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·综 述·

中药复方疏泄方调节节律系统改善代谢稳态的研究进展

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摘要:[**背景**]节律系统是生物体内在的时间调节机制,对维持代谢稳态至关重要.它通过精确调控生物过程的周期性变化,确保生物体适应环境的周期性变化,并通过协调代谢活动促进能量的有效利用和平衡稳态.疏泄方基于中医"肝主疏泄,调节气机升降出入"理论,研究表明疏泄方基于"肝"的神经内分泌属性治疗糖尿病具有良好前景.[**进展**]本文回顾了疏泄方对于"节律-代谢"稳态的作用.已有研究显示睡眠剥夺诱导代谢指标紊乱,小鼠下丘脑和肝脏的节律基因 *Bmal1* 相位偏移与表达抑制;疏泄方可调节肝脏成纤维细胞生长因子 21(FGF21)的表达,并逆转睡眠剥夺所致节律和代谢失衡;此外,分子对接提示疏泄方核心成分与 FGF21 结合.[**展望**]未来结合中医理论,进一步揭示"肝主疏泄"的科学内涵及疏泄方的效应,阐明节律和代谢稳态的协同作用,将为治疗节律和代谢失衡疾病提供新思路和新靶点.

关键词:疏泄方;节律系统;代谢稳态

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Research progress in the regulation of circadian system by Shuxie formula for improving metabolic homeostasis

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Abstract:[**Background**] The circadian rhythm system is an intrinsic biological timing mechanism that plays a pivotal role in maintaining metabolic homeostasis. It regulates the periodic fluctuations of various biological processes with precision, ensuring adaptation to environmental cycles and promoting energy efficiency and balance through the coordination of metabolic activities. In traditional Chinese medicine (TCM), the concept of "the liver governing dispersion and regulating vital energy flow" mirrors the intrinsic regulation of human circadian rhythms. Emerging evidence supports the potential of targeting the liver's neuroendocrine functions in diabetes treatment. This review explores the significance of circadian rhythm in metabolic regulation and the alignment of TCM principles with modern scientific findings. [**Progress**] This review synthesizes current understanding of how Shuxie formula, a TCM, impacts the interplay between circadian rhythms and metabolic homeostasis. The review encompasses a series of studies that elucidate the intricate connections between circadian rhythms and metabolic processes, particularly within the context of diabetes and its complications. 1) Sleep deprivation and metabolic dysregulation: Research indicates that sleep deprivation leads to significant metabolic dysregulation, evidenced by perturbations in the circadian gene *Bmal1 in* the hypothalamic and hepatic tissues of mice. This gene is a key component of the molecular clock, and its disruption can result in a cascade of metabolic imbalances, including altered glucose metabolism and energy homeostasis. 2) Modulation of hepatic fibroblast growth factor 21 (FGF21) expression: Shuxie formula has demonstrated its efficacy in modulating the expression of hepatic FGF21, a protein known to play a crucial role in metabolic regulation, particularly in response to stress and nutritional status. By normalizing FGF21 levels, Shuxie formula may

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counteract the metabolic disruptions associated with sleep deprivation, thus restoring metabolic homeostasis. 3) Molecular docking insights: Molecular docking studies have provided insights into the potential molecular mechanisms of Shuxie formula's action. The data indicate a significant binding affinity between the key constituents of Shuxie formula and the FGF21 protein. This suggests that the formula may exert its effects through direct interactions with metabolic regulatory proteins, offering a new perspective on the molecular basis of TCM treatments. 4) Restoration of feeding patterns and energy expenditure: In a series of study utilizing a deprivation of light model (CRD) and sleep deprivation model (ASD), Shuxie formula was observed to restore normal feeding patterns and energy expenditure in rhythm-disrupted mice. The formula's treatment led to a normalization of diurnal activity and feeding rhythms, which had been disrupted by the models, and transitioned the energy allocation strategy, recalibrating it to revert to a protein-centric paradigm, indicating a regulatory effect on the metabolic processes. 5) Ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF/MS) analysis of active components: Utilizing UPLC-Q-TOF/MS, researchers have identified the main active components of Shuxie formula, including baicalin, schisandrin, and other bioactive constituents. These components are believed to contribute to the pharmacokinetics and metabolic processes of the formula. 6) Gene expression and metabolic pathway analysis: Liver RNA sequencing has revealed significant changes in genes related to glucose metabolism in rhythm-disrupted mice. Shuxie formula's intervention has shown potential in modulating these genes, particularly those involved in the PPAR and FOXO signaling pathways, both critical for glucose homeostasis. 7) Antioxidant and anti-inflammatory effects: Further studies have suggested that Shuxie formula mediates antioxidant responses through the NRF2 pathway, mitigating oxidative stress in the colon and other tissues. This effect is particularly important in the context of metabolic disorders, where oxidative stress is a common contributing factor. The collective findings from these studies underscore the multifaceted potential of Shuxie formula in addressing rhythm-metabolic dysregulation. By targeting key molecular players and modulating metabolic pathways, the formula offers a promising therapeutic approach. Future research is warranted to dissect the complex mechanisms and optimize the clinical application of this traditional compound formula. [**Perspective**] Future research should further integrate TCM theory to elucidate the functional medium of "the liver's role in dispersing and discharging" and the efficacy mechanism of Shuxie formula, clarifying the synergistic action between circadian rhythms and metabolic homeostasis. This approach is expected to provide new insights and therapeutic targets for the treatment of disorders involving rhythmic and metabolic dysregulation.

Keywords: Shuxie formula; circadian system; metabolic homeostasis

2021 年国际糖尿病联盟发布的糖尿病地图显示,全球约 10.5%的人罹患糖尿病,直接医疗支出已接近 1 万亿美元[1]. 中国是目前世界上糖尿病患者最多的国家. 2023 年首部《中国糖尿病地图》统计数据显示,2018 年中国糖尿病患病率约 12.4%[2],远高于世界平均水平,对人民的生命健康造成了巨大威胁. 代谢稳态对于血糖目标管理的重要性近年来愈发受到关注[1]:代谢稳态是维持生命活动的重要机制之一,即在一定条件下,生物体内代谢物的生成和消耗达到动态平衡. 在代谢稳态中,生物体内产生代谢产物的速率和消耗代谢产物的速率保持一定平衡,从而保持了稳定的代谢水平. 代谢稳态的破坏可能导致生理功能障碍和疾病发生. 常见代谢疾病如糖尿病、高血压、高胆固醇、肥胖等,都与代谢稳态受损有关. 胰岛素抵抗[3]、血糖波动[4]、葡萄糖感应[5]等代谢稳态相关机制已成为当前糖尿病研究的热点与重点.

生物节律参与代谢稳态的塑造,节律紊乱可从中枢到外周破坏代谢稳态,导致血糖波动,涉及节律调控与代谢稳态的密切交互作用[6]. 中医经典理论提出"法于阴阳,和于术数,食饮有节,起居有常,不妄作劳",强调遵照昼夜节律是预防疾病、颐养生命的关键[7]. 古亦有"故非出入,则无以生长壮老已;非升降,则无以生长化收藏"的论述,揭示生命的活动规律都是气机的"节律、节奏、节制"变化[8]. 基于此,厦门大学杨叔禹教授课题组提出了"调节律—稳代谢"的思路[9],基于中医"肝藏血,主疏泄"经典理论,根据古代经典名方酸枣仁汤合温胆汤化裁而成疏泄方,并在基础研究方面进行相应的验证,进一步揭示了中医方剂疏泄方通过恢复节律以调畅心身、重塑代谢稳态的作用. 本文从中药复方疏泄方调节节律系统改善代谢稳态的角度对相关研究进展进行综述,以为糖尿病及其并发症的中医药治疗提供参考.

1 节律系统对于维护代谢稳态的重要意义

节律系统在许多生物学过程中起着关键作用,包

括睡眠-觉醒周期、激素分泌和葡萄糖稳态. 近年来的研究结果显示,昼夜节律紊乱引起的能量消耗增加、饥饿感和食物摄入量增加等一系列加速代谢过程的变化,可能是节律紊乱与血糖波动叠加放大的机制之一[10-13]. 长期睡眠限制和节律紊乱会损害胰岛素分泌,干扰静息代谢率而导致体质量增加,与肥胖、葡萄糖耐受不良、糖尿病、精神障碍多种病理状况相关[14-15]. 节律紊乱对糖耐量受损和糖尿病患病风险增加的影响跨越儿童、青年到老年人群各年龄段[16-18]. 有研究发现,成人的休息-活动节律的相对振幅增加与 2 h 血糖水平下降相关[19];当睡眠时间受限时,葡萄糖清除率降低 40%,对葡萄糖的急性胰岛素反应降低 30%[20];长期光周期干扰也会导致小鼠胰岛素和瘦素信号改变及代谢标志物的变化,受干扰小鼠的空腹血糖水平与对照组相比明显增加[21]. 这些研究结果均有力地支持了昼夜节律对血糖波动的影响. 昼夜节律会影响肠道激素的分泌,胃肠道是摄入营养物质的第一接触点,肠道激素在调节食欲、消化和营养物质吸收方面发挥作用,呈现出昼夜节律性[22]. 节律紊乱会影响褪黑激素的产生,进而影响胰岛 β 细胞的胰岛素分泌活动、肝脏葡萄糖代谢和胰岛素敏感性,作用于血糖稳态调控[23-25]. 昼夜节律对各种代谢途径的调控在限制代谢速度方面表现显著[26].

昼夜节律在器官和组织中普遍存在,是生物钟负反馈环节的调控核心[27-28],相关基因的表达受到生物钟节律中枢——下丘脑视交叉上核(SCN)的调控[29]. SCN 是整个节律网络系统至关重要的部分,发挥了类似"路由器"(即接收、传递、放大信号)的功能,广泛协调机体各组织和功能的节律变化,从而调控机体的多种代谢功能[30-31]. 重要的节律基因 *Bmal1* 参与多种代谢途径,在中枢到外周多种代谢调节中发挥作用. 在中枢层面,*Bmal1* 基因在 SCN 中表达,调控睡眠-觉醒周期和激素分泌等生理过程. 下丘脑 SCN 区的芳香烃受体核转运样蛋白 BMAL1 通过维持抗利尿激素(AVP)的表达和释放,增强胰岛 β 细胞的胰岛素释放,从而促进葡萄糖耐受,BMAL1 的缺失导致葡萄糖耐受能力受损,影响血糖波动水平[32-33]. BMAL1 在参与葡萄糖吸收过程中起到关键作用,通过控制钠-葡萄糖共转运蛋白 1(SGLT1)和胰岛特异性转录因子 4(PAX4)的转录来调节葡萄糖摄取[34],该过程受到光照-明暗周期的影响,即可能被黑暗抑制[35]. *Bmal1* 基因在胰岛素分泌和胰岛素敏感性调控中起到重要作用,*Bmal1* 基因敲除小鼠胰岛素分泌显著降低,且胰岛素敏感性降低,主要胰岛素信号途径受到抑制[36],*Bmal1* 基因缺失还导致线粒体膜电位和线粒体结构的不利变化,通过线粒体信号通路影响胰岛 β 细胞功能,表现为线粒体融合蛋白 1 和 2(MFN1 和 MFN2)的表达降低及分裂蛋白 1(FIS1)的表达增加[37]. BMAL1 过表达则会增大胰岛的昼夜节律振幅,促进体内和体外的胰岛素分泌,并保护小鼠免受肥胖诱导的葡萄糖耐受不良影响[38]. 此外,BMAL1 对下游的血糖波动调节还表现出多基因协调互作的特点:*Clock* 基因和 *Bmal1* 基因双敲除小鼠葡萄糖代谢异常,BMAL1 与 CLOCK 蛋白共同调节胰岛素分泌和血糖波动稳态[39-40];BMAL1 与隐花色素(CRY)协同作用于环磷酸腺苷(cAMP)信号通路,调控葡萄糖合成和释放,从而调节肝细胞的糖代谢活动[41]. 而在外围组织(如肝脏)中,*Bmal1* 基因同样发挥着重要作用,通过影响代谢途径,包括糖异生和脂质代谢,进而精细调控全身的代谢活动. 肝脏 *Bmal1* 基因通过调节代谢调控,影响激素信号传导,从而调控睡眠-觉醒周期[42],在介导糖异生、协调葡萄糖产生和利用中发挥重要作用[43].

2　疏泄方的理论来源

"法于阴阳,和于术数,食饮有节,起居有常,不妄作劳"是经典中医理论,强调遵从自然节律是预防疾病的关键,这也是"治未病"理论提出的基础[41]. 目前已有越来越多的研究开始关注规律的生活行为对于重塑代谢稳态动态平衡的作用. 睡眠、进食和运动是人体基础的生命活动,也是节律系统驱动代谢功能的动态表征形式,对重塑代谢稳态、减轻胰岛素抵抗、改善代谢障碍具有重要意义.

本课题组在前期临床研究中发现,血糖波动异常与糖尿病患者的睡眠质量存在重要联系[43],提升糖尿病患者的睡眠质量对改善血糖波动也有助益[44];同时糖尿病合并失眠患者既存在"消渴病"的普遍性,其病机多以气阴两虚与肝胃郁热为主,也具有"不寐"的特殊性,情志方面"虚烦、气郁"症状明显[45]. "代谢-节律"稳态失衡的患者常呈现"情志多抑、少动多逸、肥甘多溢"的特点,与"肝主疏泄"功能具有密切关系. 故基于中医"肝藏血,主疏泄"经典理论,根据古代经典名方酸枣仁汤合温胆汤化裁[46],在前期"养血柔肝复方"的研究基础上加以改良,结合临床实践调整形成了新的中药复方——疏泄方[47]. 全方由酸枣仁、五味子、知母、茯苓、川芎、白芍、黄芩、半夏、枳实、竹茹等中药组成[9],具有疏泄气机、养血柔肝、清热除烦的功

效,驱动系统环境-生物节律相互作用,以期改善代谢.疏泄正常的标志是气机的升降出入正常.疏泄功能由肝主导,但需要五脏协同,心身合一,如肠肝轴、肠脑轴、肝脑轴、下丘脑—垂体—肾上腺(HPA)轴等纵向联系;代谢稳态、节律稳态等机体平衡系统与气机升降出入的动态平衡相一致,应关注各系统功能振荡在时间维度上的横向联系[48].

3 疏泄方对代谢稳态的调节机制探析

3.1 构建疏泄方改善节律紊乱动物模型

为了模拟人类在轮班工作中面临的昼夜节律失调及功能性节律系统的紊乱,本课题组前期使用剥夺光照模型(CRD)和剥夺睡眠模型(ASD)进行节律紊乱造模,观察疏泄方对节律紊乱小鼠的"节律-代谢"障碍的改善作用[49](图 1).

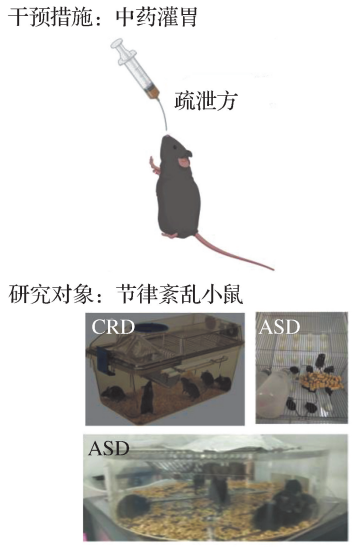
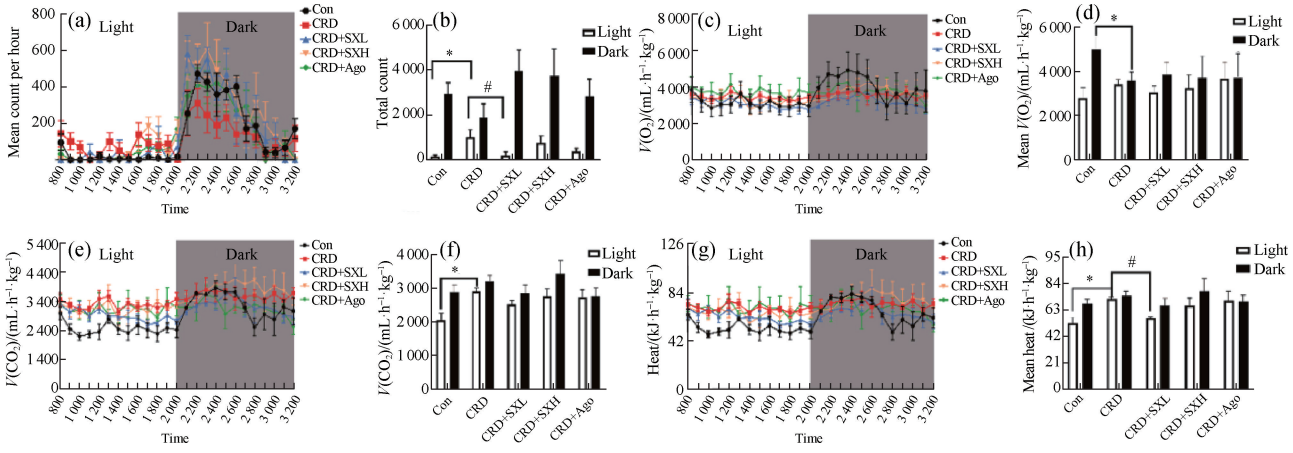


图 1 疏泄方治疗节律紊乱小鼠所致代谢紊乱的效应研究平台构建

Fig. 1 Effect study platform construction for Shuxie formula treatment on rhythm-disrupted mice with metabolic disorders

Zhang 等[50]采用跑轮及代谢笼自动检测小鼠活动、进食及与能量代谢相关的氧气消耗量、二氧化碳排放量、呼吸熵(RQ)和热量消耗的改变,以明确疏泄方对节律紊乱小鼠基础节律的影响.结果显示(图 2)造模后小鼠运动量、进食规律和基础能量代谢发生明显改变.模型组小鼠白天(休息期)的运动量显著增加,存在进食情况,且热量消耗增加,提示昼夜运动和进食规律被扰乱;氧气消耗量和二氧化碳排放量均有明显升高,提示代谢增强;白天-夜间的 RQ 高于 0.8,提示模型组小鼠呼吸底物以碳水化合物及蛋白质为主.以上结果说明小鼠在造模后表现为白天高消耗、高代谢状态.给予疏泄方治疗使其进食量、进食峰值恢复至正常水平,调整能量来源为蛋白质,在一定程度上恢复了小鼠的基础节律.



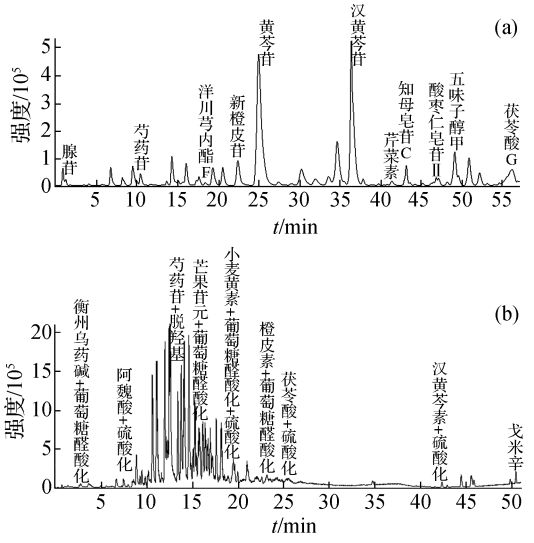
从白天 8:00(即 800 时刻)开始统计,每隔 1 h 记录一次,至第二天白天 8:00(即 3 200 时刻)结束.(a)各组小鼠自主跑轮平均每小时转数;(b)各组小鼠白天和夜间跑轮转数总和;(c)各组小鼠每小时氧气消耗量;(d)各组小鼠白天和夜间每小时平均氧气消耗量;(e)各组小鼠每小时二氧化碳排放量;(f)各组小鼠白天和夜间每小时平均二氧化碳排放量;(g)各组小鼠每小时热量;(h)各组小鼠白天和夜间每小时平均热量.Con 表示对照组(下同),CRD 表示光剥夺组,CRD+SXL 表示光剥夺+疏泄方低剂量组(下同),CRD+SXH 表示光剥夺+疏泄方高剂量组(下同),CRD+Ago 表示光剥夺+阳性药物组.* 与 Con 组比较,$P<0.05$;# 与 CRD 组比较,$P<0.05$.

图 2 疏泄方治疗节律紊乱小鼠基础节律改变[50]

Fig. 2 Impact of Shuxie formula on the fundamental rhythm alterations in rhythm-disrupted mice[50]

3.2　疏泄方成分及含药血清的质控分析

利用超高效液相色谱-四极杆-飞行时间质谱联用(UPLC-Q-TOF/MS)方法,深入分析疏泄方水煎浓缩剂的入血成分和代谢物[49]. 根据样品多级 MS 信息,结合天然产物高分辨 MS 数据库(https://www.mzcloud.org/)及相关文献[50-51],从疏泄方样品中鉴定的主要有效成分包括黄芩苷、酸枣仁皂苷Ⅱ、知母皂苷 C 等,进一步分析含药血清中的化学成分,发现芍药苷、知母苷、汉黄芩素、茯苓酸及其代谢产物可能是参与疏泄方药代动力学过程的主要成分(图 3).



(a)疏泄方水煎剂的主要成分正离子图谱;(b)疏泄方含药血清的主要代谢成分正离子图谱.

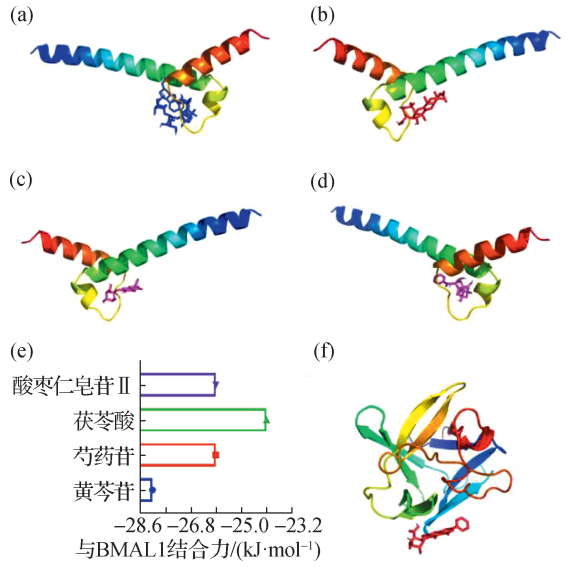
图 3　UPLC-Q-TOF/MS 鉴定疏泄方及其含药血清

Fig. 3　Identification of Shuxie formula and its containing drug serum using UPLC-Q-TOF/MS

前期筛选肝脏 RNA 测序结果[52]发现模型组成纤维细胞生长因子 21(*Fgf21*)基因显著升高;采用分子对接技术对疏泄方有效成分与 BMAL1、FGF21 蛋白进行结合力预测,显示疏泄方有效成分酸枣仁皂苷Ⅱ、茯苓酸、黄芩苷及芍药苷与 BMAL1、FGF21 蛋白具有较高的结合力(图 4),初步锁定 *Bmal1* 和 *Fgf21* 为主要研究靶点基因[53-54].

3.3　疏泄方改善节律紊乱小鼠的血糖波动和代谢障碍

Zhang 等[55]研究结果显示,空腹血糖检测、口服葡萄糖耐量试验(OGTT)、胰岛素耐量试验(ITT)和稳态模型的胰岛素抵抗指数(HOMA-IR)等指标均提示节律紊乱模型小鼠对葡萄糖分解代谢的能力下降,而疏泄方可改善节律紊乱小鼠空腹血糖、血清胰岛素



(a)～(d)疏泄方有效成分酸枣仁皂苷Ⅱ、茯苓酸、黄芩苷、芍药苷与 BMAL1 对接图;(e)酸枣仁皂苷Ⅱ、茯苓酸、黄芩苷、芍药苷与 BMAL1 的结合力分析;(f)疏泄方有效成分黄芩苷与 FGF21 对接图.

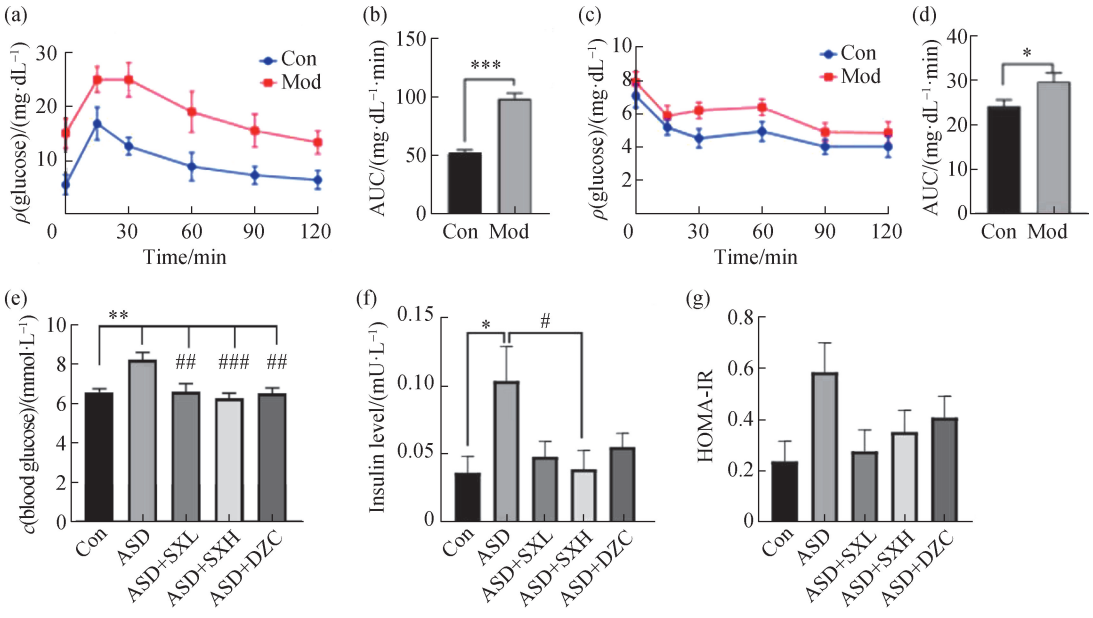
图 4　疏泄方有效成分与 BMAL1 和 FGF21 的分子对接图

Fig. 4　Molecular docking illustrations of the active components of Shuxie formula with BMAL1 and FGF21

水平及 HOMO-IR(图 5). 肝脏 RNA 测序结果显示,节律紊乱小鼠肝脏葡萄糖代谢通路相关的基因被改变. 根据"京都基因与基因组百科全书"(KEGG)注释分析发现过氧化物酶体增殖物激活受体(PPAR)和叉形头转录因子 O 亚型(FOXO)等信号通路显著改变,而 FOXO1 是葡萄糖稳态的重要调节剂,说明肝脏内葡萄糖代谢发生明显变化,疏泄方可能在基因层面调控. 由此初步验证了疏泄方治疗节律紊乱小鼠所致代谢紊乱的效应.

3.4　疏泄方介导 *Bmal1* 基因下游抗氧化因子改善肠道的氧化应激

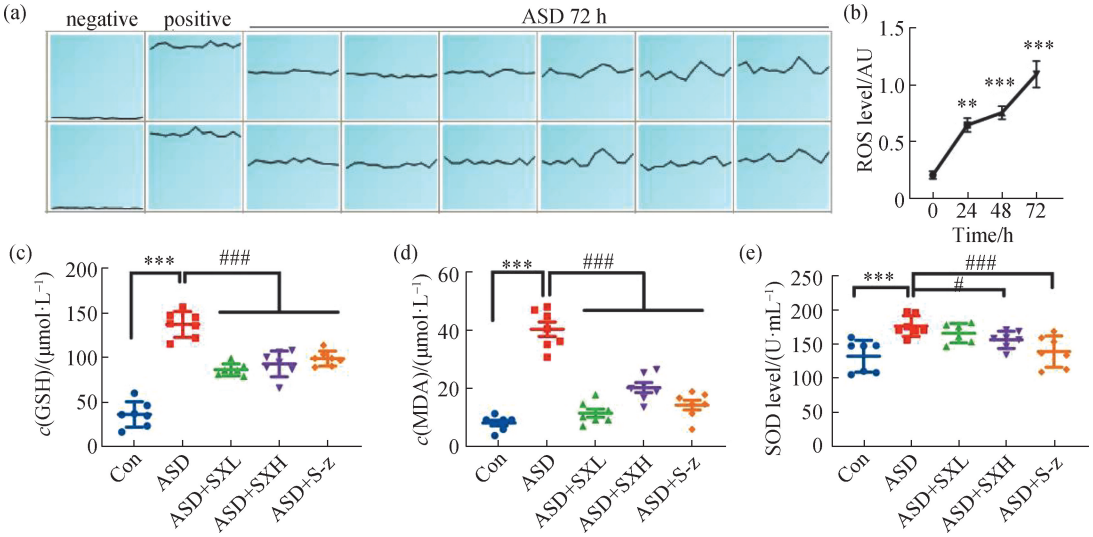
肠道的氧化应激是睡眠剥夺后的主要病理反应之一[56],Wang 等[57]的实验结果提示:节律紊乱导致小鼠血清内活性氧(ROS)生成水平明显增高,诱导 ASD 后连续 3 d 使用 ROS 敏感染料荧光酶标记剂估算血细胞内 ROS 水平,通过酶标记多点分析模式的波形,展示了 72 h 内 ROS 荧光强度的变化,结果显示(图 6):ASD 组小鼠血细胞中 ROS 水平在第 1 天(24 h)急剧升高,并在第 3 天(72 h)显著升高($P<0.001$);同时 GSH、SOD 和 MDA 的水平显著增加. 疏泄方通过 *Bmal1* 基因下游调控的抗氧化反应元件核因子红系 2 相关因子 2(NRF2)通路恢复了 ROS 的产生和清



(a)～(b)小鼠 OGTT 及曲线下面积(AUC);(c)～(d)小鼠腹腔注射 ITT 及 AUC;(e)小鼠空腹血糖水平;(f)小鼠空腹胰岛素水平;(g)小鼠 HOMO-IR. Mod 表示模型组,ASD 表示节律紊乱组(下同),DZC 表示阳性对照药物. 与 Con 组比较,* $P<0.05$,** $P<0.01$,*** $P<0.001$;与 ASD 组比较,# $P<0.05$,## $P<0.01$,### $P<0.001$(下同).

图 5 疏泄方改善节律紊乱模型小鼠对葡萄糖分解代谢异常[55]

Fig. 5 Improvement of glucose metabolic dysregulation in rhythm-disrupted mice model by Shuxie formula[55]



(a)～(b)血细胞内 ROS 水平;(c)血清谷胱甘肽(GSH)水平;(d)血清丙二醛(MDA)水平;(e)血清超氧化物歧化酶(SOD)水平. S-z 表示阳性对照药物(下同).

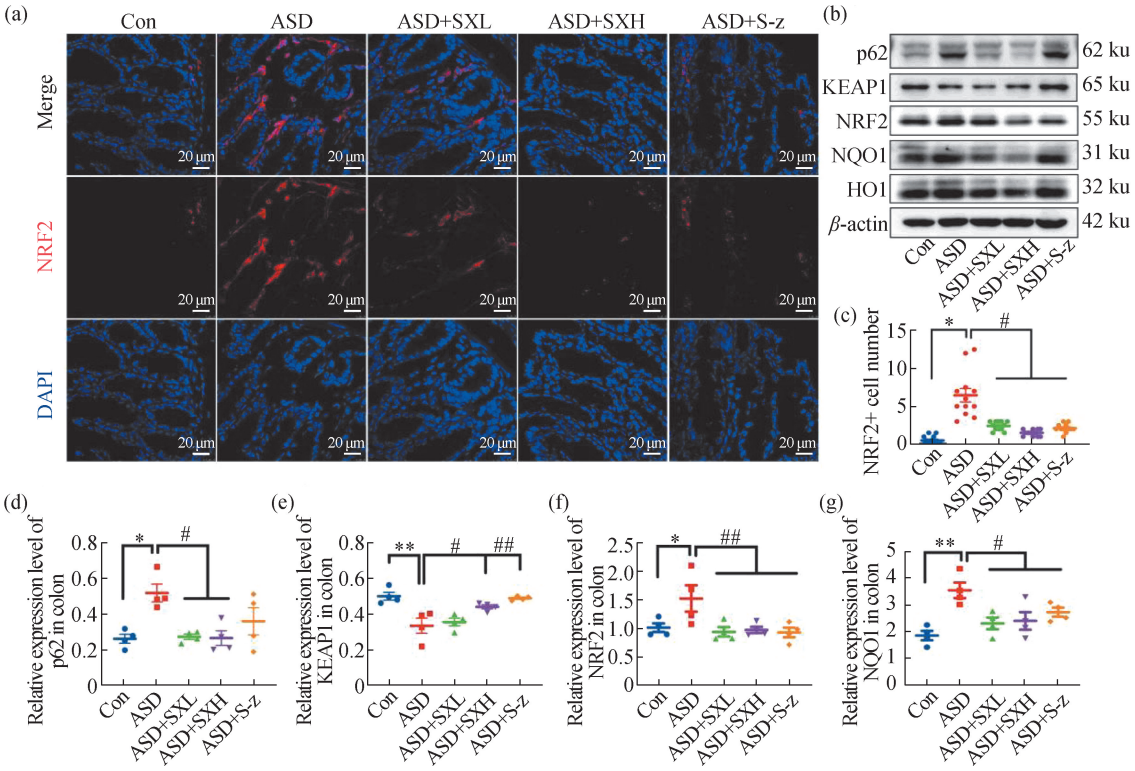
图 6 疏泄方改善节律紊乱小鼠机体氧化应激状态[57]

Fig. 6 Mitigation of oxidative stress in rhythm-disrupted mice by Shuxie formula[57]

除机制平衡,结果显示(图 7):与 Con 组相比,ASD 组小鼠的结肠切片中 NRF2 和 HO1 或 NQO1 表达水平更高,但疏泄方或阳性药物处理逆转了这些影响. 这些数据证实疏泄方通过 NRF2/NQO1/HO1 信号通路调节 ASD 诱导的结肠抗氧化反应,减轻节律紊乱模型小鼠的氧化应激水平.

4 总结与展望

本文综述了杨叔禹教授团队应用中药复方疏泄



(a)和(c)节律紊乱小鼠结肠 NRF2 免疫荧光染色图像及统计结果，DAPI. 4′，6-二脒基-2-苯基吲哚；(b)和(d)～(g)结肠氧化应激相关蛋白 p62、KEAP1、NRF2、NAD(P)H：醌氧化还原酶 1(NQO1)、血红素氧合酶 1(HO1)蛋白免疫印迹图像及统计结果.

图 7　疏泄方通过调节 NRF2/NQO1/HO1 通路改善节律紊乱小鼠氧化应激[57]

Fig. 7　Regulation of the NRF2/NQO1/HO1 pathway by Shuxie formula ameliorates oxidative stress in rhythm-disrupted mice model[57]

方对调节生物节律系统和改善代谢稳态的研究进展. 疏泄方基于中医“肝主疏泄”的理论，通过调节人体内部的气机升降出入，对糖尿病及其并发症的中医药治疗提供了新的视角和方法. 未来的研究需要进一步阐明疏泄方的作用机制，特别是其如何通过调节 *Bmal1*、*FGF21* 等关键基因和相关蛋白来影响代谢稳态；结合个体的代谢节律特征，开发个性化的疏泄方治疗方案，实现更精准的治疗效果；通过中西医结合的跨学科研究，整合现代生物学、药理学和中医药理论，以发现新的治疗方法和药物靶点.

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