•综述•

脑卒中−心脏综合征: 昼夜节律调节的新视角

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摘要: 脑卒中引发的心脏并发症被称为脑卒中−心脏综合征 (stroke-heart syndrome, SHS)。最新研究表明, 脑卒中可通过直接损伤或间接调控导致视交叉上核 (suprachiasmatic nucleus, SCN) 功能障碍, 进而引发内源性昼夜节律系统紊乱。这种节律紊乱不仅表现为睡眠−觉醒周期失调, 更通过免疫炎症反应的节律性失调、肠道微生物菌群的稳态破坏和神经内分泌激素失调三大机制, 成为继发性心脑血管事件的关键病理基础。本文创新性地提出了“脑卒中−昼夜节律紊乱−心脏综合征”的级联反应观点, 系统阐述了包括免疫炎症通路的节律调控、肠道菌群−生物钟协同调控、褪黑素节律重塑的昼夜节律靶向治疗SHS策略和中药干预潜力, 为临床预防和治疗SHS提供了新的视角和思路。

关键词: 昼夜节律; 脑卒中−心脏综合征; 免疫炎症反应; 肠道菌群; 褪黑素

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Stroke-heart syndrome: a new perspective from circadian rhythm regulation

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Abstract: Cardiovascular complications triggered by stroke are known as stroke-heart syndrome (SHS). Emerging evidence indicates that stroke triggers dysfunction of the suprachiasmatic nucleus (SCN) through direct neural injury or indirect regulatory pathways, leading to disruption of the endogenous circadian rhythm system. This circadian disruption manifests as sleep-wake cycle dysregulation. It serves as a critical pathological driver of secondary cardio-cerebrovascular events *via* three interconnected mechanisms: rhythmic dysregulation of immune-inflammatory responses, destabilization of gut microbial homeostasis, and neuroendocrine hormonal imbalance. This paper innovatively proposed a cascade response of "stroke-circadian disturbance-heart syndrome", systematically elaborating on the circadian rhythm-targeted therapy strategy for SHS, including rhythm regulation of immune inflammatory pathways, synergistic regulation of gut microbiota circadian clock, and melatonin rhythm remodeling, as well as the potential of traditional Chinese medicine intervention, providing new perspectives and ideas for clinical prevention and treatment of SHS.

Key words: circadian rhythms; stroke-heart syndrome; immune inflammatory response; gut microbiota; melatonin

脑卒中−心脏综合征 (stroke-heart syndrome, SHS) 是在脑卒中基础上继发的心血管病并发症, 临床表现主要包括心律失常、心肌缺血、心功能不全等。该综合征在全球范围内呈现出高发病率与高死亡率特征[1]。临床研究表明, SHS的发生风险与脑卒中后脑损伤程度和神经功能缺损呈显著正相关[2,3], 且SHS可能通过加剧原有的脑损伤或引发新的脑损伤, 导致神经功能进一步恶化[1]。目前, 临床上主要采用重组组织型纤

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溶酶原激活剂进行静脉溶栓和机械取栓治疗脑卒中及预防SHS等相关二级心血管并发症[4]。然而, 受限于溶栓治疗的严格时间窗 (通常 ≤ 4.5 h) 及适应症的筛选, 仅有不足10%的患者符合治疗条件, 因此总体患者预后效果不佳, SHS相关并发症的发生率和死亡率仍居高不下[5]。这一现状凸显了开发新型治疗SHS策略的迫切需求。

昼夜节律作为生物体适应地球自转周期的内源性计时系统, 通过核心生物钟基因及其调控网络产生的昼夜节律振荡维持机体稳态[6]。研究表明, 昼夜节律紊乱可通过破坏生物钟基因表达节律, 降低内源性基因节律同步性。值得注意的是, 近期研究揭示了昼夜节律在SHS治疗中的多重作用机制: 免疫炎症通路的昼夜节律调控、肠道菌群代谢物–生物钟协同调控和外源性褪黑素节律重塑, 可促进脑卒中后神经功能恢复并减轻心脏并发症。这些发现提示, 基于昼夜节律调控的干预策略可能为SHS的防治提供新的治疗靶点。

1 SHS的临床表现和作用机制

SHS是脑卒中后心脏并发症的统称[1]。最新临床证据表明, 在无基础心脏病或心电图异常的缺血性卒中 (ischemic stroke, IS) 患者中, 约4.1%的患者最终因心脏原因死亡, 19%的患者在卒中后72 h内至少发生一次严重心脏不良事件[7]。值得注意的是, 10%～24%的患者出现左心室射血分数 (left ventricular ejection fraction, LVEF) 降低的左心室功能障碍[8,9], 13%～15%的患者进展至中重度左心室功能障碍 (LVEF < 40%)[10]。针对急性缺血性卒中 (acute ischemic stroke, AIS) 人群的研究发现: 25.3%患者存在卒中后急性心肌损伤[11]; 约33%患者出现心电图异常, 主要表现为QTc间期延长 (20%～65%)、T波形态异常 (16%～40%) 及ST段改变 (15%～25%)[12,13]。SHS的发生可能涉及多个复杂生理机制, 包括中央自主神经网络 (central autonomic network, CAN) 的功能紊乱、下丘脑–垂体–肾上腺 (hypothalamic-pituitary-adrenal, HPA) 轴的过度激活、炎症和免疫系统的失衡, 以及肠道微生物组的失调。简单来说, AIS引起CAN损伤, 进而触发交感神经系统和HPA轴的过度激活, 导致皮质醇和儿茶酚胺水平急剧上升[14]。这种神经内分泌的变化可能导致神经元细胞死亡、炎症细胞的激活以及炎症介质的释放, 从而引发全身性或心脏局部的炎症反应[1]以及急性心力衰竭[15,16]。此外, 在AIS后, 外周免疫系统被激活, 促使巨噬细胞向受损区域迁移[17]。巨噬细胞释放的细胞因子和趋化因子促进炎症细胞的移动。卒中后的应激反应也可导致皮质醇水平升高, 破坏肠道屏障的通透性, 扰乱肠道菌群, 使得细菌和内毒素更容易进入血液循环, 从而引发或加剧炎症反应[18]。这些机制之间的相互作用共同导致心脏损伤。

2 昼夜节律的生理学意义、器官分布和分子机制

昼夜节律作为生物体内源性的时间调控系统, 由生物钟基因网络精确驱动, 对睡眠–觉醒周期[19]、进食行为[20]、激素分泌[21,22]、体温波动[21,22]及代谢稳态等生理功能进行周期性调节。哺乳动物的生物钟系统呈现层次化调控特征分为核心生物钟和外周生物钟[23]。核心生物钟位于视交叉上核 (suprachiasmatic nucleus, SCN), 作为中枢昼夜节律起搏器, 通过神经体液信号同步和协调遍布全身的各个外周生物钟[23]。外周生物钟广泛存在于心脏、肝脏等实质器官以及肌肉等组织细胞中[24], 形成器官特异性的局部节律调控单元, 这种“中心–外周”双层级架构既保障了多器官节律的全局同步性, 又赋予外周生物钟根据自身情况对核心昼夜节律信号进行独立或微调的反应。

在分子层面, 生物钟由多层级联的转录–翻译反馈环 (transcription-translation feedback loop, TTFL) 组成, 其相互作用导致时钟控制基因的节律表达, 最终导致蛋白质组和细胞功能的振荡。如图1所示: 在哺乳动物中, 生物钟的正反馈回路由时钟生物节律调节因子 (clock circadian regulator, CLOCK) 及其旁系同源物神经元PAS结构域蛋白2 (neuronal PAS domain protein 2, NPAS2) 和其异二聚体伴侣脑和肌肉ARNT样蛋白1 [(basic helix-loop-helix ARNT like 1, BMAL1), 又称芳基烃受体核转运体样蛋白 (aryl hydrocarbon receptor nuclear translocator-like, ARNTL)] 组成。CLOCK和BMAL1蛋白含有bHlh-PAS结构域, 这些结构域相互结合形成异二聚体复合物进入细胞核, 并与含有E-box的特定DNA序列结合[25]。CLOCK-BMAL1蛋白复合物构成环的正肢, 并与负调控因子时钟基因周期蛋白 (period, Per) 和隐花色素 (cryptochrome, Cry) 中的E-box元件结合, 激活其转录。*Clock*和*Bmal1*基因在上午激活, 导致*Per*和*Cry*基因在下午转录, 以及PER和CRY蛋白在下午晚些时候或晚上的积累[26]。在细胞质中, *Per*和*cry*的mRNA翻译成蛋白质, 并相互作用形成异二聚体。PER-CRY异二聚体被酪蛋白激酶Iε (casein kinase Iε, CKIε) 磷酸化, 磷酸化产物在夜间易位到细胞核中并与CLOCK-BMAL1复合物相互作用, 从而抑制自己的基因转录。随着抑制的进行, *Per*和*Cry*转录下降, PER和CRY蛋白水平降低。当PER和CRY蛋白达到临界浓度时, 它们就会在负反馈回路中减弱CLOCK/BMAL1介导的自身基因抑制, 从而*Clock*和*Bmal1*的转录就可以开始新的转录周期 (第

一负反馈环)。除了 *Per* 和 *Cry* 靶基因外, CLOCK-BMAL1 激活的第 2 个转录涉及核受体亚家族 1 组 D 成员 1 (nuclear receptor subfamily 1, group D, member 1, *Nr1d1*) 和核受体亚家族 1 组 D 成员 2 (nuclear receptor subfamily1, group D, member 2, *Nr1d2*) 的转录[27]。NR1D1 和 NR1D2 蛋白与视黄酸相关孤儿受体 (retinoic acid-related orphan receptor, ROR) 竞争, 以结合 *Bmal1* 基因启动子上的 RORE 元件, 从而调控 *Bmal1* 转录的正 (ROR) 和负 (*Nr1d1* 和 *Nr1d2*) 反馈调节 (第二负反馈环)[27-29]。CLOCK-BMAL1 异二聚体正向调节白蛋白 D 位点结合蛋白 (D-site albumin promoter binding protein, DBP) 和 E4 启动子结合蛋白 4 (E4 promoter-binding protein 4, E4BP4) 的合成, 而 DBP 和 E4BP4 蛋白能改变 *Nr1d1*、*Nr1d2*、*Cry* 和 *Per* 的表达, 从而负调节细胞中 CLOCK-BMAL1 的浓度 (第三负反馈环)。这三个互锁的转录反馈环可以共同产生具有不同表达阶段的转录循环, 具体取决于特定靶基因的启动子和增强子。此外, CLOCK/BMAL1、ROR/REV-ERB 和 DBP/NFIL3 调控许多其他时钟输出基因的转录[30], 如 CLOCK (NPAS2)/BMAL1 复合物参与控制氧化还原基因的表达, NAD(P)H 脱氢酶 [NAD(P)H dehydrogenase]、醛脱氢酶 2 (aldehyde dehydrogenase 2, Aldh2)、醌氧化还原酶 1 (quinone oxidoreductase 1, Nqo1) 和其他参与过氧化物还原蛋白循环的基因。沉默信息调节因子 1 (silent information regulator 1, Sirt1) 与过氧化物还原蛋白循环产生的 NAD^+ 分子结合, 从而调节 CLOCK (NPAS2)/BMAL1 复合物的活性。昼夜节律通过由生物钟核心基因及其调控网络构成的精密系统驱动, 产生周期性振荡信号, 进而动态调节机体代谢稳态的平衡状态。

3 昼夜节律紊乱与心脑血管疾病

昼夜节律紊乱是指生物钟系统与外环境同步性失调的病理状态, 涵盖相位偏移、振幅衰减及时相分离等多种形式[31]。在轮班工作等昼夜节律紊乱高发人群中, 中枢与外周生物钟的同步性破坏, 可导致机体代谢、心血管功能等生理活动紊乱。流行病学研究证实, 此类节律紊乱显著升高心肌梗死、冠心病、高血压、脑卒中等疾病的发病风险, 且风险暴露程度与轮班工作时长呈正相关[32,33]。

3.1 卒中导致昼夜节律紊乱

昼夜节律系统与脑卒中病理进程之间存在双向互作关系。基础研究表明, 昼夜节律紊乱不仅是诱发 IS 的重要风险因素[34], 另一方面, 卒中事件本身可引发继发性昼夜节律紊乱, 二者形成持续加剧的病理循环。临床研究证实, 约 63% 的卒中患者出现褪黑素分泌节律相位延迟伴振幅降低[35], 同时伴心率变异性昼夜波

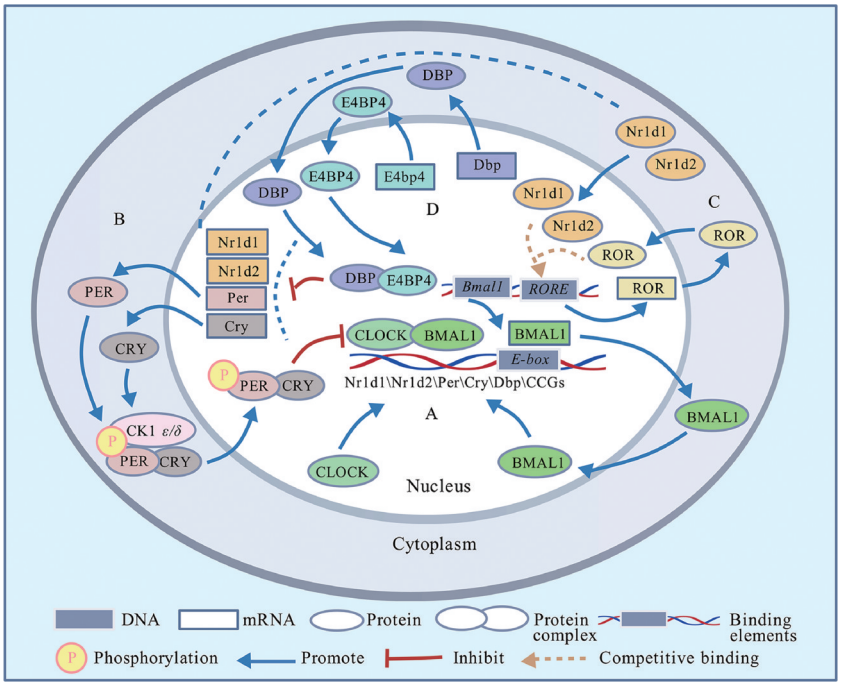


Figure 1 Molecular mechanism of circadian rhythm. A: Positive feedback loop; B: First negative feedback loop; C: Second negative feedback loop; D: Third negative feedback loop. *Clock*/CLOCK: Clock circadian regulator; *Bmal1*/BMAL1: Basic helix-loop-helix ARNT like 1; *Per*/PER: Period; Cry: Cryptochrome; *Nr1d1*/NR1D1: Nuclear receptor subfamily 1, group D, member 1; *Nr1d2*/NR1D2: Nuclear receptor subfamily 1, group D, member 2; ROR: Retinoic acid-related orphan receptor; *Dbp*/DBP: D-site albumin promoter binding protein; *E4bp4e4*/E4BP4E4 promoter-binding protein 4; *CCGs:* Clock-controlled genes

动特征消失及非杓型血压节律异常[36]。在分子调控层面, IS 可导致 *Per1*、*Cry2* 等核心时钟基因表达出现 4～6 h 的相位偏移, 同时抑制松果体褪黑素分泌节律, 进而下调 *Bmal1* 基因转录表达水平[37]。*Bmal1* 表达降低会通过增强氧化应激反应促进神经元凋亡, 进一步扩大缺血半暗带范围[38]。因此, 针对昼夜节律系统的干预可能成为卒中病理循环的关键策略。

3.2 昼夜节律紊乱对心脏疾病的影响

临床研究表明, 短期昼夜节律失调可引发心房电活动异常及心律失常, 而长期紊乱则导致心室重构与收缩功能障碍[39,40]。对 412 例 ST 段抬高型心肌梗死患者的影像学分析发现, 存在昼夜节律紊乱的轮班工作者经再灌注治疗后其梗死面积和微血管阻塞的发生率增加, 且 LVEF 显著降低[41]。这些临床发现提示昼夜节律紊乱可能加重心肌缺血损伤效应。

目前, 研究者主要通过两类模型探究昼夜节律紊乱对心脏生理和病理学的影响: ① 环境干预模型: 模拟轮班制的研究显示, 以周为周期的慢性节律紊乱使心肌病仓鼠死亡率升高 2.4 倍[42], 而每日时相偏移则加重主动脉弓缩窄 (transverse aortic constriction, TAC) 模型小鼠的心肌肥厚[43]并通过 NR1D1/心肌营养因子样细胞因子 1 (cardiotrophin-like cytokine factor 1, CLCF1) 信号轴异常使心肌缺血再灌注损伤加重和预后不良[41]。② 基因敲除模型: *Bmal1* 敲除小鼠出现扩张型心肌病伴肌节结构紊乱[44], *Dbp*/*Hlf*/*Tef* 三重敲除小鼠进展为左室肥厚伴功能障碍[45], 而 *Per2* 缺失使小鼠心肌对缺血再灌注损伤的耐受阈值降低 60%[37]。

综上所述, 脑卒中导致昼夜节律紊乱, 昼夜节律紊乱可通过直接心肌损伤和卒中后神经内分泌失调双重途径, 促进心脑协同病变。

4 脑卒中–昼夜节律紊乱–心脏综合征的级联反应轴

脑卒中可通过诱发昼夜节律紊乱, 导致心血管、代谢及免疫系统等多维度生理功能失调, 形成脑卒中–昼夜节律紊乱–心脏综合征的级联反应[46]。本文将从以下关键生理指标系统阐述昼夜节律紊乱对 SHS 的影响和机制, 如图 2 所示。

4.1 心率变异性 (heart rate variability, HRV)

HRV 是指连续心跳 RR 间期的自然波动, 是评估心血管健康、自主神经功能及应激适应能力的重要指标。健康人群的心率呈现显著昼夜节律波动: 睡眠期间降至日间最低值, 活动期升至峰值。然而, 脑卒中患者常表现为整体心率降低, 且睡眠/活动期昼夜节律性波动丧失[47,48]。HRV 频谱分析包含高频 (HF, 反映副交感神经活性)、低频 (LF, 反映交感与副交感协同作用)、极低频 (VLF) 和超低频 (ULF) 成分。尽管 LF/HF 比值并非绝对精准量化指标, 但其动态变化可提示自主神经平衡状态: 较低比值提示副交感神经活动相对占优势, 较高比值则暗示交感神经活动较为活跃[49]。在健康人群中, LF/HF 比值呈现显著昼夜差异 (夜间低于日间), 而脑卒中患者昼夜比值差异消失, 这提示迷走神经夜间优势丧失及自主昼夜节律紊乱[48]。这种 AIS 后节律紊乱可能通过降低心电稳定性, 增加急性

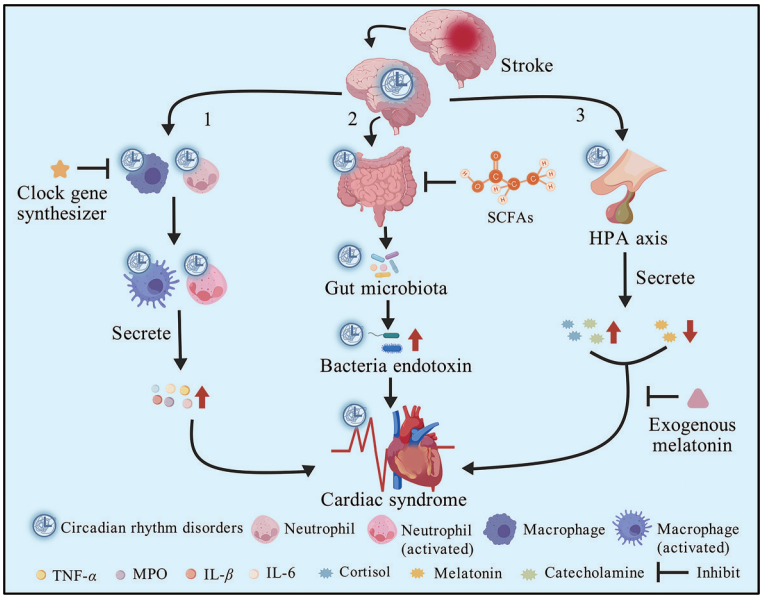


Figure 2 The cascade axis and targeted therapy for "stroke-circadian disturbance-cardiac syndrome". 1: Rhythmic dysregulation of immune inflammatory response and targeted therapy; 2: Intestinal microbiota homeostasis imbalance and targeted therapy; 3: Dysregulation of neuroendocrine hormones and targeted therapy. HPA: Hypothalamic-pituitary-adrenal; TNF-*α*: Tumor necrosis factor-alpha; MPO: Myeloperoxidase; IL: Interleukin; SCFAs: Short-chain fatty acids

期心律失常及心血管并发症事件风险。

4.2 心肌肌钙蛋白T

健康个体的心肌肌钙蛋白T水平呈现昼夜节律波动模式, 表现为日间逐渐下降、夜间上升并于清晨达峰[50]。脑卒中后心肌肌钙蛋白T昼夜节律特征显著改变, 其相对振幅异常升高提示继发性心肌损伤的SHS风险增加[51]。

4.3 血压

正常人体生理状态下血压遵循“双峰一谷”的昼夜节律特征: 清晨觉醒后达第一峰值, 日间维持较高水平, 傍晚出现第二峰值, 凌晨03:00左右降至谷值, 夜间血压较日间平均降低10%。脑卒中患者常表现为血压昼夜波动幅度增大, 这种昼夜节律紊乱可通过损害左心室充盈动力学[52]并诱发舒张功能障碍[53], 加剧心脏损伤进程。

4.4 神经内分泌激素调节失调

4.4.1 皮质醇 作为HPA轴的核心效应的糖皮质激素, 皮质醇的分泌具有显著的昼夜节律特征[54,55]。皮质醇在人类呈现日高夜低分泌的昼夜节律特征, 而夜行性动物 (如啮齿类) 则相反[56]。IS患者因应激反应导致HPA轴过度激活, 表现为皮质醇水平异常升高且昼夜节律消失。高水平皮质醇可通过抑制心肌细胞电生理稳定性增加室颤等心律失常风险及心源性猝死风险[57]。

4.4.2 儿茶酚胺 儿茶酚胺中的肾上腺素与去甲肾上腺素在人体血液中呈现白天高、夜间低的昼夜节律模式[58], 而夜行啮齿类动物 (大鼠、小鼠) 则相反[59]。脑卒中后儿茶酚胺水平急剧升高, 通过激活β1肾上腺素受体引发细胞内钙超载、线粒体氧化应激及ATP合成障碍, 最终导致心肌细胞渗透性肿胀和程序性死亡[60], 进而引发心脏肥厚或心肌缺血[61,62]。

4.4.3 褪黑素 褪黑素是一种主要由SCN控制松果体合成, 并以昼夜节律方式分泌的激素[63,64]。其分泌水平在夜间达到高峰, 白天降至低谷[65]。其生理功能包括调节睡眠−觉醒周期以及抗氧化应激。临床证据显示: AIS患者血清中褪黑素水平显著降低且节律紊乱[35,66], 这种节律异常可能通过诱发睡眠障碍及交感神经过度激活, 加剧心功能恶化与恶性心律失常风险[67]。

4.5 免疫炎症反应的节律性失调

巨噬细胞和中性粒细胞作为固有免疫系统的核心效应细胞, 其募集、活化及功能执行均受昼夜节律的精准调控。脑卒中导致昼夜节律基因*Sirt1*和*Bmal1*表达相位下移, 引发中性粒细胞异常浸润至损伤组织并过量释放髓过氧化物酶 (myeloperoxidase, MPO)、基质金属蛋白酶 (matrix metalloproteinase-9, MMP-9) 及促炎因子肿瘤坏死因子α (tumor necrosis factor-alpha, TNF-α)、白细胞介素1β (interleukin-1 beta, IL-1β)、白细胞介素6 (interleukin-6, IL-6) 及单核细胞趋化蛋白1 (monocyte chemoattractant protein-1, MCP-1), 形成脑−心轴炎症级联反应[38]。这些炎性介质进一步促进脾源性巨噬细胞向心肌迁移, 加速心脏纤维化与病理性重构进程[17]。

4.6 肠道微生物菌群稳态失衡

近年研究逐步揭示“肠−心轴”与“脑−肠轴”在SHS中的重要作用, 其交互作用受昼夜节律的精密调控。值得注意的是, 肠道菌群组成及代谢产物均呈现昼夜振荡特征, 这种节律性波动与宿主生理功能形成动态耦合[68,69]。AIS引发肠道菌群稳态失衡, 其典型特征表现为机会致病菌异常增殖与有益菌群丰度下降[70]。菌群失衡通过破坏肠道屏障结构完整性, 促进肠道内细菌及其毒性代谢产物 (如内毒素) 易位进入循环系统。这种病理性的细菌/内毒素移位激活全身性炎症反应, 经由细胞因子风暴和氧化应激等机制进一步加剧心脏功能障碍[18]。

5 靶向昼夜节律紊乱治疗SHS的策略

5.1 免疫炎症通路的节律调控

生物钟基因通过多维度调控免疫炎症网络, 在SHS的病理发生发展中发挥核心调控作用。SIRT1作为昼夜节律系统的关键调控蛋白, 通过去乙酰化修饰激活核心昼夜节律基因*Clock*和*Bmal1*的转录活性, 构成SIRT1-BMAL1分子调控枢纽[38]。该调控轴对MPO、脂质过氧化终产物丙二醛 (malondialdehyde, MDA) 及促炎因子IL-6、TNF-α具有显著抑制作用。NR1D1则通过三重机制调控炎症从而改善心肌损伤: ① 直接抑制核苷酸结合寡聚化结构域样受体蛋白3 (nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3, NLRP3) 炎症小体转录及其介导的IL-1β、IL-18等细胞因子成熟[71]; ② 阻断Toll样受体4 (Toll-like receptor 4, Tlr4)/核因子κB (nuclear factor kappa B, NF-κB) 信号通路, 降低*Tlr4*等炎症相关基因表达; ③ 阻断NF-κB信号通路间接抑制NLRP3活化[72]以间接降低MMP-9、MCP-1及促炎因子IL-1β、IL-6和TNF-α表达[73,74], 同时减少免疫细胞向心脏的异常募集[75]。这一发现为通过生物钟−免疫互作网络改善SHS提供了新靶点 (图2-1)。

5.2 肠道菌群代谢物

作为菌群−宿主互作的重要介质, 短链脂肪酸 (short-chain fatty acids, SCFAs), 由肠道微生物发酵膳食纤维产生的特征性代谢物, 其生物合成过程同样受

到昼夜节律的精确调控[76]。SCFAs通过激活趋化因子 (C-X3-C 基序) 受体1阳性细胞 (CX3C chemokine receptor 1 positive cells, $CX3CR1^{+}$) 促进心衰后的心肌修复[76], 并通过调节 *Per2* 和 *Bmal1* 基因表达实现代谢–生理节律同步化[77] (图2～2)。这些突破性发现提示, 靶向调控菌群–生物钟轴可能为SHS的治疗提出创新性策略。

5.3 外源性褪黑素的神经心脏保护

外源性褪黑素可通过激活AKT通路增强AIS后 *Bmal1* 表达[78], 同时提升超氧化物歧化酶 (superoxide dismutase, SOD) 活性、调节一氧化氮代谢并抑制交感神经张力, 从而以改善心功能[79] (图2-3)。补充外源性褪黑素为干预脑心综合征提供新方向。

5.4 中药多靶点节律调控研究

现代药理学研究揭示, 丹参主要活性成分——丹酚酸B (salvianolic acid B, Sal B)、丹参素 (Danshensu, DSS) 及丹参酮ⅡA (tanshinone IIA, Tan IIA) 通过调控Sirt1昼夜节律因子抑制心肌细胞炎症因子 (如TNF-α、IL-6等) 表达, 从而在心肌缺血再灌注损伤 (myocardial ischemia reperfusion injury, MIRI) 模型中表现出显著的心肌保护作用[80-82]。作为丹参–红花 (2∶1) 药对的标准化复方制剂, 丹红注射液 (Danhong Injection, DHI) 在心肌梗死 (myocardial infarction, MI) 及脑卒中等心脑血管疾病的临床治疗中展现出多维度治疗优势。本课题组前期研究通过建立SHS动物模型及体外细胞实验, 首次发现DHI可通过精准调控肾上腺素能受体信号通路改善心脏功能[83]。值得指出的是, 天然多酚中药单体化合物白藜芦醇通过激活生物钟调控因子Sirt1, 显著增强CLOCK/BMAL1转录复合体活性, 进而调控Per2等核心节律基因的相位同步化。这种作用机制在创伤性出血模型中显示出改善心脏收缩力和降低室性心律失常发生率的双重作用[84]。以上研究发现为中药靶向昼夜节律治疗SHS提供了理论依据。

6 总结与展望

本文通过系统地整合现有研究成果, 首次提出“脑卒中–昼夜节律紊乱–心脏综合征”级联反应的观点, 揭示了脑卒中后昼夜节律紊乱可能通过以下关键途径介导SHS的病理进程: ① 干扰免疫–炎症反应稳态, 诱发系统性炎症风暴; ② 破坏肠道菌群稳态, 导致肠道菌群及代谢紊乱; ③ 自主神经系统失衡导致神经内分泌激素失调; ④ 干扰心血管调控中枢功能, 影响心脏电生理稳定性。基于上述可能的机制, 本文创新性地提出靶向昼夜节律调控治疗SHS的策略, 并为发掘新的SHS治疗方法提供了合理而有价值的参考。然而, 昼夜节律干预策略在SHS临床转化中仍面临多重挑战: 首先, 实验动物与人类在昼夜节律系统层面存在显著种属差异性。尽管啮齿类动物与人类共享约80%的核心生物钟基因同源性, 但在活动–休息周期相位 (啮齿类动物为夜间活动型)、睡眠–觉醒模式 (人类单相睡眠 *vs* 啮齿类多相睡眠) 及光周期敏感性等关键生理特征上呈现显著差异, 这对临床前研究成果的转化效度提出重要挑战。其次, 在靶向“卒中–昼夜节律紊乱–心脏综合征”级联反应的药物研发领域, 潜在药物白藜芦醇溶解度低、稳定性差、生物利用度极低 (< 5%) 且首过效应显著及易被代谢等药代动力学特性, 这些特性极大地限制了其作为单一药物的成药潜力。针对上述挑战, 未来研究可从以下维度开展: ① 开展多中心临床队列研究, 建立SHS患者昼夜节律参数与心脏不良事件的量化关联模型; ② 开发新型药物递送系统, 通过联合用药策略或新型制剂开发, 如通过纳米技术、脂质体包载或其他创新剂型来改善其药代动力学特性[85], 开发安全有效、质量稳定、价格适宜的白藜芦醇制剂。

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