesthesia. In groups 2 and 3, an aseptic bandage was applied to the wound every day for 20 days after TI. MT (FLAMMA S.P.A., Italy) was used intraperitoneally at a daily single dose of 10 mg / kg for 5 days. The levels of LPO and PO products were assessed in the tissue homogenate from the burn wound on days 5, 10, and 20.

To prepare a 10% tissue homogenate, the burn wound was excised, after that about 40 mg of the tissue was immersed in a cooled buffer solution, dried, and then homogenized at a temperature of 2–4 °C in 0.4 ml (1 : 10) of a cooled 0.1 M phosphate buffer (pH 7.4). A SF-56 spectrophotometer (LOMO-Spectr, St. Petersburg) was used to determine the content of LPO products in the tissue homogenate [16]. Optical density was measured in heptane and isopropanol lipid extraction at 220 nm (isolated double bonds), 232 nm (conjugated dienes, CD), 278 nm (ketodienes and conjugated trienes, KD and CT), and 400 nm (Schiff bases, SB). The relative content of LPO products was expressed in units of oxidation indices (u.o.i): E_{232}/E_{220} (CD), E_{278}/E_{220} (KD and CT), and E_{400}/E_{220} (SB).

The PO products in the tissue homogenate were determined according to the reaction between protein carbonyl derivatives and 2,4-dinitrophenylhydrazine with the following registration of aldehyde dinitrophenylhydrazine (ADNPH) and ketone dinitrophenylhydrazine (KDNPH) in the ultraviolet (UV) region of the spectrum and visible light region [17]. The results were expressed in units of optical density per 1 mg of protein (c.u. / mg). IBM SPSS Statistics 19 software was used for statistical processing of the data presented as the median and the interquartile range (Me (Q_{25}; Q_{75})). The significance of differences was assessed using the Kruskal – Wallis and Mann – Whitney tests. The differences were considered statistically significant at $p < 0.05$.

RESULTS

On day 5 of TI, the content of KD, CT, and SB increased in the heptane and isopropanol phases of lipid extraction in the wound (Table 1). On days 10 and 20 of the experiment, the content of KD, CT, and SB increased in the heptane phase of the burn wound, while only SB increased in the isopropanol phase. No significant changes were observed in the content of CD in the heptane and isopropanol phases on days 5, 10, and 20, as well as in the content of KD and CT in the isopropanol phase on days 10 and 20. In the dynamics of TI, the content of SB in the heptane and isopropanol phases was lower on day 10 ($p < 0.01$) than on day 5, and on day 20 it was higher ($p < 0.01$) than on day 10.

The total amount of PO products increased on days 5, 10, and 20 (Table 2). This is due to an increase in the total content of ADNPH on days 5, 10, and 20, the content of KDNPH on days 10 and 20, and the total amount of PO products in the UV spectrum region on days 5, 10, and 20. The total amount of PO products in the visible light region decreased on day 10 of TI. On day 5, an increase in ADNPH was revealed in the UV part of the spectrum. On day 10, an increase in ADNPH and KDNPH was observed in the UV region, with a decrease in ADNPH and KDNPH in the visible light region. On day 20, ADNPH increased in the UV region of the spectrum and in the visible light region, an increase in KDNPH was noted in the UV region of the spectrum.

In dynamics, the total amount of PO products and KDNPH, as well as the amount of KDNPH in the UV region of the spectrum is greater on days 10 and 20 ($p < 0.01$) than on day 5. The total amount of PO products and the amount of ADNPH in the UV region of the spectrum on day 10 is greater ($p < 0.01$) than on days 5 and 20; the amount of ADNPH and KDNPH in the visible light region is lesser on day 10 ($p < 0.01$) than on days 5 and 20.

Table 1

The effect of melatonin (MT) on the content of LPO products in the burn wound with TI, *Me* (Q_{25}; Q_{75})

Parameter	Group 1 (intact), $n = 20$	Group 2 (TI), day 5, $n = 16$	Group 2 (TI), day 10, $n = 20$	Group 2 (TI), day 20, $n = 21$	Group 3 (TI + MT), day 5, $n = 13$	Group 3 (TI + MT), day 10, $n = 10$	Group 3 (TI + MT), day 20, n =16
CD (h.), u.o.i.	0.920 (0.863; 0.975)	0.889 (0.834; 0.966)	0.891 (0.836; 0.944)	0.927 (0.873; 0.951)	0.891 (0.885; 0.908)	0.893 (0.881; 0.915)	0.906 (0.887; 0.931)
KD and CT (h.), u.o.i.	0.049 (0.013; 0.088)	0.123 (0.112; 0.141)*	0.115 (0.101; 0.141)*	0.126 (0.092; 0.155)*	0.134 (0.094; 0.140)*	0.133 (0.086; 0.141)*	0.089 (0.085; 0.095)* #
SB (h.), u.o.i.	0 (0; 0.011)	0.018 (0.013; 0.031)*	0.009 (0.003; 0.018)*	0.025 (0.015; 0.056)*	0.013 (0.012; 0.014)* #	0 (0; 0.002)#	0.002 (0.001; 0.004)#
CD (i.) u.o.i.	0.601 (0.596; 0.622)	0.594 (0.570; 0.732)	0.580 (0.568; 0.614)	0.613 (0.590; 0.647)	0.538 (0.534; 0.545)#	0.556 (0.550; 0.558)*#	0.562 (0.558; 0.569)*#
KD and CT (i.), u.o.i.	0.217 (0.209; 0.228)	0.259 (0.200; 0.213)*	0.210 (0.169; 0.264)	0.224 (0.211; 0.263)	0.209 (0.195; 0.228)*#	0.209 (0.200; 0.220)	0.199 (0.173; 0.213)*#
SB (i.), u.o.i.	0 (0; 0.011)	0.030 (0.015; 0.04)*	0.007 (0.004; 0.026)*	0.034 (0.016; 0.039)*	0.009 (0.007; 0.015)*#	0.007 (0.004; 0.009)*	0.011 (0.009; 0.016)*#

* statistically significant differences ($p < 0.05$) with group 1, # with group 2 (here and in Table 2).
Note: extracts: h. – heptane, i. – isopropanol.

Table 2

The effect of melatonin on the content of PO products in the burn wound in TI, *Me* (Q_{25}; Q_{75})

Parameter	Group 1 (intact), $n = 20$	Group 2 (TI), day 5, $n = 16$	Group 2 (TI), day 10, $n = 20$	Group 2 (TI), day 20, $n = 21$	Group 3 (TI + MT), day 5, $n = 13$	Group 3 (TI + MT), day 10, $n = 10$	Group 3 (TI + MT), day 20, n =16
ADNPH uv, c.u. / mg	29.85 (24.69; 32.84)	51.49 (48.03; 55.81)*	60.50 (52.95; 93.13)*	52.08 (35.14; 82.61)*	44.44 (35.14; 49.70) *#	49.82 (47.09; 55.59)*#	39.81 (32.79; 53; 80) *#
ADNPH vs, c.u. / mg	6.93 (5.32; 8.71)	6.91 (5.72; 9.75)	3.53 (2.09; 5.07)*	8.36 (7.06; 15.36)*	5.29 (3.97; 6.67)	7.68 (5.24; 9.16)	8.69 (6.25; 22.08)*
KDNPH uv, c.u. / mg	8.19 (7.37; 10.59)	7.79 (7.34; 9.43)	15.19 (9.05; 25.63)*	15.27 (11.44; 31.38)*	6.48 (3.42; 7.86)	12.11 (9.21; 13.06)*#	6.22 (4.16; 8.39)#
KDNPH vs, c.u. / mg	0.89 (0.69; 1.14)	0.91 (0.69; 1.41)	0.50 (0.35; 0.66)*	1.09 (0.72; 1.67)	0.79 (0.41; 1.09)	0.74 (0.43; 1.00)	1.82 (1.44; 4.14)*#
S PO, c.u. / mg	47.83 (41.94; 55.40)	66.87 (60.56; 76.11)*	79.30 (62.59; 122.34)*	82.04 (55.79; 35.89)*	55.79 (51.53; 64.65)*#	71.03 (67.38; 72.93)*#	66.05 (56.70; 74;87)*#
S_{ADNPH}, c.u. / mg	38.54 (30.64; 41.39)	59.19 (52.29; 62.31)*	65.04 (54.51; 96.45)*	65.04 (42.19; 97.89)*	47.78 (42.19; 57.09)*#	57.71 (54.26; 62.64)*	54.92 (50.75; 65.43)*#
S_{KDNPH}, c.u. / mg	10.12 (8.23; 11.31)	8.81 (8.09; 10.67)	15.49 (9.56; 26.11)*	16.99 (12.18; 33.88)*	6.75 (5.05; 8.83)*	13.21 (10.29; 13.88)	8.74 (5.95; 12.49)#
S uv, c.u. / mg	38.47 (34.05; 45.31)	59.10 (53.57; 68.66)*	74.97 (60.81; 118.45)*	65.17 (48.02; 114.01)*	49.24 (42.57; 57.19)*#	61.32 (59.49; 63.87)*	46.49 (39.24; 58.45)*#
S vs, c.u. / mg	7.87 (6.02; 9.73)	7.81 (6.41; 11.16)	4.05 (2.35; 5.85)*	9.22 (7.77; 17.56)	6.03 (4.50; 7.77)	8.41 (5.66; 10.16)#	10.51 (7.97; 26.29)*

Note: S – total content, vs – visible light region, uv – ultraviolet region of the spectrum.

Under the conditions of MT administration, on day 5 of TI, the amount of SB in the heptane phase decreased; in the isopropanol phase, the amount of CD, KD and CT, and SB decreased (see Table 1). On day 10, the amount of SB decreased in the heptane phase, and the level of CD decreased in the isopropanol phase. By day 20, a fall in the content of KD and CT and SB was recorded in the heptane phase, while the content of CD, KD, CT, and SB decreased in the isopropanol phase. During all periods of observation, MT did not result in complete restoration of LPO parameters in the wound. Significant differences with intact animals persisted in the heptane phase for KD and CT on day 20 of TI, for SB – on days 5, 10, and 20; for KD, CT and SB in the isopropanol phase – on days 5 and 20.

On days 5, 10, and 20, the content of CD in the isopropanol phase was lower than in the skin of the intact animals. Under the conditions of MT application in the wound, on days 5, 10, and 20, the total amount of PO products decreased (Table 2). On day 5, the total amount of ADNPH and PO products in the UV region of the spectrum and the content of ADNPH in the UV spectrum decreased. On day 10, the content of ADNPH and KDNPH decreased in the UV region, and the total content of PO products increased in the visible light region. On day 20, the total amount of ADNPH, KDNPH, and PO products in the UV region and the amount of ADNPH and KDNPH in the UV region of the spectrum decreased; the amount of KDNPH in the visible light region increased. During all periods of observation, the total amount of PO products, the total amount of ADNPH and PO products in the UV region of the spectrum, as well as the amount of ADNPH in the UV spectrum differed from the values in the intact group, which suggests partial recovery of parameter values.

DISCUSSION

In the burn wound with TI, secondary and end LPO products accumulate, which are extracted into the heptane phase mainly concentrating triacylglycerides (non-polar lipids) and LPO end products in the isopropanol phase, which contains mainly membrane phospholipids. The absence of significant changes in the content of primary LPO products in the heptane and isopropanol phases may be a consequence of their excessive formation on day 1 and participation in the formation of secondary and end products. Against this background, the total content of PO products in the burn wound increases due to neutral primary (ADNPH) and secondary (KDNPH) products, reflecting aggregation and fragmentation of protein molecules.

The content of the basic primary and secondary PO products decreases, most likely due to depletion of the reserves of protein products and their possible consumption in the first 5 days. It is believed that the accumulation of primary POM products, early markers, mainly reflects protein aggregation under the influence of $OH^{\cdot}$, while the accumulation of secondary products, late markers, reflects protein fragmentation under the combined action of $OH^{\cdot}$ and $O_2^{\cdot-}$. Protein fragments are resistant to proteolysis, trigger apoptosis and necrosis, and expand the area of alteration. The increase in SB reflects features and sources of their formation as products of non-enzymatic interaction of LPO products with products of free radical-mediated degradation of proteins under conditions of oxidative and carbonyl stress. There are no specific mechanisms for elimination of SB formed in this way; therefore, they are prone to accumulation, which increases their damaging effects. An increase in the content of LPO and PO products in the TI focus reflects activation of FRO under conditions of excessive generation of free radicals and / or a decrease in the activity of antioxidant defense systems.

FRO inducers in TI are NADPH oxidase, MPO of neutrophils and monocytes / macrophages, endothelial xanthine oxidase, NO-synthase of monocytes / macrophages, and mitochondrial complex I [18, 19]. A decrease in the activity of antioxidant defense systems may be due to their consumption for inactivation of excess free radicals, a decrease in the level of zinc and copper in the body (components of superoxide dismutase), and deficiency of selenium (a component of glutathione peroxidase) [20]. FRO and LPO and PO products formed in the skin in TI are associated with *in situ* cytotoxic effects, damage to internal organs, and possible advancement to systemic inflammatory response syndrome (SIRS) in the context of the OxInflammation concept. They are involved in skin repair due to activation of matrix metalloproteinases, modification of extracellular matrix components, and activation of stem cells [6, 21–23].

The use of MT in TI leads to a decrease in the content of LPO end products in the heptane phase, as well as primary, secondary, and end products in the isopropanol phase of the tissue homogenate. Apparently, a pronounced decrease in the level of primary LPO products in the isopropanol phase reflects MT-dependent limitation of early LPO stages and shielding of phospholipids due to predominant oxidation of pro-

teins. Firstly, the antioxidant effect of MT entering the burn wound from the systemic circulation through passive diffusion, as well as via glucose transporters and oligopeptides, may be due to direct absorption of reactive oxygen species (ROS) [24]. Secondly, it may be due to an increase in the synthesis of glutathione and the activity of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and hemoxidase-1 and a decrease in the activity of NOS [13]. Finally, the antioxidant effect of MT is realized by maintaining the mitochondrial membrane potential and increasing oxidative phosphorylation and production of ATP, and not ROS [25].

CONCLUSION

In experimental TI, an increase in the content of secondary and end products of LPO in the heptane phase was noted in the wound; the LPO end products increased in the isopropanol phase of lipid extraction; the total content of PO products increased due to primary and secondary products of a neutral nature. The use of MT reduced mainly the content of LPO end products in the heptane phase and secondary and end products of LPO in the isopropanol phase, as well as reduced and partially restored the amount of primary and secondary PO products of a neutral nature. In the TI focus, decreased damage to proteins and lipids limited secondary alteration, reduced the time of vascular and exudative reactions, promoted early activation of regeneration, and accelerated wound healing.

The results obtained expand the understanding of the role of changes in the redox state in the pathogenesis of TI and are a prerequisite for studying FRO in the skin to designate LPO and PO products as markers and predictors of complications and the effectiveness of therapy. LPO- and PO-limiting effect of MT suggests further study of the mechanism of MT action and the effectiveness of its use.

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