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褪黑素在不同疾病细胞焦亡作用中的研究进展

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摘要: 褪黑素(melatonin, MT)是机体释放的一种神经激素,具有抗感染、抗炎和抗氧化作用,调节机体的正常睡眠周期等生理功能。它可以作为一种有效的自由基清除剂或免疫增强剂,作用于全身各个系统与组织,对机体正常生理功能的维持有重要作用。细胞焦亡是细胞的一种程序性死亡模式,炎症小体与GSDMD(gasdermin D)家族是其重要的组成成分。当机体受到外界损伤后,炎症小体和GSDMD蛋白先后发生活化,导致细胞膜产生膜孔,大量胞液以及胞内物质释放,引发一系列炎症级联反应,造成细胞的继发性损伤。细胞焦亡与机体多种疾病的发生有密切的关系。作为一种抗炎和抗氧化的神经激素,褪黑素通过抑制细胞焦亡的发生,在心肌损伤、糖尿病、中枢神经系统疾病、肥胖、退行性变性疾病的发生发展与治疗中发挥重要作用。本文就褪黑素在机体不同疾病细胞焦亡中的影响和作用机制进行概述。

关键词: 褪黑素(MT); 细胞焦亡; 心肌损伤; 糖尿病; 中枢神经系统疾病; 退行性变性疾病

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Research Progress of Effects of Melatonin on Pyroptosis in Different Diseases

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Abstract: Melatonin (MT) is a neurohormone released by the body. It has anti-infection, anti-inflammatory and antioxidant effects, and regulates the body's normal sleep cycle. As an effective free radical scavenger and immune enhancer, it plays an important role in maintaining the normal physiological functions by acting on all systems and tissues of the body. Pyroptosis is a type of programmed cell death, in which the inflammasomes and GSDMD (gasdermin D) family are the most important components. When the inflammasomes and the GSDMD protein are activated, membrane pores in the cell surface are generated, and a large amount of cellular fluid and intracellular substances are released, leading to a series of inflammatory cascade reactions, followed by secondary cell damage. Pyroptosis is closely related to the occurrence of many diseases. Melatonin, as an antioxidant and anti-inflammatory neurohormone, can cope with occurrence and development of myocardial damage, diabetes, central nervous system disease, obesity and degenerative disease by inhibiting pyroptosis. Herein, the effects of melatonin on pyroptosis in different diseases are reviewed.

Key words: melatonin (MT); pyroptosis; myocardial damage; diabetes; central nervous system disease; degenerative disease

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褪黑素(melatonin, MT)是一种吲哚胺,可由包括松果体在内的许多器官产生,具有抗炎、抗凋亡

以及调节机体正常睡眠周期的功能^[1]。在动物体内,褪黑素主要是松果体在黑暗条件下合成的,

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皮肤、骨髓、视网膜和胃肠道^[2]等也可以合成褪黑素,褪黑素的合成和分泌主要受下丘脑视交叉上核(suprachiasmatic nucleus, SCN)的“主生物钟”调节^[3]。然而,最大数量的褪黑素不是由松果体产生的,而是在肠道和皮肤中产生的^[4],其产量大约是松果体中的400倍^[5]。褪黑素一旦形成,就会释放到毛细血管中,并以较高浓度释放到脑脊液中^[6],然后迅速分布到身体各个部位,参与机体正常的生理功能。

细胞焦亡是一种发生在细胞中的程序性死亡模式,与多种疾病的发生、进展有关。炎症小体与GSDMD (gasdermin D)蛋白是细胞焦亡发生过程中的重要组分,介导炎症的发生,引起组织的继发性损伤。许多疾病都伴随着细胞焦亡的发生,其诱导机体出现炎症反应,而炎症具有双重作用:一方面,免疫细胞被招募到损伤部位,清除细胞碎片,这对存活的细胞有负面影响;另一方面,免疫细胞释放促炎细胞因子、自由基和金属蛋白酶,增加组织损伤^[7]。因此,抑制细胞焦亡的发生,减轻炎症,对于组织损伤的遏制有一定作用。

由于许多疾病的发生、发展过程大都伴随有细胞焦亡的发生,而褪黑素具有显著的抗炎、抗氧化作用,对于细胞焦亡的发生有一定的抑制作用。因此,本文就褪黑素在发生细胞焦亡的疾病中的作用机制进行综述。

1 褪黑素功能简介

1.1 褪黑素的生理功能

褪黑素既是一种重要的神经内分泌激素,也是一种内源性暗信号,是人体内部计时系统的重要组成部分,其调节的生理过程主要包括:睡眠-觉醒周期、青春期发育和季节性适应。褪黑素昼夜节律的紊乱会导致许多疾病的发生,包括神经退行性疾病、心脏病、高血压和癌症。研究报道,褪黑素在心肌缺血再灌注^[8]、青少年脊柱侧弯^[9]、血管内皮损伤^[10]、高血压^[11]、心力衰竭^[12]、癌症^[13]中发挥有益作用。迄今为止,褪黑素已被证明对抗缺血性脑损伤有多种药理作用^[14],包括昼夜节律调节、抗氧化、抗炎和抗凋亡等。不同物种以及同一物种的年龄不同、性别不同,其褪黑素的含量不同^[15]。褪黑素的释放与人体的年龄变化也有很大关系,在松果体来源的血液(可能还有脑脊液)中,褪黑素浓度通常随着个体年龄的增长而下降,从而导致褪黑素稳定昼夜节律的能力降低,同时降低的

还有其自由基猝灭能力^[16]。因此,随着年龄的增长,褪黑素的含量会不断下降,其清除机体活性氧(reactive oxygen species, ROS)的功能也会不断下降,这可能与老年人易出现中枢神经系统退行性变性有一定关系。此外,褪黑素的水平不断下降,也会进一步促进细胞以及器官的衰老。研究表明,褪黑素在体外促进骨髓间充质干细胞成骨,并减轻衰老小鼠的骨质疏松症进展;在临床上,老年性骨质疏松症的严重程度与骨髓中的褪黑素水平呈负相关^[17]。因此,提高机体内褪黑素的含量,可能会抑制衰老的速度并减少疾病的产生。

1.2 褪黑素的抗氧化作用

褪黑素具有抗氧化保护作用,这种保护作用可能涉及多种途径(图1),包括自由基的清除^[18],也包括其他氧化剂的失活和金属诱导的脂质过氧化的抑制^[19]。褪黑素可上调抗氧化防御系统,包括增加过氧化物酶(peroxidase, POD)、超氧化物歧化酶(superoxide dismutase, SOD)和谷胱甘肽(glutathione, GSH)的活性。褪黑素也可以下调促氧化酶,如诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)、脂氧合酶(lipoxygenase, LOX)^[20-22]等。褪黑素限制氧化应激的能力有时也依赖于它与褪黑素受体的相互作用。褪黑素受体存在于多种细胞^[23-24],褪黑素通过与受体结合,激活下游的一系列反应,从而参与抗氧化过程。褪黑素的抗氧化机制是复杂的,主要与抑制炎症的发生相关,例如: NO 释放;环氧合酶-2 (cyclooxygenase-2, COX-2) 激活;沉默信息调节因子1 (sirtuin 1, SIRT1) 激活;核因子 E2 相关因子 2 (nuclear factor-erythroid 2-related factor 2, Nrf2) 上调;核因子 κ B (nuclear factor- κ B, NF- κ B) 下调;抗炎细胞因子白介素(interleukin, IL)-4 和 IL-10 的释放;炎症小体 NLR 家族 pyrin 域蛋白 3 (NLR family pyrin domain containing 3, NLRP3)、GSDMD、Toll 样受体 4 (Toll-like receptor 4, TLR4) 和哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR) 信号以及衰老相关分泌表型(senescence-associated secretory phenotype, SASP) 释放细胞因子的抑制^[25]。因此,当机体受到外界病原体损伤时,补充褪黑素,提高机体褪黑素的水平,在一定程度上可以提高机体的抵抗力,减轻炎症反应。

作为一种有效的抗氧化剂,褪黑素的级联反应使其区别于其他经典抗氧化剂(如 SOD、GSH 等)。褪黑素及其次级和三级代谢产物能够中和许多有

毒的氧衍生物,这被称为其级联反应^[26]。通过这种方式,1个褪黑素分子可以清除多达10个ROS,而传统的抗氧化剂只能清除1个或更少的ROS。研究表明,褪黑素能够螯合多种金属离子,包括铁、铜、铝、铅、镍、镉和锌^[27]。目前,已经有多项研究报告,褪黑素在金属离子对机体造成损害时有一定的保护作用,例如:镍引起的肝纤维化^[28],铅引起的肠上皮细胞损伤^[29],都可以通过给予褪黑素得到一定的减轻。通过结合这些金属离子,褪黑素可以延缓芬顿反应,抑制羟基自由基($\cdot\text{OH}$)产生。褪黑素因抗氧化作用和结合过渡金属的能力^[30],成为氧化应激的有效抑制剂。此外,机体内产生的多种褪黑素类似物也具有抗氧化作用^[31]。褪黑素代谢涉及多种酶,它们是类似于细胞色素c (cytochrome c, CYC)的血红素蛋白质。这些酶包括细胞色素P450 (cytochrome P450, CYP450)、吲哚胺2,3-双加氧酶(indoleamine 2,3-dioxygenase, IDO)、辣根过氧化物酶(horseradish peroxidase, HRP)、髓过氧化物酶(myeloperoxidase, MPO)和嗜酸性粒细胞过氧化物酶(eosinophil peroxidase, EPO)。每一种酶都能切割褪黑素形成 N^1 -乙酰基- N^2 -甲酰基-5-甲氧基犬尿胺(N^1 -acetyl- N^2 -formyl-5-methoxykynurenamine, AFMK)^[32]。AFMK可以被相应酶进行再次切割,形成 N^1 -乙酰基-5-甲氧基犬尿胺(N^1 -acetyl-5-methoxykynurenamine, AMK)。褪黑素及

其次级和三级代谢物(AFMK和AMK)都具有显著的抗氧化作用,它们在体内参与清除ROS或iNOS。这不仅提高了褪黑素的抗氧化效率,而且扩大了其清除谱,对于维持机体正常生理功能以及清除其他氧化物有重要作用。

2 细胞焦亡概述

细胞焦亡是一种通过激活炎症小体NLRP3,最终使胱天蛋白酶(caspase)-1或caspase-11激活的程序性细胞死亡,主要表现为细胞持续扩张直至细胞膜破裂,是导致强烈炎症反应激活^[33]的一种免疫反应。细胞焦亡与细胞凋亡不同,细胞凋亡不会产生炎症反应,而细胞焦亡会引起强烈的炎症反应,进而损伤细胞。研究发现,细胞焦亡可由caspase-1介导的经典炎症体途径和caspase-4/5/11介导的非经典炎症体途径触发^[34](图2)。

在经典细胞焦亡途径中,机体受到外界病原体、物理因素以及化学因素直接或者间接损伤后,大量细胞死亡,细胞内容物释放,最终使机体内ROS释放增多、组织损伤和代谢异常^[35-36]。上述变化又会刺激相邻细胞胞质内发生NLRP3炎症小体的组装。然后,炎症小体在pyrin结构域(pyrin domain, PYD)与凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a caspase recruitment domain, ASC)相互作用下招募前胱天蛋

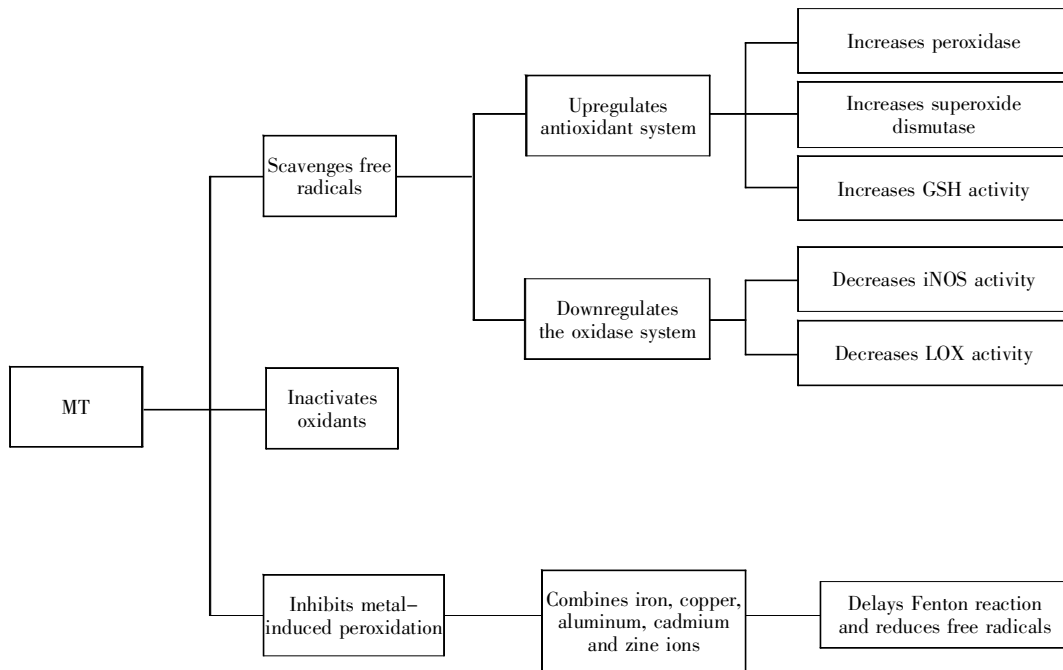


图 1 褪黑素的主要抗氧化作用
Fig.1 The main antioxidant actions of melatonin

白酶-1 (pro-caspase-1)^[37], pro-caspase-1 经切割形成 caspase-1, caspase-1 一边切割前 IL-1 β 与前 IL-18, 形成 IL-1 β 与 IL-18, 一边切割 GSDMD 蛋白, 使之释放 N 端结构域, N 端结构域识别并在细胞膜上穿孔, 形成许多直径为 10~15 nm 的蜂窝状孔^[38]。由于 GSDMD N 端结构域(GSDMD-NT)前体富含负电位, 因此其通过静电依赖的方式^[39]优先释放带正电的成熟 IL-1 β , 但不释放带负电的前 IL-1 β 。炎症因子 IL-1 β 与 IL-18 的释放会引起一系列级联反应, 最终导致机体出现剧烈的炎症反应。

在细胞焦亡的非经典途径中, caspase-4/5/11 (人的 caspase-4 和 caspase-5 以及小鼠的 caspase-11)通过其 caspase 招募域(caspase recruitment domain, CARD)直接与革兰氏阴性菌的脂多糖(lipopolysaccharide, LPS)结合, 促进 caspase-4/5/11 寡

聚和激活^[40-41]。活化的 caspase-4/5/11 切割泛连接蛋白 1 (pannexin 1, Panx1), 导致 ATP 释放以诱导嘌呤能受体 P2X7 活化, P2X7 直接介导 K⁺外流以激活 NLRP3 炎症小体^[42]。Swanson 等^[43]证明, 干扰素诱导的鸟苷酸结合蛋白(guanylate binding protein, GBP)是 LPS 诱导的非经典炎症小体激活和细胞焦亡的重要胞浆调节因子。

无论是经典途径还是非经典途径, 它们最终的结果都是促进 GSDMD 蛋白发生结构变化, 释放 N 端结构域, N 端结构域在细胞膜上形成孔隙, 使细胞内容物释放出来, 引起一系列炎症免疫反应。

3 褪黑素在多种疾病细胞焦亡中的作用

褪黑素具有强的抗氧化性, 在生物体内有多种作用, 分布于全身各个部位, 影响广泛。研究报道, 褪黑素可在体外阻止 LPS 和 ATP 诱导的小鼠

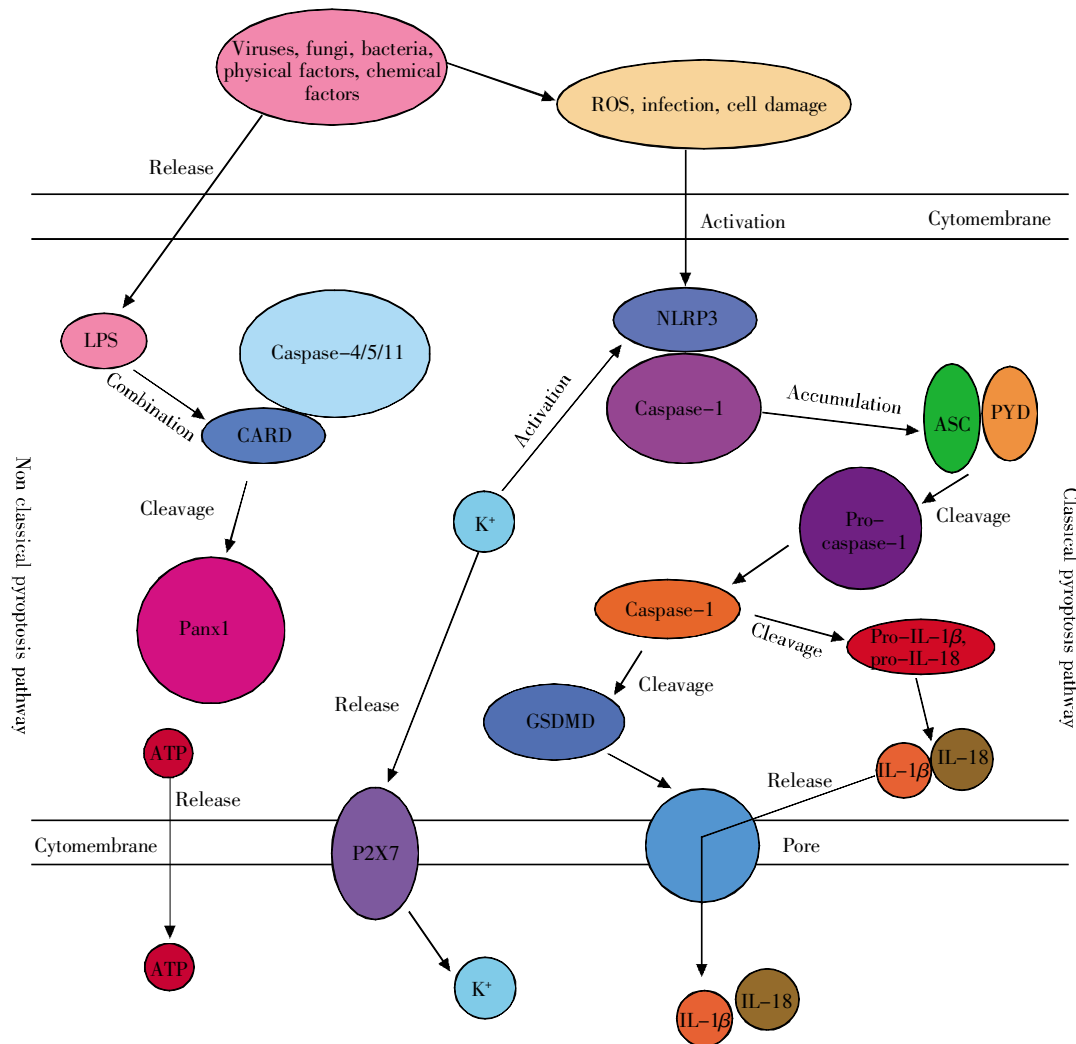


图2 细胞焦亡的经典途径与非经典途径
Fig.2 Classical and non-classical pathways of pyroptosis

小胶质细胞 NLRP3 炎症小体激活,这可通过抑制 NLRP3 表达、ASC 形成、caspase-1 裂解以及 IL-1 β 成熟和分泌来证明^[44]。在动物研究中给予外源性褪黑素^[45],研究人员发现,炎症反应降低,IL-1 β 和肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)减少,血清中抗炎细胞因子 IL-4 水平升高,同时高浓度前列腺素和白三烯的产生减少,炎症过程的其他介质(如趋化因子和黏附分子)^[46]也不断减少。上述研究在体外和体内证明了褪黑素具有强大的抗炎、抗焦亡作用。

3.1 褪黑素在心肌损伤中的作用

多项研究表明,褪黑素可以通过调节细胞焦亡、细胞凋亡、自噬以及改善线粒体功能来预防心肌损伤^[47-51]。心肌细胞损伤以后,机体会产生大量的炎性介质,其中 NLRP3、caspase-1 和 GSDMD 的表达增加,并且 ROS 的产生也增多,高水平的 ROS 可以触发心肌细胞发生细胞焦亡,进一步加重心肌细胞损伤。褪黑素预处理可以减少 ROS 的产生,从而导致 NLRP3、caspase-1 和 GSDMD 的表达减少,同时 IL-1 β 的释放也减少^[52],进而减轻心肌损伤。

心肌组织的血管损伤与堵塞会造成心肌细胞的缺血,加重心肌损伤。研究报道,褪黑素可能通过 Nrf2/ROS/NLRP3 信号通路有效地减轻吸烟诱导的血管损伤和动脉粥样硬化^[53],褪黑素的应用可促进 Nrf2 激活,降低 ROS 水平,抑制 NLRP3 炎症小体的激活,减轻细胞焦亡。此外,动脉粥样硬化经常造成血管内皮损伤,损伤的内皮细胞释放大量炎症物质,导致损伤加重,而褪黑素的应用可减轻内皮细胞焦亡和细胞间黏附分子-1 (intercellular adhesion molecule-1, ICAM-1)的表达,并增加内皮细胞中 NO 的生成^[54],最终减轻心肌损伤(图 3)。因此,褪黑素通过减少机体 ROS 的释放,可以减轻心肌细胞焦亡的发生,这对于心肌功能的保护有重要作用。

3.2 褪黑素在中枢神经系统疾病中的作用

细胞焦亡现象在中枢神经系统的多种细胞中已被报道^[55]。人类小胶质细胞、神经元和星形胶质细胞都表现出强烈的 NLRP3 炎症小体相关反应。在大鼠卒中模型中,蛋白质 GSDMD 在缺血后 24~48 h 迅速增加,然后攀升至峰值,表明脑缺血损伤期间机体发生了细胞焦亡^[56]。Wang 等^[57]研究发现,血浆外泌体治疗会抑制由缺血和炎症小体介导的细胞焦亡引起的炎症反应,而褪黑素可增

加血浆外泌体的治疗效果,其通过调节 TLR4/NF- κ B 信号通路降低脑梗塞并促进其恢复(图 3)。小鼠和大鼠脑损伤模型的研究表明,褪黑素可以通过抑制 NLR 家族的 NLRP3 炎症小体的激活,降低 NLRP3 炎症小体和促炎性细胞因子的表达,减轻脑损伤后的炎症和炎症依赖性细胞焦亡反应^[58]。在神经性疼痛方面,褪黑素也有重要作用,研究表明,褪黑素通过抑制 NF- κ B/NLRP3 依赖性信号来调节细胞焦亡,减轻神经性疼痛^[59](图 3)。综上可知,褪黑素在中枢神经系统疾病的细胞焦亡中有重要调控作用。

3.3 褪黑素在糖尿病中的作用

糖尿病是一组以高血糖为特征的代谢紊乱的慢性疾病。糖尿病和糖尿病相关并发症是人们常见的疾病之一。糖尿病与心脏、眼睛和肾脏等多器官的损害有关。相关研究报道,炎症反应相关的程序性细胞死亡形式——细胞焦亡,与糖尿病心肌病的发病机制有关,糖尿病动脉粥样硬化、糖尿病肾病、糖尿病相关的心肌缺血再灌注损伤以及糖尿病相关的脑损伤也和细胞焦亡有很大关系^[60]。褪黑素水平降低以及褪黑素和胰岛素之间的功能联系与 2 型糖尿病的发病机制有关,细胞系、啮齿动物模型和糖尿病患者的外源性褪黑素治疗在减轻糖尿病及其相关并发症方面显示出强大的作用^[61]。研究发现,褪黑素的应用可上调糖尿病脑损伤小鼠神经元中的 miR-214-3p 水平;随着 miR-214-3p 水平的升高,caspase-1 和下游细胞因子 IL-1 β 的水平降低,表明褪黑素通过调节 miR-214-3p/caspase-1 轴改善糖尿病引起的脑损伤后的神经元细胞焦亡^[62](图 3),进而减轻糖尿病引起的脑部损伤,具有神经保护作用。

3.4 褪黑素在肥胖中的作用

肥胖是由热量摄入和能量消耗过程之间的持续不平衡造成的。机体摄入的剩余能量通常会存储在脂肪组织中,期间白色脂肪组织起重要作用,然而,当脂肪组织的扩大不能够缓冲过量的营养物质时,大量相互关联的细胞和组织异常就会出现,且主要发生在内脏组织中^[63]。脂肪细胞增生和肥大会改变脂肪组织结构,由增生和肥大引起的脂肪细胞功能受损会导致脂肪分解加剧,释放脂肪酸(如棕榈酸和月桂酸),并触发神经酰胺和胆固醇晶体的形成^[64]。增生性脂肪细胞中的线粒体分解代谢增加会导致氧化应激反应和大量自由基的产生^[65]。自由基的大量释放会破坏正常细胞功能,

引起炎症反应,造成脂肪细胞死亡。光学显微镜的观察结果显示,脂肪细胞发生死亡的时候,大量巨噬细胞浸润肥胖脂肪组织的部位是脂肪细胞发生坏死的部位,它们形成了独特的结构,称之为冠状结构(crown-like structure, CLS)^[66]。在电子显微镜下,CLS是由巨噬细胞环绕死亡或垂死的脂肪细胞所形成的。基于这个发现,Giordano等^[67]认为肥胖小鼠和人的肥胖脂肪的细胞死亡可能是巨噬细胞招募和脂肪组织炎症的触发器,在肥胖小鼠(ob/ob和db/db)和肥胖人类中,NLRP3炎症小体在内脏和皮下脂肪中都被激活,并驱动局部IL-1 β 的产生。有研究表明,在缺乏NLRP3、ASC或caspase-1的小鼠中^[68],NLRP3依赖的caspase-1激活和炎性细胞因子的产生在代谢综合征中发挥重要作用,这些小鼠可抵抗高脂饮食诱导的肥胖和胰岛素抵抗的发展。肥大脂肪细胞的超微结构和生化改变显示,胆固醇结晶在细胞质中大量存在,这可能是一种“危险信号”,它能够激活NLRP3

炎症小体^[69],可引起脂肪细胞焦亡的发生。有研究表明,褪黑素可减轻小鼠脂肪组织中LPS诱导的炎症和NLRP3炎症小体的形成^[70],而且NLRP3炎症小体介导的细胞焦亡也被脂肪细胞中的褪黑素抑制。

3.5 褪黑素在退行性变性疾病中的作用

褪黑素减轻细胞焦亡反应在退行性变性疾病中也有重要作用。褪黑素具有的两亲性(亲水亲脂性)使得其能够轻易地跨越生理障碍^[71-72],如血脑屏障,作用于神经系统,从而减少神经系统炎症、ROS、活性氮(reactive nitrogen species, RNS)和脂质过氧化,发挥很高的神经保护能力^[73]。有报道显示,褪黑素可以有效抑制 β 淀粉样蛋白合成和tau丝形成^[74],这对于阿尔茨海默病的发生有一定的抑制作用。研究表明,各种神经病理学疾病的产生或恶化伴随着低度炎症和血脑屏障损伤,这些疾病可能与睡眠和褪黑素分泌的改变有关^[75]。几项动物模型的研究表明,褪黑素治疗可降低局灶

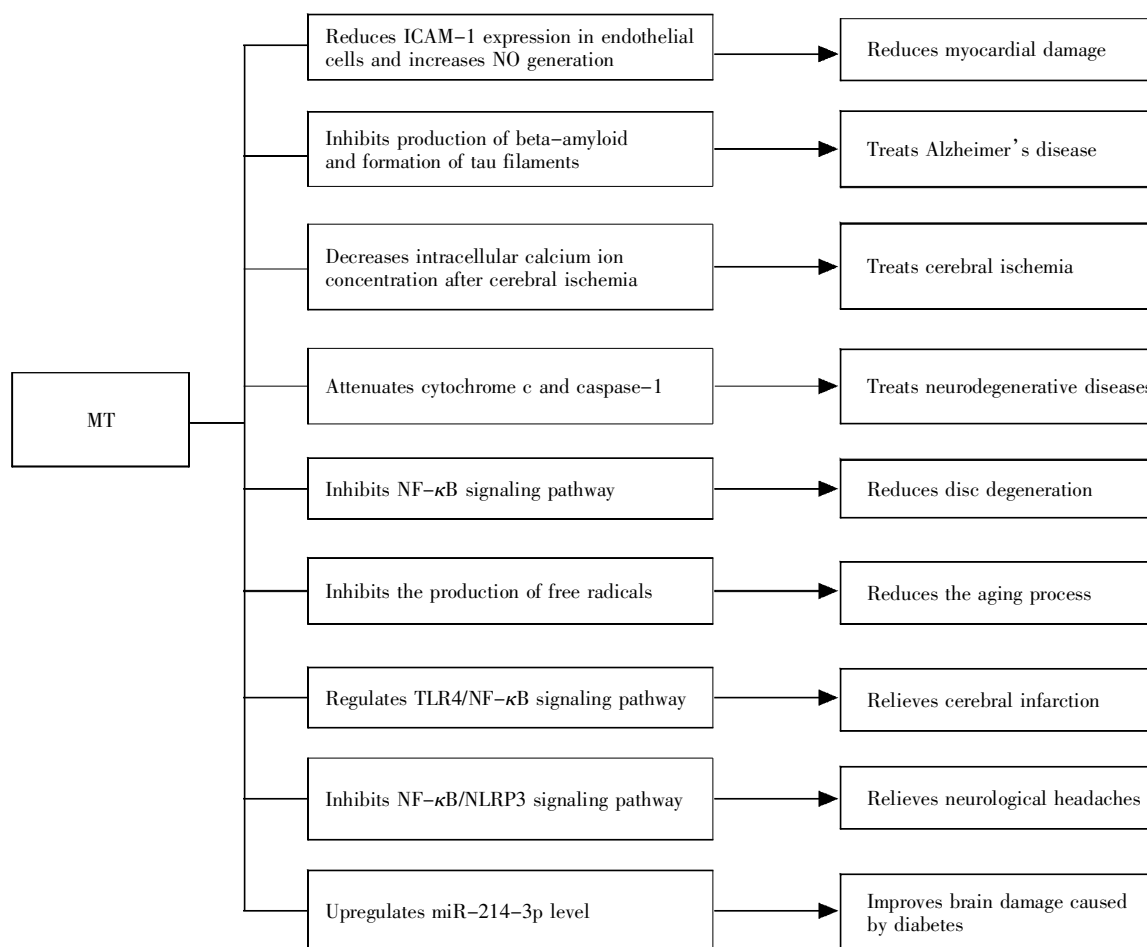


图3 褪黑素在多种疾病中的作用

Fig.3 The role of melatonin in a variety of diseases

性脑缺血时谷氨酸触发的细胞内钙增加引起的毒性^[76](钙离子浓度的升高会引起细胞焦亡的发生),提高存活率,并减少神经退行性变和缺血后神经元丢失^[77];褪黑素也可通过减少细胞色素 c 的释放和 caspase-1 的激活,减轻神经细胞焦亡反应,减少促炎细胞因子的激活,从而减轻神经退行性变,显示出神经保护作用^[78]。在脊柱退行性变疾病中,褪黑素也有很重要的作用。在椎间盘退变中,经过褪黑素治疗后髓核细胞 p-p65 表达降低,线粒体内超氧化物歧化酶表达增加,椎间盘中的炎症反应减轻,表明褪黑素在椎间盘退变中可以发挥抗炎作用^[79]。此外,褪黑素也可以抑制 NF- κ B 信号激活,减少线粒体 ROS 的产生,从而抑制 NLRP3 炎症小体激活和 IL-1 β 的表达^[80],减轻细胞焦亡反应,减轻椎间盘的退变(图 3)。

4 总结与展望

综上所述,多种疾病的发生、发展与细胞焦亡的发生有密切关系。外部原因与机体自身原因等因素均可导致疾病的发生,这些因素可以通过多种途径,诱导细胞内的炎性小体激活,进而激活多种信号通路(NF- κ B、ROS/NLRP3 等),造成细胞和组织损伤,最终使机体的正常功能受到影响。褪黑素作为一种机体释放的神经激素,通过其显著的抗感染、抗炎、抗氧化作用,不仅在机体正常生理功能的维持中发挥重要作用,也在多种疾病的治疗中起重要作用。褪黑素的多种功能对于细胞焦亡的发生和发展有显著的抑制作用,因此,合理运用褪黑素,可以有效地减轻机体功能受到的损伤。这对今后运用褪黑素治疗多种疾病,改善人们的生活质量,有很大的帮助。然而,褪黑素抑制细胞焦亡后对其他组织的影响仍然不明确,这有待今后进一步研究。

参考文献(References):

- [1] PANDI-PERUMAL S R, BAHAMMAM A S, BROWN G M, *et al.* Melatonin antioxidative defense: therapeutical implications for aging and neurodegenerative processes[J]. *Neurotoxicity Research*, 2013, 23(3): 267-300.
- [2] TALIB W H. Melatonin and cancer hallmarks[J]. *Molecules*, 2018, 23(3): 518.
- [3] LI Y, LI S, ZHOU Y, *et al.* Melatonin for the prevention and treatment of cancer[J]. *Oncotarget*, 2017, 8(24): 39896-39921.
- [4] SLOMINSKI A, TOBIN D J, ZMIJEWSKI M A, *et al.* Melatonin in the skin: synthesis, metabolism and functions[J]. *Trends in Endocrinology and Metabolism*, 2008, 19(1): 17-24.
- [5] TALAFI NOGHANI M, NAMDAR H. Migraine associated with gastrointestinal disorders: a pathophysiological explanation[J]. *Medical Hypotheses*, 2019, 125: 90-93.
- [6] TRICOIRE H, MØLLER M, CHEMINEAU P, *et al.* Origin of cerebrospinal fluid melatonin and possible function in the integration of photoperiod[J]. *Reproduction Supplement*, 2003, 61: 311-321.
- [7] DAI W Y, WANG X G, TENG H L, *et al.* Celastrol inhibits microglial pyroptosis and attenuates inflammatory reaction in acute spinal cord injury rats[J]. *International Immunopharmacology*, 2019, 66: 215-223.
- [8] YANG Y, SUN Y, YI W, *et al.* A review of melatonin as a suitable antioxidant against myocardial ischemia-reperfusion injury and clinical heart diseases[J]. *Journal of Pineal Research*, 2014, 57(4): 357-366.
- [9] GRIVAS T B, SAVVIDOU O D. Melatonin the "light of night" in human biology and adolescent idiopathic scoliosis[J]. *Scoliosis*, 2007, 2: 6.
- [10] ZHANG H M, ZHANG Y Q. Melatonin: a well-documented antioxidant with conditional pro-oxidant actions[J]. *Journal of Pineal Research*, 2014, 57(2): 131-146.
- [11] RODELLA L F, FAVERO G, ROSSINI C, *et al.* Aging and vascular dysfunction: beneficial melatonin effects[J]. *Age*, 2013, 35(1): 103-115.
- [12] REITER R J, ROSALES-CORRAL S, TAN D X, *et al.* Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas[J]. *Cellular and Molecular Life Sciences*, 2017, 74(21): 3863-3881.
- [13] REITER R J, TAN D X, FUENTES-BROTO L. Melatonin: a multitasking molecule[J]. *Progress in Brain Research*, 2010, 181: 127-151.
- [14] GOU Z X, SU X J, HU X, *et al.* Melatonin improves hypoxic-ischemic brain damage through the Akt/Nrf2/Gpx4 signaling pathway[J]. *Brain Research Bulletin*, 2020, 163: 40-48.
- [15] STEHLE J H, VON GALL C, KORF H W. Melatonin: a clock-output, a clock-input[J]. *Journal of Neuroendocrinology*, 2003, 15(4): 383-389.
- [16] HICKIE I B, ROGERS N L. Novel melatonin-based therapies: potential advances in the treatment of major depression[J]. *The Lancet*, 2011, 378(9791): 621-631.
- [17] XIE Y, HAN N, LI F, *et al.* Melatonin enhances osteoblastogenesis of senescent bone marrow stromal cells through NSD2-mediated chromatin remodelling[J]. *Clinical and Translational Medicine*, 2022, 12(2): e746.
- [18] FENG D Y, WANG B, WANG L, *et al.* Pre-ischemia melatonin treatment alleviated acute neuronal injury after ischemic stroke by inhibiting endoplasmic reticulum stress-dependent autophagy via PERK and IRE1 signalings[J]. *Journal of Pineal Research*, 2017, 62(3): e12395.
- [19] KANG K, LEE K, PARK S, *et al.* Enhanced production of melatonin by ectopic overexpression of human serotonin N-acetyltransferase plays a role in cold resistance in transgenic rice seedlings[J]. *Journal of Pineal Research*, 2010, 49(2): 176-182.
- [20] BAJWA V S, SHUKLA M R, SHERIF S M, *et al.* Role of melatonin in alleviating cold stress in *Arabidopsis thaliana*[J]. *Journal of Pineal Research*, 2014, 56(3): 238-245.
- [21] POSMYK M M, KURAN H, MARCINIAK K, *et al.* Presowing seed treatment with melatonin protects red cabbage seedlings against toxic copper ion concentrations[J]. *Journal of Pineal Research*, 2008, 45(1): 24-31.
- [22] HARDELAND R, PANDI-PERUMAL S R, CARDINALI D P. Melatonin[J]. *The International Journal of Biochemistry & Cell Biology*, 2006, 38(3): 313-316.
- [23] RODRIGUEZ C, MAYO J C, SAINZ R M, *et al.* Regulation of antioxidant enzymes: a significant role for melatonin[J]. *Journal of Pineal Research*, 2004, 36(1): 1-9.

- [24] TOMÁS-ZAPICO C, COTO-MONTES A. A proposed mechanism to explain the stimulatory effect of melatonin on antioxidative enzymes[J]. *Journal of Pineal Research*, 2005, 39(2): 99–104.
- [25] BARBERINO R S, MENEZES V G, RIBEIRO A E A S, *et al.* Melatonin protects against cisplatin-induced ovarian damage in mice via the MT1 receptor and antioxidant activity[J]. *Biology of Reproduction*, 2017, 96(6): 1244–1255.
- [26] DENG S L, SUN T C, YU K, *et al.* Melatonin reduces oxidative damage and upregulates heat shock protein 90 expression in cryopreserved human semen[J]. *Free Radical Biology & Medicine*, 2017, 113: 347–354.
- [27] PRASAD K N, WU M X, BONDY S C. Telomere shortening during aging: attenuation by antioxidants and anti-inflammatory agents[J]. *Mechanisms of Ageing and Development*, 2017, 164: 61–66.
- [28] LIU Q, SUN Y, ZHU Y, *et al.* Melatonin relieves liver fibrosis induced by Txnr3 knockdown and nickel exposure via IRE1/NF- κ B/NLRP3 and PERK/TGF- β 1 axis activation[J]. *Life Sciences*, 2022, 301: 120622.
- [29] MIAO Z Y, MIAO Z R, TENG X H, *et al.* Melatonin alleviates lead-induced intestinal epithelial cell pyroptosis in the common carps (*Cyprinus carpio*) via miR-17-5p/TXNIP axis[J]. *Fish & Shellfish Immunology*, 2022, 131: 127–136.
- [30] TAN D X, MANCHESTER L C, ESTEBAN-ZUBERO E, *et al.* Melatonin as a potent and inducible endogenous antioxidant: synthesis and metabolism[J]. *Molecules*, 2015, 20(10): 18886–18906.
- [31] LIMSON J, NYOKONG T, DAYA S. The interaction of melatonin and its precursors with aluminium, cadmium, copper, iron, lead, and zinc: an adsorptive voltammetric study[J]. *Journal of Pineal Research*, 1998, 24(1): 15–21.
- [32] GALANO A, MEDINA M E, TAN D X, *et al.* Melatonin and its metabolites as copper chelating agents and their role in inhibiting oxidative stress: a physicochemical analysis[J]. *Journal of Pineal Research*, 2015, 58(1): 107–116.
- [33] CHITIMUS D M, POPESCU M R, VOICULESCU S E, *et al.* Melatonin's impact on antioxidative and anti-inflammatory reprogramming in homeostasis and disease[J]. *Biomolecules*, 2020, 10(9): 1211.
- [34] CHEN F, JIANG G W, LIU H, *et al.* Melatonin alleviates intervertebral disc degeneration by disrupting the IL-1 β /NF- κ B-NLRP3 inflammasome positive feedback loop[J]. *Bone Research*, 2020, 8: 10.
- [35] YUAN Y Y, XIE K X, WANG S L, *et al.* Inflammatory caspase-related pyroptosis: mechanism, regulation and therapeutic potential for inflammatory bowel disease[J]. *Gastroenterology Report*, 2018, 6(3): 167–176.
- [36] GAO J N, CHEN X T, WEI P C, *et al.* Regulation of pyroptosis in cardiovascular pathologies: role of noncoding RNAs[J]. *Molecular Therapy Nucleic Acids*, 2021, 25: 220–236.
- [37] BERGSBAKEN T, FINK S L, COOKSON B T. Pyroptosis: host cell death and inflammation[J]. *Nature Reviews Microbiology*, 2009, 7(2): 99–109.
- [38] HAQUE M E, AKTHER M, JAKARIA M, *et al.* Targeting the microglial NLRP3 inflammasome and its role in Parkinson's disease[J]. *Movement Disorders*, 2020, 35(1): 20–33.
- [39] FARKHONDEH T, SAMARGHANDIAN S, AZIMIN-NEZHAD M, *et al.* Effect of chrysin on nociception in formalin test and serum levels of noradrenalin and corticosterone in rats[J]. *International Journal of Clinical and Experimental Medicine*, 2015, 8(2): 2465–2470.
- [40] WU D B, CHEN Y F, SUN Y X, *et al.* Target of MCC950 in inhibition of NLRP3 inflammasome activation: a literature review[J]. *Inflammation*, 2020, 43(1): 17–23.
- [41] EVAVOLD C L, HAFNER-BRATKOVIČ I, DEVANT P, *et al.* Control of gasdermin D oligomerization and pyroptosis by the Regulator-Rag-mTORC1 pathway[J]. *Cell*, 2021, 184(17): 4495–4511.e19.
- [42] LEE S H, KWAK C H, LEE S K, *et al.* Anti-inflammatory effect of ascochlorin in LPS-stimulated RAW 264.7 macrophage cells is accompanied with the down-regulation of iNOS, COX-2 and proinflammatory cytokines through NF- κ B, ERK1/2, and p38 signaling pathway[J]. *Journal of Cellular Biochemistry*, 2016, 117(4): 978–987.
- [43] SWANSON K V, DENG M, TING J P Y. The NLRP3 inflammasome: molecular activation and regulation to therapeutics[J]. *Nature Reviews Immunology*, 2019, 19(8): 477–489.
- [44] KELLEY N, JELTEMA D, DUAN Y H, *et al.* The NLRP3 inflammasome: an overview of mechanisms of activation and regulation[J]. *International Journal of Molecular Sciences*, 2019, 20(13): 3328.
- [45] BOLÍVAR B E, VOGEL T P, BOUCHIER-HAYES L. Inflammatory caspase regulation: maintaining balance between inflammation and cell death in health and disease[J]. *The FEBS Journal*, 2019, 286(14): 2628–2644.
- [46] ARIÖZ B I, TASTAN B, TARAKCIOĞLU E, *et al.* Melatonin attenuates LPS-induced acute depressive-like behaviors and microglial NLRP3 inflammasome activation through the SIRT1/Nrf2 pathway[J]. *Frontiers in Immunology*, 2019, 10: 1511.
- [47] PAN P, ZHANG H M, SU L X, *et al.* Melatonin balances the autophagy and apoptosis by regulating UCP2 in the LPS-induced cardiomyopathy[J]. *Molecules*, 2018, 23(3): 675.
- [48] ZHAI M G, LI B Y, DUAN W X, *et al.* Melatonin ameliorates myocardial ischemia reperfusion injury through SIRT3-dependent regulation of oxidative stress and apoptosis[J]. *Journal of Pineal Research*, 2017, 63(2): e12419.
- [49] ZHANG Y, WANG Y, XU J N, *et al.* Melatonin attenuates myocardial ischemia-reperfusion injury via improving mitochondrial fusion/mitophagy and activating the AMPK-OPA1 signaling pathways[J]. *Journal of Pineal Research*, 2019, 66(2): e12542.
- [50] DI S Y, WANG Z, HU W, *et al.* The protective effects of melatonin against LPS-induced septic myocardial injury: a potential role of AMPK-mediated autophagy[J]. *Frontiers in Endocrinology*, 2020, 11: 162.
- [51] ZHONG J K, TAN Y, LU J H, *et al.* Therapeutic contribution of melatonin to the treatment of septic cardiomyopathy: a novel mechanism linking Ripk3-modified mitochondrial performance and endoplasmic reticulum function[J]. *Redox Biology*, 2019, 26: 101287.
- [52] SU Z D Z, WEI X B, FU Y B, *et al.* Melatonin alleviates lipopolysaccharide-induced myocardial injury by inhibiting inflammation and pyroptosis in cardiomyocytes[J]. *Annals of Translational Medicine*, 2021, 9(5): 413.
- [53] ZHAO Z W, WANG X B, ZHANG R, *et al.* Melatonin attenuates smoking-induced atherosclerosis by activating the Nrf2 pathway via NLRP3 inflammasomes in endothelial cells[J]. *Aging*, 2021, 13(8): 11363–11380.
- [54] YI S, YANG Y. Melatonin attenuates low shear stress-induced pyroptosis and endothelial cell dysfunction via the ROR α /miR-223/STAT-3 signalling pathway[J]. *Experimental and Therapeutic Medicine*, 2021, 22(6): 1392.
- [55] WALSH J G, MURUVE D A, POWER C. Inflammasomes in the CNS[J]. *Nature Reviews Neuroscience*, 2014, 15(2): 84–97.
- [56] ZHANG D P, QIAN J H, ZHANG P, *et al.* Gasdermin D serves as a key executioner of pyroptosis in experimental cerebral ischemia and reperfusion model both *in vivo* and *in vitro*[J]. *Journal of Neuroscience Research*, 2019, 97(6): 645–660.
- [57] WANG K K, RU J N, ZHANG H L, *et al.* Melatonin enhances the therapeutic effect of plasma exosomes against cerebral ischemia-induced pyroptosis through the TLR4/NF- κ B pathway[J]. *Frontiers in Neuroscience*, 2020, 14: 848.

- [58] CAO S L, SHRESTHA S, LI J R, *et al.* Melatonin-mediated mitophagy protects against early brain injury after subarachnoid hemorrhage through inhibition of NLRP3 inflammasome activation[J]. *Scientific Reports*, 2017, 7: 2417.
- [59] WANG Y H, GAO X, TANG Y R, *et al.* The role of NF- κ B/NLRP3 inflammasome signaling pathway in attenuating pyroptosis by melatonin upon spinal nerve ligation models[J]. *Neurochemical Research*, 2022, 47(2): 335-346.
- [60] WANG Z V, HILL J A. Diabetic cardiomyopathy: catabolism driving metabolism[J]. *Circulation*, 2015, 131(9): 771-773.
- [61] CHE H, LI H, LI Y, *et al.* Melatonin exerts neuroprotective effects by inhibiting neuronal pyroptosis and autophagy in STZ-induced diabetic mice[J]. *The FASEB Journal*, 2020, 34(10): 14042-14054.
- [62] PATEL R, PARMAR N, PRAMANIK PALIT S, *et al.* Diabetes mellitus and melatonin: where are we? [J]. *Biochimie*, 2022, 202: 2-14.
- [63] JOHNSON A M F, OLEFSKY J M. The origins and drivers of insulin resistance[J]. *Cell*, 2013, 152(4): 673-684.
- [64] LÓPEZ-REYES A, MARTINEZ-ARMENTA C, ESPINOSA-VELÁZQUEZ R, *et al.* NLRP3 inflammasome: the stormy link between obesity and COVID-19[J]. *Frontiers in Immunology*, 2020, 11: 570251.
- [65] CODOÑER-FRANCH P, VALLS-BELLÉS V, ARILLA-CODOÑER A, *et al.* Oxidant mechanisms in childhood obesity: the link between inflammation and oxidative stress[J]. *Translational Research*, 2011, 158(6): 369-384.
- [66] CINTI S, MITCHELL G, BARBATELLI G, *et al.* Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans[J]. *Journal of Lipid Research*, 2005, 46(11): 2347-2355.
- [67] GIORDANO A, MURANO I, MONDINI E, *et al.* Obese adipocytes show ultrastructural features of stressed cells and die of pyroptosis[J]. *Journal of Lipid Research*, 2013, 54(9): 2423-2436.
- [68] STIENSTRA R, VAN DIEPEN J A, TACK C J, *et al.* Inflammasome is a central player in the induction of obesity and insulin resistance[J]. *Proceedings of the National Academy of Sciences of USA*, 2011, 108(37): 15324-15329.
- [69] DUEWELL P, KONO H, RAYNER K J, *et al.* NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals[J]. *Nature*, 2010, 464(7293): 1357-1361.
- [70] LIU Z J, GAN L, XU Y T, *et al.* Melatonin alleviates inflammation-induced pyroptosis through inhibiting NF- κ B/GSDMD signal in mice adipose tissue[J]. *Journal of Pineal Research*, 2017, 63(1): e12414.
- [71] TAN D X, MANCHESTER L C, REITER R J, *et al.* Significance of melatonin in antioxidative defense system: reactions and products[J]. *Biological Signals and Receptors*, 2000, 9(3/4): 137-159.
- [72] TAN S H, KARRI V, TAY N W R, *et al.* Emerging pathways to neurodegeneration: dissecting the critical molecular mechanisms in Alzheimer's disease, Parkinson's disease[J]. *Biomedicine & Pharmacotherapy*, 2019, 111: 765-777.
- [73] REITER R J, TAN D X, ROSALES-CORRAL S, *et al.* The universal nature, unequal distribution and antioxidant functions of melatonin and its derivatives[J]. *Mini Reviews in Medicinal Chemistry*, 2013, 13(3): 373-384.
- [74] HEVIA D, GONZÁLEZ-MENÉNDEZ P, QUIROS-GONZÁLEZ I, *et al.* Melatonin uptake through glucose transporters: a new target for melatonin inhibition of cancer[J]. *Journal of Pineal Research*, 2015, 58(2): 234-250.
- [75] TAN D X, REITER R J, MANCHESTER L C, *et al.* Chemical and physical properties and potential mechanisms: melatonin as a broad spectrum antioxidant and free radical scavenger[J]. *Current Topics in Medicinal Chemistry*, 2002, 2(2): 181-197.
- [76] WONGPRAYOON P, GOVITRAPONG P. Melatonin attenuates methamphetamine-induced neurotoxicity[J]. *Current Pharmaceutical Design*, 2016, 22(8): 1022-1032.
- [77] HURTADO-ALVARADO G, DOMÍNGUEZ-SALAZAR E, PAVON L, *et al.* Blood-brain barrier disruption induced by chronic sleep loss: low-grade inflammation may be the link[J]. *Journal of Immunology Research*, 2016, 2016: 4576012.
- [78] KOH P O. Melatonin regulates the calcium-buffering proteins, parvalbumin and hippocalcin, in ischemic brain injury[J]. *Journal of Pineal Research*, 2012, 53(4): 358-365.
- [79] HE R J, CUI M, LIN H, *et al.* Melatonin resists oxidative stress-induced apoptosis in nucleus pulposus cells[J]. *Life Science*, 2018, 199: 122-130.
- [80] CUZZOCREA S, COSTANTINO G, GITTO E, *et al.* Protective effects of melatonin in ischemic brain injury[J]. *Journal of Pineal Research*, 2000, 29(4): 217-227.

(上接第 391 页)

- [78] BUITING K. Prader-Willi syndrome and Angelman syndrome[J]. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, 2010, 154C(3): 365-376.
- [79] SCHWARTZ L, CAIXÀS A, DIMITROPOULOS A, *et al.* Behavioral features in Prader-Willi syndrome (PWS): consensus paper from the International PWS Clinical Trial Consortium[J]. *Journal of Neurodevelopmental Disorders*, 2021, 13(1): 25.
- [80] UEMURA Y, OKA A, KUROSAKA H, *et al.* Comprehensive orthodontic treatment of a patient with Prader-Willi syndrome[J]. *The Cleft Palate-Craniofacial Journal*, 2021, 58(11): 1459-1467.
- [81] BIRD L M. Angelman syndrome: review of clinical and molecular aspects[J]. *The Application of Clinical Genetics*, 2014, 7: 93-104.
- [82] SPRITZ R A, BAILIN T, NICHOLLS R D, *et al.* Hypopigmentation in the Prader-Willi syndrome correlates with *P* gene deletion but not with haplotype of the hemizygous *P* allele[J]. *American Journal of Medical Genetics*, 1997, 71(1): 57-62.
- [83] NICHOLLS R D, SAITOH S, HORSTHEMKE B. Imprinting in Prader-Willi and Angelman syndromes[J]. *Trends in Genetics*, 1998, 14(5): 194-200.
- [84] SAITOH S, OISO N, WADA T, *et al.* Oculocutaneous albinism type 2 with a *P* gene missense mutation in a patient with Angelman syndrome[J]. *Journal of Medical Genetics*, 2000, 37(5): 392-394.
- [85] 周秋君, 龚潘, 焦荃如, 等. 1 例 Angelman 综合征合并眼皮肤白化病 2 型患者的临床和遗传学分析及文献回顾[J]. *北京大学学报(医学版)* (ZHOU QiuJun, GONG Pan, JIAO Xianru, *et al.* Clinical and molecular genetic analysis of Angelman syndrome with oculocutaneous albinism type 2: a case report and literature review[J]. *Journal of Peking University (Health Sciences)*), 2023, 55(1): 181-185.
- [86] CHAHAL H S, LIN Y, RANSOHOFF K J, *et al.* Genome-wide association study identifies novel susceptibility loci for cutaneous squamous cell carcinoma[J]. *Nature Communications*, 2016, 7: 12048.
- [87] HAWKES J E, CASSIDY P B, MANGA P, *et al.* Report of a novel *OCA2* gene mutation and an investigation of *OCA2* variants on melanoma risk in a familial melanoma pedigree[J]. *Journal of Dermatological Science*, 2013, 69(1): 30-37.