Медицинская иммунология
2021, Т. 23, № 4,
стр. 705-710

Краткие сообщения
Short communications

Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2021, Vol. 23, № 4, pp. 705-710

ЦИТОКИНОВЫЙ ПРОФИЛЬ В КРОВИ И РЕПАРАЦИЯ В ОЧАГЕ ПОВРЕЖДЕНИЯ В ДИНАМИКЕ ЭКСПЕРИМЕНТАЛЬНОЙ ТЕРМИЧЕСКОЙ ТРАВМЫ В УСЛОВИЯХ ЛОКАЛЬНОГО ИЛИ СИСТЕМНОГО ПРИМЕНЕНИЯ МЕЛАТОНИНА

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Резюме. Ожоговый травматизм представляет одну из ключевых медико-социальных проблем. Несмотря на значительные достижения в комбустиологии, медленное заживление и присоединение инфекции составляют ключевые проблемы у ожоговых больных, приводящие к удлинению сроков госпитализации, снижению качества жизни и эмоциональным расстройствам. До 70% всех осложнений после термической травмы (ТТ) связаны с инфекцией – это, прежде всего, пневмония, инфекции мочевыводящих путей. Формирование инфекционных осложнений, включая сепсис, после ТТ связывают с избыточными иммуносупрессивными реакциями, в том числе как компенсацию на длительный, устойчивый провоспалительный ответ, в частности обусловленными гиперпродукцией и эффектами IL-10, IL-4, TGF-β. Цель работы: изучить влияние системного и локального в составе оригинальной дермальной пленки (ДП) применения МТ на показатели репарации и концентрацию в сыворотке некоторых цитокинов в динамике экспериментальной ТТ. Работа выполнена на 84 крысах – самцах линии Wistar массой 240±20 г, которые случайным образом разделены на 4 группы: группа 1 (n = 12) – интактный контроль, группа 2 (n = 30) – животные с ТТ, группа 3 (n = 21) – животные с ТТ и наложением ДП с МТ на область ожога, группа 4 (n = 21) – животные с ТТ и внутрибрюшинным введением МТ. Для моделирования ТТ IIIA степени и относительной площадью 3,5% изолированный участок кожи межлопаточной области погружали в дистиллированную воду с температурой 98-990 С на 12 с. ДП с МТ (в концентрации 0,005 г/г) площадью 12 см^2 в группе 3 наносили сразу после ТТ, закрепляя асептической повязкой, перевязку осуществляли ежедневно в течение 5 суток. Внутрибрюшинно вводили МТ ежедневно в дозе 10 мг/кг в течение 5 суток. На 5-е, 10-е и 20-е сутки от момента индукции ТТ вычисляли площадь раны, скорость эпителизации в сыворотке определяли концентрацию интерлейкина-4 (IL-4), фактора некроза опухолей альфа (TNFα), интерферона-гамма (IFNγ). При экспериментальной ТТ в динамике наблюдений от 5-х к 20-м суткам уменьшается абсолютная и относительная площадь раневого дефекта, в связи с чем прогрессивно увеличивается скорость эпителизации раны и доля уменьшения ее площади, на 5-е, 10-е и 20-е сутки в сыворотке увеличивается концентрация TNFα и IL-4 с максимальными значениями на 10-е сутки наблюдения. Локальное применение МТ в составе ДП при ТТ ускоряет заживление ожоговой раны и снижает в

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Образец цитирования:

М.В. Осиков, А.А. Агеева «Цитокиновый профиль в крови и репарация в очаге повреждения в динамике экспериментальной термической травмы в условиях локального или системного применения мелатонина» // Медицинская иммунология, 2021. Т. 23, № 4. С. 705-710. doi: 10.15789/1563-0625-BCP-2214

For citation:

M.V. Osikov, A.A. Ageeva "Blood cytokine profile and lesion site repair in dynamics of experimental thermal trauma after local and systemic melatonin administration", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2021, Vol. 23, no. 4, pp. 705-710.
doi: 10.15789/1563-0625-BCP-2214

DOI: 10.15789/1563-0625-BCP-2214

сыворотке концентрацию TNFα и IL-4 на 5-е, 10-е и 20-е сутки. Внутрибрюшинное применение МТ при ТТ ускоряет заживление ожоговой раны и снижает в сыворотке концентрацию TNFα на 10-е и 20-е сутки. Ускоряющий репарацию эффект МТ при ТТ более выражен при локальном применении в составе ДП по сравнению с внутрибрюшинным введением.

Ключевые слова: термическая травма, мелатонин, репарация, цитокины, TNFα, IFNγ, IL-4

BLOOD CYTOKINE PROFILE AND LESION SITE REPAIR IN DYNAMICS OF EXPERIMENTAL THERMAL TRAUMA AFTER LOCAL AND SYSTEMIC MELATONIN ADMINISTRATION

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Abstract. Burn injuries are one of the key medical and social problems. Despite the significant achievements in combustiology, the slow healing and the appearance of infection are the key problems in burn patients, which lead to a longer hospitalization period, to reduction of life quality and to emotional disorders. Up to 70% of all complications after thermal trauma (TT) are connected with infection – first of all, pneumonia, infections of urinal tract. The forming of infectious complications, including sepsis, after TT is associated with excessive immunosuppressive reactions, as compensation for a long, stable proinflammatory response, in particular, owing to hyperproduction and effects of IL-10, IL-4, TGF-β. Aim: to study the influence of systemic and local usage of MT with original dermal film (DF) on reparation and serum cytokine concentration indicators in dynamics of experimental TT. The study was conducted using 84 rats – males of Wistar line, which were divided randomly into 4 groups: 1st group (n = 12) – intact monitoring, 2nd group (n = 30) – animals with TT, 3rd group (n = 21) – animals with TT and DF with MT use on the region of burn, 4th group (n = 21) – animals with TT and intraperitoneal injection of MT. To model TT of IIIA degree and relative area 3,5%, isolated skin area of interscapular area was immersed in distilled water at a temperature of 98-99 °C at 12 s. The DF with MT (at a concentration of 0.005 g/g) on 12 sm^2 – area in 3rd group was used daily for 5 days. The MT was injected intraperitoneally daily at the dose of 10 mg/kg for 5 days. The wound area was calculated, the interleukin-4 (IL-4), tumor necrosis factor alpha (TNFα), interferon-gamma (IFNγ) were determined in serum on 5th,10th and 20th day from the moment of TT induction in each group. During experimental TT in dynamic monitoring from 5th to 20th day the absolute and relative areas of wound defect are reduced, because of that the epithelization speed and its part of area reduction are progressively increasing, on 5th,10th and 20th day the concentration of TNFα and IL-4 in serum is increasing with maximum values on 10th day of monitoring. Local usage of MT in DF during TT accelerates the healing of burn wound and lowers the TNFα and IL-4 concentration in serum on 5th, 10th and 20th day. Intraperitoneal use of MT during TT accelerates the healing of burn wound and lowers the TNFα and IL-4 concentration in serum on 5th and 20th day. The reparation accelerating effect of MT during TT is more expressed in locale usage in DF rather than using intraperitoneal injection.

Keywords: thermal trauma, melatonin, reparation, cytokine, TNFα, IFNγ, IL-4

The study was carried with support of the Federal State Budgetary Institution "Fund for assistance to the development of small forms of enterprises in the scientific and technical sphere" under the program U. M. N. I. K. (agreement No. 15583GU/2020, dated of 05.07.2020).

The research study was funded by the RFBR and Chelyabinsk Region, Project No. 20-415-740016.

Introduction

Burn injuries are one of the key medical and social problems. Despite the significant achievements in combustiology, slow healing and appearance of infection are the key issues in burn patients, which lead to prolonged hospitalization period, lowered quality of life and emotional disorders [1]. Up to 70% of all complications after thermal trauma (TT) are connected to infections primarily pneumonia and urinal tract infections. Development of infectious complications, including sepsis, after TT is associated with excessive immunosuppressive reactions to compensate for long-lasting stable proinflammatory response particularly owing to overproducted IL-10, IL-4, TGF-β [2]. Immune reactions hold the key place in TT pathogenesis at each stage, the main factors of TT mortality reduction are due to knowledge of burn pathophysiology, development of pathogenetical substantiation of therapy methods, as well as methods

of safe necrectomy and wound closures [3]. In this regard, endogenic homeostasis regulators, which can interfere in mounting immune response to TT and to be involved as immunocorrectors attract special interest. Earlier, we showed that erythropoietin applied locally and systemically as well as local EGF administration in TT accelerate healing of burn injury and restoration of the immune status in clinical and experimental conditions [4, 5]. Melatonin (MT) regulates homeostasis exerting pleotropic effects: regulation of sleep-wake cycle (change of the MT secretion rhythm in TT is considered as the key factor of sleep disorders), regulation of redox-factor with predominant antioxidant effect, pro- and anti-inflammatory, immunomodulatory, anti-apoptogenic, regulating cell proliferation and differentiation [6]. Skin cells produce MT, so that its metabolites are found in keratinocytes, melanocytes, dermal fibroblasts [7]. MT1, MT2, RORα receptors were found in keratinocytes, skin fibroblasts, the cells of the hair follicle and dermal blood vessels, and melanocytes [8]. Nowadays, the pharmaceutical MT forms are not available in the RF for local use in skin injuries, and oral MT forms are not indicated for use in TT. **Aim:** to study an influence of systemic and local MT application with original dermal film (DF) on repair and dynamic serum cytokine profile in experimental TT.

Materials and methods

The study was conducted using 84 males Wistar rats, weighted 240±20g, reared on standard diet in experimental and biological clinic (vivarium) FSBEI HE SUSMU MOH Russia, under strict compliance with the requirements for the care and maintenance of laboratory animals. The research is approved by the ethics committee of FSBEI HE SUSMU MOH Russia (Protocol No. 10, dated of 15.11.2019). The animals were randomized into 4 groups: group 1 (n = 12) – intact monitoring, group 2 (n = 30) – animals with TT, group 3 (n = 21) – animals with TT and DF, MT applied on the region of burn, group 4 (n = 21) – animals with TT and intraperitoneally inoculated MT. To model IIIA degree TT and relative area 3,5%, isolated skin area of interscapular area was immersed in distilled water at temperature of 98-99 °C for 12 sec. The burn depth was measured by morphological methods. The preparation "Zoletil-100" (Virbac Sante Animale, France) at dose of 20mg/kg was used for anesthesia. The aseptic dressing was applied on the area of burn every day for 20 days in group 2, 3 and 4. The DF with MT on 12 cm^2 area in group 3 was used immediately after TT, sealed with aseptic bandage, the dressing was carried out daily for 5 days. In preliminary studies, the composition of the DF sodium carboxymethylcellulose-based containing MT at concentration of 0.005 g/g, was developed and evaluated in accordance with pharmacological parameters: organoleptic parameters (appearance, color, transparency, elasticity, presence of impurities and microcracks), adhesive ability, mechanical tensile strength, thickness (patent application № 2020118766 from 29.05.2020). The MT (FLAMMA S.P.A., Italy) was inoculated intraperitoneally daily at dose of 10 mg/kg for 5 days. The wound area was calculated by digital planimetric method with camera "Nikon Coolpix S2800" (China) and software package "Microsoft Office Visio". Epithelialization speed (VS) was calculated by using formula: VS = S-Sn/t using S as the initial wound area before treatment (hereinafter, the area in the previous measurement); Sn – the area in the subsequent measurement; t – the

TABLE 1. INDICATORS OF INJURY REPARATION IN EXPERIMENTAL THERMAL TRAUMA (TT) IN CASE OF LOCAL (DF) AND SYSTEMIC USE OF MELATONIN (MT), Me ($Q_{0.25}$-$Q_{0.75}$)

Indicators	Group 2 TT 5th day	Group 2 TT 10th day	Group 2 TT 20th day	Group 3 TT + MT DF 5th day	Group 3 TT + MT DF 10th day	Group 3 TT + MT DF 20th day	Group 4 TT + MT 5th day	Group 4 TT + MT 10th day	Group 4 TT + MT 220th day
Burn area, cm^2	11.66 (11.50-11.94)	9.48 (9.28-9.93)	7.59 (7.23-7.84)	10.33 (10.17-10.56)#	8.34 (8.19-8.51)#	5.54 (5.24-5.88)#	10.92 (10.73-11.03)#	9.11 (8.53-9.50)	6.27 (6.18-6.42)# ^
Relative area, %	3.34 (3.25-3.39)	3.17 (3.10-3.29)	2.99 (2.94-3.12)	3.36 (3.23-3.42)	3.02 (2.91-3.13)#	1.98 (1.87-2.23)#	3.43 (2.91-3.46)	3.10 (3.01-3.15)	2.54 (2.17-2.86)# ^
Epithelization speed, % / day	0.89 (0.86-0.89)	1.90 (1.88-1.95)	2.26 (2.14-2.55)	1.33 (1.29-1.35)#	6.57 (5.92-6.93)#	14.30 (13.38-15.17)#	1.15 (1.04-1.22)	2.90 (2.62-3.27)# ^	8.89 (7.80-9.90)# ^
Injury area reduction, %	2.61 (2.59-2.64)	3.68 (3.53-4.23)	11.49 (11.43-11.64)	9.80 (9.64-10.08)#	16.10 (14.62-17.73)#	19.98 (19.30-20.38)#	3.31 (3.17-3.58)^	9.48 (8.81-10.22)# ^	15.09 (13.39-16.87)# ^

Note. #, significant (p < 0.05) differences with group 2. ^, with group 3 on the corresponding day.

number of days between measurements. The wound area in the subsequent measurements was estimated in percentage %, taking the day 1 area as 100%, the data were expressed as % per day. On day 5,10 and 20 after the TT onset blood sampling was conducted under anesthesia after thoracotomy by heart left ventricle puncture into vacuum tubes "Vacuette" (Greiner Bio-One, Austria). In immunoassay "Personal LAB" (Italy) with specific test-systems for rat (Bender Medsystems, Austria) the interleukin-4 (IL-4), tumor necrosis factor-alpha (TNFα), interferon-gamma (IFNγ) concertation were measured (pg/ml) in the serum. Statistic data processing was performed by using IBM SPSS Statistics v. 19 software. Characteristics of the samples are presented as "Me ($Q_{0.25}$-$Q_{0.75}$)", Me – median, $Q_{0.25}$ and $Q_{0.75}$ – the values of the lower and higher quartile, respectively. The testing of statistical hypothesis in groups was conducted by using non-parametric criteria Kruskal–Wallis and Mann–Whitney. To assess a relationship between parameters studied, a Spearman correlation coefficient (R) was used. The differences were considered at significance level of $p < 0.05$.

Results and discussion

The repair indicators in experimental TT are presented in Table 1. On day 10 *vs* day 5 after TT burn absolute and relative area were decreased ($p < 0.05$), the epithelization speed and reduced wound area were increased ($p < 0.05$). Similar tendency was found on day 20 *vs* day 10 after TT: the skin burn absolute and relative area were decreased ($p < 0.05$), the epithelization speed and the reduced wound area were increased ($p < 0.05$). In addition, on day 20 after TT the absolute burn area, the rate of epithelialization and reduced wound area significantly ($p < 0.05$) differed from those on day 5, suggesting a progressive decrease in the burn absolute square, increased rate of epithelialization and reduced wound size in dynamics monitoring.

The concentration of serum cytokines after TT is presented in Table 2. On day 5, 10 and 20 after TT an increased concentration of TNFα, IL-4 without significant changes in IFNγ concentration was found. In dynamics of TT, the concentration of TNFα and IL-4 in serum on day 10 *vs* day 5 was higher ($p < 0.05$) and didn't differ from those on day 20, that allows to note about peak level of TNFα and IL-4 on day 10 of monitoring. Use of MT in DF during experimental TT leads to significantly reduced burn area in absolute values on day 5, 10 and 20 *vs* day 10 and 20 (Table 1). On day 5, 10 and 20 of monitoring the epithelization speed and relative wound area decline was increased. Maximal differences were found on day 20, whereas absolute wound area decreased by 54%, and median epithelization speed increased more than by 10-fold compared to animals with TT without use of DF with MT. Analyzing serum cytokine concentration after use of DF with MT it was found that TNFα and IL-4 level was decreased on day 5, 10 and 20 as well as on day 10 and 20, respectively. At the same time, the concentration of TNFα on day 5 did not differ, whereas on day 10 and 20 it was increased in intact animals, the concentration of IL-4 at all timepoints was higher than in the intact animals. Comparing effects of MT in DF *vs* intraperitoneally injected MT, it was found that absolute and relative burn area on day 20 were higher, on day 5, 10 and 20 epithelization speed was lowered, day 10 and 20 the relative decrease in wound area was lowered compared to animals with TT applied with MT in DF. We found no significant differences in concentration of TNFα, IFNγ and IL-4 in TT after using MT intraperitoneally *vs* use of MT in DF. The change of gene expression, cytokines production and secretion in the TT focus were noticed in many studies for pro- (IL-1β, IL-6, IL-8, IL-22,

TABLE 2. CONCENTRATION OF CYTOKINES IN SERUM IN EXPERIMENTAL THERMAL TRAUMA (TT) IN CASE OF LOCAL (DF) AND SYSTEMIC USE OF MELATONIN (MT), Me ($Q_{0.25}$-$Q_{0.75}$)

Indicators	Group 1 Intact	Group 2 TT 5th day	Group 2 TT 10th day	Group 2 TT 20th day	Group 3 TT + MT DF 5th day	Group 3 TT + MT DF 10th day	Group 3 TT + MT DF 20th day	Group 4 TT + MT 5th day	Group 4 TT + MT 10th day	Group 4 TT + MT 20th day
TNFα, pg/ml	1.18 (0.84-1.96)	2.25 (2.02-2.92)*	3.42 (2.72-6.14)*	3.48 (1.77-5.05)*	1.77 (1.07-2.30)#	1.96 (1.35-4.32)* #	1.57 (1.35-2.69)* #	2.33 (1.85-3.03)*	2.69 (2.19-3.03)* #	1.91 (1.35-3.03)* #
IFNγ, pg/ml	0.83 (0.29; 1.24)	0.73 (0.12-1.15)	0.98 (0.59-1.35)	1.06 (0.65-1.74)	0.94 (0.54-1.24)	0.78 (0.44-1.34)	1.19 (0.37-1.44)	0.84 (0.51-1.49)	0.76 (0.52-1.08)	1.08 (0.66-1.22)
IL-4, pg/ml	0.79 (0.50-1.75)	1.93 (1.36-2.51)*	3.26 (2.58-5.65)*	2.97 (1.57-4.97)*	1.72 (1.36-1.86)*	2.36 (1.29-4.22)* #	2.08 (1.29-2.65)* #	2.11 (1.79-2.86)*	2.79 (2.43-3.36)*	2.18 (1.79; 3.01)*

Note. #, significant ($p < 0.05$) differences with group 1. ^,with group 2 on the corresponding day.

IFNγ, TNFα, G-CSF, GM-CSF, MIP-2α, MSR-1) and anti-inflammatory (IL-4, IL-10) cytokines depending on depth, area and localization of burn, age, concomitant pathology, and other factors [2]. The sources of cytokines in the TT focus are presented by activated neutrophils, macrophages (Langerhans cells, M1 and M2 subset), dendritic cells, and diverse lymphocyte populations. The release of cytokines from TT focus into systemic blood circulation leads to activation of circulated leukocytes, platelets and endotheliocytes as an additional source of cytokines. It is noteworthy that dysfunction of specified cells, their altered phenotype lead to controversial results in different studies and require further investigation. Heterogeneity of neutrophil phenotype, function and plasticity in TT, as well as the dysfunction after concomitant secondary infection, largely determine the pathogenesis scenario, likelihood of complications and the outcome. The presence of PGE2 in TT focus leads to shift in neutrophil pro- to anti-inflammatory and pro-reparative phenotype [9]. The M1 dysfunction on early stage of TT restricts the scar healing, however the dysfunction of M2 caused long-lasting oedema and alteration, delayed wound closure, however, excessive M2 activity caused excessive scarring, increased fibroblast proliferation, and angiogenesis [10]. Long-lasting increase of serum pro-inflammatory cytokine levels after TT is coupled to adverse outcome as a result of SIRS, shock. As a result, the serum and TT focus IL-4 and IL-10 concertation increase is a post-burn immunosuppression marker. We suspect that local use of MT in DF with lipophilic properties allowed to diffuse rapidly in intracellular space and enter into the cells in the lesion site via passive diffusion, as well as glucose transporters (GLUT1) and oligopeptides (PEPT1/2) [11]. The possible mechanism of MT effect is provided by at least 18 specific receptors. Plasma membrane receptors, associated with G-peptides are MT1 (Mel1a), MT2 (Mel1b), GPR50 (Mel1c), cytosolic receptor MT3 (chinonreductase-2), metalloproteinase-9, protein-phosphotase-2, the loci of connection of MT in nucleus, as well as RORα, vitamin D receptors (VDR) [11]. MT is considered as key skin antioxidant [7]. Due to direct absorption of APK, stimulated glutathione synthesis, activation of glutathione peroxidase, glutathione reductase, SOD, catalase, hemoxidase-1 activation of quionreductase-2, NOS-1 was decreased. Antioxidant effect of MT is enabled by ingesting mitochondria via the PEPT1/2 transporter, maintaining the mitochondrial membrane potential, and increasing oxidative phosphorylation, the production of ATP rather than APK. All of them contributed to restricted area of secondary alteration and subsequently decreased activation of neutrophils, monocytes/macrophages, endotheliocytes, lowered synthesis and secretion of autokiodes (что это), including pro-inflammatory cytokines.

Protective effect of MT in TT focus may be caused by its anti-apoptogenic effect, decrease in proapoptotic protein expression in keratinocytes due to redcued cytochrome C release from mitochondria, as well as caspase 9, 3 and 7 activation. DNA repair in skin cells is regulated by MT both indirectly due to the antioxidant effect mentioned above, and directly due to increased p53 expression [13]. The anti-inflammatory effect of MT is associated with the restriction of NF-κB-dependent intracellular signaling pathways. Moreover, after ultraviolet B irradiation of keratinocytes, which leads to the activated NF-κB, MT inhibits the expression of many pro-inflammatory factors: iNOS, COX-2, TNFα [14]. MT inhibits the NLRP3-dependent signaling pathway activated by mitochondrial oxidative damage and associated with the expression of pro-apoptogenic factors IL-1β and IL-18. An important mediator of the anti-inflammatory MT effect is sirtuin SIRT1, which suppresses the activation of NF-κB-, NLRP3-dependent pathways [15]. Consequently, protective effect of MT in skin after thermal injury may be caused by antioxidative and anti-apoptogenic action that reduces the area of secondary alteration and shortened inflammatory phase, alterative and vascular-exudative reactions selected to cell proliferation and repair reactions at the repair phase and the remodeling phase. This as well as direct restriction of NF-κB-dependent and NLRP3-dependent intracellular signaling pathways, leads to decreased activity of cytokine-producing cells in the lesion site and systemic blood flow. A more pronounced effect of MT within DP, which stimulates repair and reduces the serum concentration of TNFα and IL-4 compared with the systemic use of MT, may be associated with the autonomy of the TT focus, which restricts the MT influx from the bloodstream.

Conclusion

Dynamic monitoring of experimental TT from day 5 to day 20 revealed that the absolute and relative wound areas were reduced due to the epithelization speed and its part of area reduction progressively increased, whereas serum concentration of TNFα and IL-4 on day 5, 10 and 20 increased with peak values on day 10. Local usage of MT in DF during TT accelerates the burn wound healing and lowers the serum TNFα and IL-4 concentration on day 5, 10 and 20. Intraperitoneal use of MT during TT accelerates the burn wound healing and lowers the serum TNFα and IL-4 concentration on day 5 and 20. The repair accelerating effect of MT during TT is more evident after locally *vs* intraperitoneally used DF.

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Поступила 02.03.2021
Отправлена на доработку 31.05.2021
Принята к печати 03.06.2021

Received 02.03.2021
Revision received 31.05.2021
Accepted 03.06.2021