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PROTECTIVE EFFECTS OF MELATONIN ON REDOX IMBALANCE IN GASTRODUODENAL LESIONS UNDER CONTINUOUS LIGHT EXPOSURE

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Ключові слова:
peptic ulcer, melatonin, free radical oxidation, antioxidant system, desynchronosis.

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The aim of research *– to investigate the effect of melatonin at a dose of 5 mg/kg body weight on free radical oxidation of biomolecules and blood antioxidant system in rats with gastroduodenal erosive-ulcerative lesions (EUL) under conditions of continuous light exposure.*

Material and methods. *Experiments were performed on 40 male rats weighing 180-200 g. EUL was induced by daily oral administration of indomethacin (3 mg/kg) acetylsalicylic acid (100 mg/kg), and 10% medical bile (10 ml/kg) mixture for 14 days. Melatonin was administered intragastricaly at 8 p.m. at a dose of 5 mg/kg.*

The study was performed in compliance with the Rules of the work using experimental animals (1977) and the Council of Europe Convention on the Protection of Vertebrate Animals used in experiments and other scientific purposes (Strasbourg, 1986). It was performed according to directions of International Committee of Medical Journals Editors (ICMJE), as well as «Bioethical expertise of preclinical and other scientific research performed on animals» (Kyiv, 2006). The results were statistically processed using the STATISTICA 10 software (StatSoft Inc.). A Shapiro-Wilk test and Mann-Whitney test were performed to verify normality of data distribution. Data are illustrated as arithmetical mean±SEM (n=6 animals per group). P<0.05 was considered as statistically significant differences.

Results. *Experimental modeling of non-steroidal anti-inflammatory drugs (NSAIDs)-induced EUL in rats led to significant oxidative stress, as evidenced by elevated levels of malondic aldehyde (54%) and oxidatively modified proteins (72%), reduced glutathione depletion (24%), and increased glutathione peroxidase and ceruloplasmin activity. Continuous light exposure strengthened redox imbalance, intensification of lipid and protein peroxidation and further suppression of antioxidant defenses. Melatonin administration (5 mg/kg) against a background of EUL under constant light normalized oxidative markers, improved glutathione levels, and partially restored antioxidant enzyme activity.*

Conclusions. *Constant light exposure against a background of NSAIDs-induced EUL deepens activation of free radical oxidation of biomolecules and depletion of antioxidant protection. The introduction of melatonin at a dose of 5 mg/kg for 14 days contributes to the normalization of the main indicators of oxidative stress and partial restoration of antioxidant protection even under the conditions of the combined effect of NSAIDs and light desynchronization.*

Key words:
виразкова хвороба, мелатонін, вільнорадикальне окиснення, антиоксидантна система, десинхроноз.

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ЗАХИСНИЙ ВПЛИВ МЕЛАТОНІНУ ЩОДО ПОРУШЕННЯ ОКИСНО-ВІДНОВНОГО БАЛАНСУ ПРИ УРАЖЕННЯХ ГАСТРОДУОДЕНАЛЬНОЇ ЗОНИ ЗА УМОВ ПОСТІЙНОГО ОСВІТЛЕННЯ

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Мета роботи – *дослідити вплив мелатоніну в дозі 5 мг/кг маси тіла на процеси вільнорадикального окиснення біомолекул та стан антиоксидантної системи крові щурів з ерозивно-виразковим ураженням (ЕВУ) гастродуоденальної зони за умов постійного освітлення.*

Матеріал і методи. *Експерименти проводили на 40 самцях білих щурів масою 180-200 г. ЕВУ моделювали шляхом щоденного перорального введення суміші індометацину (3 мг/кг), ацетилсаліцилової кислоти (100 мг/кг) та 10% медичної жовчі (10 мл/кг) впродовж 14 діб. Мелатонін вводили внутрішньошлунково о 20.00 у дозі 5 мг/кг. Дослідження проведено відповідно до Правил роботи з використанням експериментальних тварин (1977 р.) та Конвенції Ради Європи про захист хребетних тварин, що використовуються в експериментах та інших наукових цілях (Страсбург, 1986 р.) та виконано згідно з вказівками Міжнародного комітету редакторів медичних журналів (ICMJE), а також «Біоетичної експертизи доклінічних та інших наукових досліджень, що проводяться на тваринах» (Київ, 2006 р.). Результати статистично опрацьовані за допомогою програмного забезпечення STATISTICA 10 (StatSoft Inc.). Для перевірки нормальності розподілу даних проведено тести Шапіро-Уілка та Манна-Вітні. Дані представлені у вигляді*

середньої арифметичної вибірки (M) ± стандартна похибка (m), (n=6 тварин у кожній групі). Значення P < 0,05 вважали статистично значущим.

Результати. *Експериментальне моделювання ЕВУ у щурів призводило до вираженого оксидативного стресу: підвищення рівнів малонового альдегіду (на 54%) і окисно модифікованих білків (на 72%), зниження рівня відновленого глутатіону (на 24%), зростання активності глутатіонпероксидази та церулоплазміну. Постійне освітлення посилювало порушення редокс-гомеостазу та вільнорадикальне ушкодження ліпідів і білків і сприяло подальшому виснаженню антиоксидантного захисту. Введення мелатоніну (5 мг/кг) на фоні ЕВУ за умов постійного освітлення нормалізувало показники вільнорадикального окислення та рівень глутатіону та частково відновило активність антиоксидантних ферментів.*

Висновки. *Постійне освітлення на фоні ЕВУ гастродуоденальної зони, індукованого нестероїдними протизапальними препаратами, посилює процеси вільнорадикального окиснення біомолекул і виснаження антиоксидантного захисту. Введення мелатоніну у дозі 5 мг/кг впродовж 14 діб сприяє нормалізації основних показників оксидативного стресу та частковому відновленню антиоксидантного захисту навіть за умов комбінованого впливу нестероїдних протизапальних препаратів і світлового десинхронозу.*

Introduction

Peptic ulcer disease remains a significant clinical challenge due to its high prevalence, tendency for recurrence, and potential for serious complications. [1].

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medications worldwide for the treatment of pain, inflammation, and fever [2]. However, their widespread and often prolonged use is strongly associated with the development of gastroduodenal mucosal damage, including erosions, ulcers, and gastrointestinal bleeding [3, 4].

Activation of free radical oxidation of biomolecules and depletion of the antioxidant defense system represent universal mechanisms of injury and death of the foveolar epithelium in the gastroduodenal mucosa [5].

In recent years, significant attention has been paid to melatonin – neurohormone of the pineal gland – recognized as one of the most potent endogenous antioxidants [6,7]. Literature sources report its positive effects on the balance of pro- and antioxidant systems under ulcerative conditions [8]. However, the therapeutic doses used vary widely and are generally high [7,8].

The relevance of this topic is further underscored by the growing prevalence of light-induced circadian rhythm disruption in modern society. Exposure to artificial light at night, shift work, screen time, and urban light pollution have been shown to suppress endogenous melatonin production and disturb oxidative balance [9]. These conditions may exacerbate mucosal vulnerability and contribute to gastrointestinal disorders, including peptic ulcer disease [10]. Thus, modeling continuous light exposure in experimental animals is of particular importance for simulating real-life risk factors and exploring their impact on redox homeostasis. Melatonin secretion is known to follow circadian rhythms, and its production is suppressed by continuous light exposure [9]. Therefore, disturbance of the light–dark cycle may potentiate oxidative stress and exacerbate mucosal injury.

The aim of research

To investigate the effect of melatonin at a dose of 5 mg/kg body weight on free radical oxidation of biomolecules and the status of the blood antioxidant system in rats with erosive-ulcerative lesions (EUL) of the gastroduodenal zone under conditions of continuous light exposure.

Research materials and methods

The study was performed in compliance with the Rules of the work using experimental animals (1977) and the Council of Europe Convention on the Protection of Vertebrate Animals used in experiments and other scientific purposes (Strasbourg, 1986). It was performed according to directions of International Committee of Medical Journals Editors (ICMJE), as well as «Bioethical expertise of preclinical and other scientific research performed on animals» (Kyiv, 2006).

Experiments were performed on 40 white non-linear male rats weighing 180-200 g which were randomly grouped and kept in polycarbonate cages (4 rats per cage) in a room under controlled environmental condition. Animals received food and water ad libitum.

Animals were divided into five groups: Group 1 (control) – intact rats kept under a standard light/dark cycle (12 h:12 h). Group 2 – rats with erosive-ulcerative lesions (EUL) induced by daily oral administration of indomethacin (3 mg/kg), acetylsalicylic acid (100 mg/kg), and 10% medical bile (10 ml/kg) mixture for 14 days. Group 3 (EUL + melatonin) – rats with induced EUL receiving intragastric melatonin daily at 8 p.m. at a dose of 5 mg/kg for 14 days. Group 4 (EUL + light) – rats with induced EUL, kept under continuous 24-hour light exposure by a constant fluorescent light of 1500 lux intensity throughout the 14-day experimental period. Group 5 – (EUL + light + melatonin) – rats with induced EUL along kept under continuous 24-hour light exposure receiving intragastric melatonin for 14 days.

Groups 1-3 were maintained under a standard 12 h:12 h light-dark cycle. Groups 1, 2 and 4 received an equivalent volume of distilled water instead of melatonin.

Animals were decapitated under light ether anesthesia on the 14th day after beginning of the experiment. Blood samples were collected in the presence of anticoagulant EDTA (1 mg/ml of blood). Blood plasma was obtained by blood centrifugation at 3000 rpm for 10 min.

Erythrocytes were washed three times with five volumes of saline solution and centrifuged at 3000 rpm for 10 min.

Malonic dialdehyde (MDA) content was assayed in erythrocytes by spectrophotometric measurement of trimethine colored complex formed in reaction with thiobarbituric acid at high temperature and acidic pH [11]. The content of oxidatively modified proteins (OMP) in blood plasma was assayed by reaction of amino acids carbonyl derivatives with 2.4-dinitrophenyl hydrazine which results in formation of hydrazones having specific absorption spectrum. Aldehydes derivates were determined at 370 nm [12]. The content of glutathione was measured by SH-groups content in reaction with 5,5-dithiobis-2-nitrobenzoic acid (Ellmans' reagent) [13]. The ceruloplasmin content in the blood plasma was measured spectrophotometrically by determination of phenylenediamine oxidation products and expressed in mg/l of blood plasma [14]. The catalase activity was determined by a method based on the ability of hydrogen peroxide to form a stable colored complex with ammonium molybdate with a maximum absorption at λ=410 nm [14]. Total protein content was assayed by Lowry using standard reagent kit for clinical diagnostics («Filisit-Diagnostics» Co., Ltd.).

The results were statistically processed using the STATISTICA 10 software (StatSoft Inc.). A Shapiro-Wilk test and then Mann-Whitney test were performed to verify normality of data distribution. Data are illustrated as arithmetical mean±SEM (n=6 animals per group). P<0.05 was considered as statistically significant differences.

The work is a fragment of the research project «Morphofunctional restructuring of the structures of the nervous and endocrine systems in different periods of postnatal ontogeny and biochemical mechanisms of signal molecules metabolism, state of oxidative and antioxidant systems under conditions of experimental pathologies, and the influence of glutathione and melatonin», state registration № . 0124U002513.

Results and their discussion

Prolonged administration of non-steroidal anti-inflammatory drugs (NSAIDs) is one of the most common ulcerogenic factors [3,4]. The gastropathic effect of NSAIDs is associated with the suppression of prostaglandin synthesis, leading to reduced bicarbonate secretion, vasoconstriction, impaired mucosal blood flow, and increased neutrophil infiltration in the gastric mucosa. These changes disrupt microcirculation, cause stasis and ischemia, and provoke the generation of reactive oxygen species (ROS) [5].

Our findings confirm that modeling erosive-ulcerative lesions (EUL) of the gastroduodenal zone leads to intensified free radical damage to biomolecules. This is evidenced by a significant increase in MDA levels (by 54%) and OMP in plasma (by 72%) compared to the intact control group (table 1).

Table 1

Indicators of pro- and antioxidant system in rats' blood in terms of gastroduodenal erosive-ulcerative lesions combined with constant light exposure and melatonin intake (M±m, n=6)

Parameter/ Groups	Control (group 1)	EUL (group 2)	EUL+ melatonin (group 3)	EUL + Light (group 4)	EUL + Light + melatonin (group 5)
MDA, nmol/mL	9.94±0.622	15.33±1.45*	8.84±0.52	17.08 ±1.21*†	10.51 ±0.72
OMP, mmol/g protein	0.782 ±0.029	1.346±0.084*	0.811±0.057	1.472 ±0.09*†	0.852±0.061
Reduced GSH, μmol/mL	1.163±0.075	0.880±0.039*	1.027±0.070	0.725±0.042*†	0.950±0.052
Ceruloplasmin, mg/L plasma	123.6 ± 9.83	196.2 ± 14.4*	159.7±10.8*	211.5 ± 13.0*†	165.3 ± 12.1*
Catalase, μmol/min×L	17.77±0.863	19.60±0.88	18.04±1.14	11.44±0.98*†	15.01±0.94*
Glutathione peroxidase, μmol/min×g Hb	114.8±6.99	149.0±6.3*	125.7±9.3	167.3±7.5*†	135.5±8.0*

*Notes: * p ≤ 0.05 – significant difference vs. control group; † p ≤ 0.05 – significant difference vs. group 2*

The intensification of free radical processes correlates with disruptions in the antioxidant defense system. Specifically, the content of reduced glutathione (GSH) in erythrocytes was decreased 24%, possibly due to its increased utilization by glutathione peroxidase, whose activity exceeded the control 30%. Ceruloplasmin activity in plasma increased 59%, while catalase activity showed no statistically significant difference.

It was shown that rats with EUL kept under continuous light exposure demonstrated a more pronounced imbalance in redox homeostasis. Specifically, MDA and OMP levels were significantly higher than in both the intact and EUL-only groups (71% and 88%), indicating enhanced lipid and protein peroxidation. The depletion of reduced glutathione in this group was more severe (38% from control), alongside the highest recorded activities of glutathione peroxidase (46%). Ceruloplasmin activity also reached its peak in this group (71%), suggesting intensified acute-phase oxidative responses. Catalase activity was by 36% the level of control group that could prove depletion of antioxidant defense.

These findings support the hypothesis that circadian disruption due to constant light exposure acts as an additional oxidative stressor that aggravates NSAID-induced mucosal damage. This is in line with previous data indicating that melatonin synthesis is inhibited by light at night, which compromises antioxidant defenses [7,9].

We found (table 1) that melatonin administration at a dose of 5 mg/kg for 14 days during EUL modeling and its combination with constant light exposure normalized MDA and OMP levels, restored GSH content in the blood. Ceruloplasmin levels in group 3 and group 5 were lower than in melatonin-untreated animals but still remained higher control level 29% and 33%. Melatonin administration normalized glutathione peroxidase activities in NSAID-induced EUL rats and reduced its activity to 18% above control for rats with EUL kept under constant lights. Catalase activity in group 5 animals was still by 16% below the control group level.

Overall, melatonin demonstrated a clear protective antioxidant effect, even under conditions of combined NSAID-induced injury and circadian rhythm disruption.

Its action may be attributed to the direct scavenging of free radicals via its indole ring, and to the regulation of gene expression for antioxidant enzymes [7, 8].

Conclusions

Constant light exposure during NSAIDs-induced EUL deepens activation of free radical oxidation of biomolecules and depletion of antioxidant protection. The introduction of melatonin at a dose of 5 mg/kg for 14 days contributes to the normalization of the main indicators of oxidative stress and partial restoration of antioxidant protection even under the conditions of the combined effect of NSAIDs and light desynchronization.

Prospects for further research

To study dose-dependent effect of melatonin to determine the optimal therapeutic concentration for the correction of oxidative stress in EUL and assess the duration of its protective effect.

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