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持续光照对小鼠肝脏脂代谢和体质量的影响

朱奎成[1] 杜春燕[1] 何龙[2]*
([1]郑州大学实验动物中心, 郑州 450052; [2]郑州大学第一附属医院麻醉与围手术期及疼痛医学部, 郑州 450052)

摘要 夜间暴露于人造光(ALAN)会扰乱生物节律, 并与代谢综合征密切有关, 但发生机制尚不清楚。将C57BL/6小鼠随机分为正常光照组、24 h持续光照组和非诺贝特干预组。称量小鼠体质量、肝脏湿重, 计算肝脏指数; 酶法测定甘油三酯(TG); ELISA法检测血清载脂蛋白B(ApoB)含量; HE染色观察肝脏和棕色脂肪组织(BAT)病理学变化; 油红O染色分析肝细胞脂质蓄积; 荧光定量PCR(RT-qPCR)检测下丘脑和肝脏与应激、生物钟和脂质代谢相关基因的mRNA水平。结果表明, 与正常光照组相比, 持续光照组小鼠的体质量、肝脏湿重、肝脏指数、血清ApoB、肝脏和血清TG含量均升高, 肝细胞肿胀和脂质沉积, 脂肪细胞体积增大。持续光照组小鼠下丘脑内质网应激基因*Atf4*表达水平升高, 肝脏生物钟基因*Rev-erbα*表达水平降低, 进而抑制参与肝脏脂肪酸氧化分解代谢相关基因(如*Fgf21*、*Pgc1α*、*Pparα*、*Cpt1a*和*Aco*等)表达。非诺贝特处理4周能显著抑制持续光照组小鼠体质量增长和肝脏脂质沉积, 脂肪细胞变小, 肝脏*Pparα*及脂解相关基因表达水平显著升高。由此提示, 持续光照会扰乱生物钟导致肥胖, 这机制可能与抑制肝脏脂肪酸氧化分解代谢基因相关。

关键词 持续光照; 肝脏; 脂肪组织; 脂质代谢; 体质量; 小鼠

Effects of Constant Light Exposure on Hepatic Lipid Metabolism and Weight Gain

ZHU Kuicheng[1], DU Chunyan[1], HE Long[2]*
([1]*Laboratory Animal Center, Zhengzhou University, Zhengzhou 450052, China*; [2]*Department of Anesthesiology, Pain, and Perioperative Medicine, the First Affiliated Hospital, Zhengzhou University, Zhengzhou 450052, China*)

Abstract The exposure to ALAN (articial light at night) disrupts the biological rhythms and has been associated with metabolic disorders, but the underlying mechanism is not known. A random allocation of male 8-week C57BL/6 mice into three groups was done, including controls, light group and fenofibrate groups, which contained 20 mice each. The body weight, liver wet weight of the mice were measured. Liver index was calculated based on the percentage of liver to body weight while pathological changes of the liver and fat tissue were observed microscopically. The contents of TG (triglyceride) were analysed in both serum and liver by enzymatic assays, while oil red O staining in liver frozen sections were performed to confirm hepatic lipid cumulation. The hypothalamus and liver were collected for mechanism experimentation using RT-qPCR. Fenofibrate (agonist of PPARα) was used to confirm the relationship between PPARα and lipidolysis. The results showed that the mice exposed to ALAN developed obesity and hepatic steatosis. Biochemical analysis suggested increased hepatic lipid accumulated and

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*通信作者。Tel: 15038259986, E-mail: keycelllab@126.com
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*Corresponding author. Tel: +86-15038259986, E-mail: keycelllab@126.com

increased transport of lipid from the liver to adipose tissues in LL mice that gained weight under constant light exposure. The expression of key genes involved in fatty acid oxidation (*Pgc1α*, *Pparα*, *Cpt1a* and *Aco*, etc) was significantly increased, which was paralleled by decreased expression of *Rev-erbα*. Additionally, a decrease in adipose tissue weight and adipocyte size led to the differences in body weights when treated with fenofibrate, which reversed hepatic lipid deposition by promoting the expression of lipid decomposition gene *Pparα*. As a reminder, constant light disrupts the body clock, thus leading to obesity. The biological process may be related to inhibiting the expression of FAO (fatty acid oxidation) genes.

Keywords constant light; liver; adipose tissue; lipid metabolism; body weight; mouse

生命体在长期的进化中, 形成了与光周期同步的生物节律, 即以24 h为周期的一系列生命过程–生物钟[1]。然而, 现代社会的发展改变了人们的生活和工作方式, 异常光周期(如夜班、轮班工作或时差障碍)使高度进化的生物钟被破坏, 导致受昼夜节律影响的疾病发生, 如胰岛素抵抗、葡萄糖耐量受损和体质量增加等[2-3]。卫星数据显示, 晚上灯光更强的地区, 肥胖发病率更高[4]。临床和实验研究表明, 夜间光照使生物钟的遗传环境受到破坏, 造成脂质代谢紊乱, 增加肥胖风险[5-7]。夜间光照使女性5年内增重5 kg以上的风险为17%, 体质量指数(body mass index, BMI)增加至少10%[8]。动物实验研究证明, 与夜间处于黑暗环境的实验鼠相比, 夜间处于灯光环境的实验鼠体质量显著增加[9-10]。改变光照模式会扰乱昼夜节律, 影响新陈代谢[11]。有研究比较了大鼠暴露和黑暗阶段不同时间点的代谢特征, 发现夜间光照显著干扰能量消耗和脂质代谢相关基因表达[12], 这可能分别涉及昼夜节律系统和光感知, 仍有待研究。

下丘脑视交叉上核(suprachiasmatic nucleus, SCN)与光感受器联系[13-14], 直接感受外界输入的光信号, 产生节律信号, 通过自主神经系统、激素分泌, 调控外周组织器官的代谢活动[15]。肝脏是脂质代谢的主要器官, 参与脂肪的合成、分解和运输[16]。夜间光照可能通过SCN扰乱肝脏节律, 导致脂质代谢紊乱, 增加肥胖及相关疾病的风险[17], 相关机制尚不清楚。

过氧化物酶体增殖物激活受体α(peroxisome proliferator-activated receptor α, PPARα)作为一种配体依赖的核转录因子, 主要在肝脏中表达并呈现昼夜周期性振荡, PPARa激活可诱导肝脏脂质代谢相关基因转录[18-19]。非诺贝特(Fenofibrate, FNF)是PPARα的激动剂[20]。本研究通过构建异常光周期小鼠模型, 并采用PPARα激动剂非诺贝特进行干预治疗, 以评估异常光周期与肥胖的相关性, 探讨光照通过SCN影响肝脏节律及脂质代谢的闭环分子机制, 为生物节律紊乱诱导的肥胖及相关代谢性疾病的治疗提供新的思路。

1 材料与方法

1.1 实验试剂

非诺贝特(货号: T3941)购自美国TargetMol Chemicals公司; 油红O染色试剂盒(货号: G1262)、甘油三酯(TG)含量检测试剂盒(货号: BC0625)购自北京索莱宝科技有限公司; 载脂蛋白B(apolipoprotein B, ApoB)检测试剂盒(货号: 20221018)购自南京建成生物研究所; Trizol(货号: Y1525)购自天根生化科技有限公司; RNA逆转录及荧光定量PCR试剂盒(货号: WH2322021)购自翌圣生物科技(上海)股份有限公司。

1.2 实验动物与分组

8周龄C57BL/6雄鼠购自河南省实验动物中心, 饲养于郑州大学实验动物中心屏障环境动物房(SYXK(豫)2021-0009), 自由饮水和采食。小鼠分为正常光照组(12-h light-dark cycle, LD, n=20)、24 h持续光照组(12-h light-light cycle, LL, n=20)和非诺贝特干预组(LL+Fenofibrate, n=20), 每组20只。工作照度200 lx, 持续照射8周。干预组小鼠连续照射4周后开始给予PPARα激动剂非诺贝特, 口服灌胃, 给药浓度0.04 g/(kg·d), 给药时间为4周, 给药期间保持光线照射。

1.3 血清及肝脏组织样本收集

小鼠饲养8周, 称重后分别在给予光照时刻ZT0(zeitgeber time, ZT; 8:00记为ZT0)和结束时刻ZT12(20:00)两个时间点用3%戊巴比妥钠腹腔注射麻醉, 每个时间点处死10只动物。腹主动脉采血, 分

表1 RT-qPCR引物序列

Table 1 RT-qPCR primer sequence

基因 Genes	正向引物(5′→3′) Forward primer (5′→3′)	反向引物(5′→3′) Reverse primer (5′→3′)
Atf4	CCT GAA CAG CGA AGT GTT GG	TGG AGA ACC CAT GAG GTT TCA A
Fgf21	GTG TCA AAG CCT CTA GGT TTC TT	GGT ACA CAT TGT AAC CGT CCT C
Rev-erbα	ACT TCC CAC CAT CAC CTA CTG	GGG GAG CTATCATCACTGAGA
Pparα	GGA AGA CCA CTC GCA TT	GTA ATC AGC AAC CAT TG
Pgc1α	TAT GGA GTG ACA TAG AGT GTG CT	GTC GCT ACA CCA CTT CAA TCC
Cpt1a	AGA TCA ATC GGA CCC TAG ACA C	CAG CGA GTA GCG CAT AGT CA
Aco	AGA GAG AAA GAG AGA TGG CGA GC	ATC AAT CAA GCA GTG GGA AT
Srebp1	TGG TTG TTG ATG AGC TGG AG	GGC TCT GGA ACA GAC ACT GG
Fas	TAT CAA GGA GGC CCA TTT TGC	TGT TTC CAC TTC TAA ACC ATG CT

离血清于–20 °C保存。采血后取肝脏称重并计算肝脏指数, 肝脏指数=[肝脏质量(g)/体质量(g)]×100%, 记录肝脏质量后取4份肝脏标本, 分别用于HE染色(hematoxylin-eosin staining)(4%多聚甲醛固定)、冰冻切片(新鲜组织直接切片)、脂质指标检测(–20 °C保存)和荧光定量PCR分析(–80 °C保存); 下丘脑–80 °C保存; ZT0时取肩胛间棕色脂肪组织(brown adipose tissue, BAT), 放入4%多聚甲醛固定(室温48 h)。实验方案经郑州大学实验动物中心福利与伦理委员会审查批准(批文号: ZZU-AC20231229[03])。

1.4 TG和ApoB含量分析

称取肝组织100 mg置于研磨仪中, 加入预冷的生理盐水0.9 mL冰浴匀浆。8 000 ×*g*、4 °C离心10 min, 收集上清液, 使用甘油三酯(TG酶法)试剂盒测试肝脏和血清TG含量。酶联法(enzyme-linked immunosorbent assay, ELISA)分析血清载脂蛋白B含量。

1.5 组织病理学

取肩胛间棕色脂肪组织, HE染色, ImageJ 1.8.0软件测量脂肪细胞大小。肝脏组织分别进行HE和油红O染色, 显微镜下观察组织病理学变化及脂质蓄积情况。

1.6 实时荧光定量PCR

Trizol一步法提取下丘脑及肝脏总RNA并定量, 并使用DNase I酶消除污染的基因组DNA。紫外分光光度计分析RNA纯度及浓度。反转录为cDNA。PCR引物由擎科生物科技股份有限公司合成(表1), 包括内质网应激基因: 激活转录因子4(activating transcription factor 4, *Atf4*), 成纤维细胞生长因子21(fibroblast growth factor 21, *Fgf21*); 昼夜节律基因: *Rev-erbα*(reversed erbα); 脂质分解代谢相关基因: 过氧化物酶体增殖物活化受体共激活因子1α(peroxisome proliferator-activated receptor gamma coactivator 1α, *Pgc1α*), *Pparα*及其靶基因肉碱棕榈酰转移酶1a(carnitine palmitoyltransferase 1a, *Cpt1a*)和乙酰辅酶A羧化酶(acetyl-CoA carboxylase, *Aco*); 脂质合成代谢相关基因: 固醇调节元件结合蛋白1(sterol regulatory element-binding protein 1, *Srebp1*)和脂肪酸合成酶(fatty acid synthase, *Fas*)。反应体系: 10 μL 2× QuantiFast® SYBR® Green PCR Master Mix, 上、下游引物各1 μL, 1 μL cDNA, Nuclease-free H_2O补足至20 μL。反应程序: 95 °C预变性3min; 95 °C变性7 s, 58 °C退火35 s, 72 °C延伸35 s, 40个循环。每个样本均设置3个复孔。以*GAPDH*作为对照, 通过SYBR实时荧光定量试剂盒进行扩增反应, 结果采用$2^{-\Delta\Delta Ct}$法进行计算。

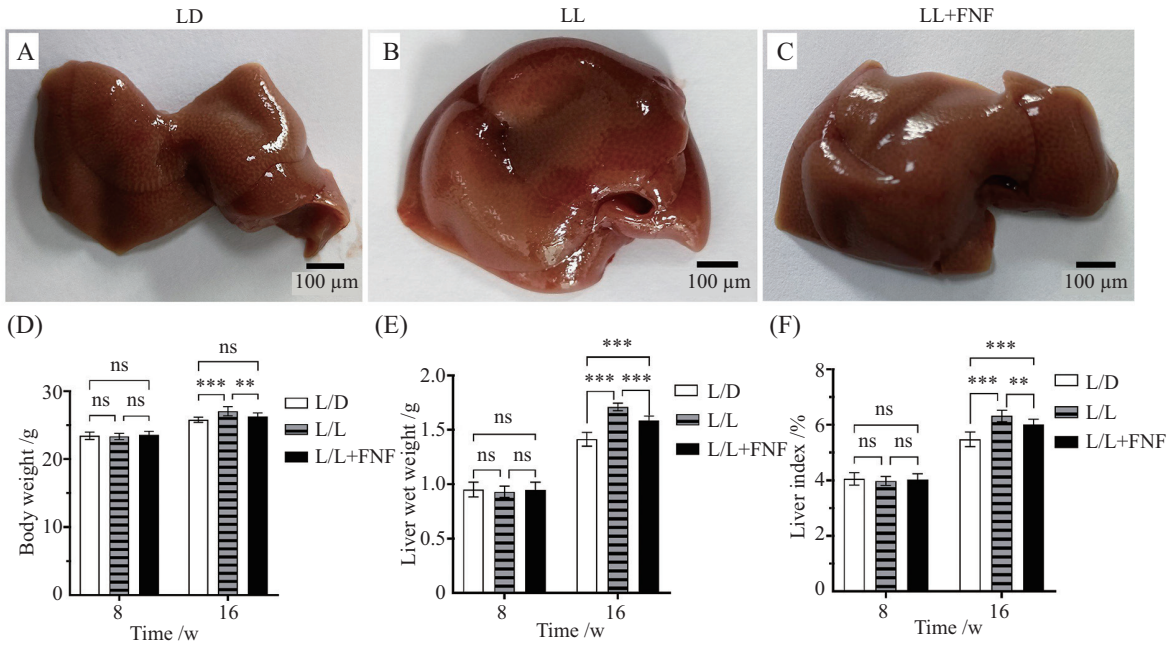
1.7 统计分析

采用SPSS 17.0软件进行数据处理, GraphPad Prism 9.5软件作图。所有数据进行正态性检验, 数据用均数±标准差($\bar{x}\pm s$)表示, 组间比较使用单因素方差(One-Way ANOVA)分析。$P<0.05$表示差异显著。

2 结果

2.1 小鼠一般状态观察及体质量变化

与LD组比较, LL组小鼠活动迟缓, 毛发无光泽; 肝脏体积增大, 质脆, 颜色变淡, 边缘较钝; 体质量、肝湿重及肝脏指数均显著升高($P<0.001$)。与LL组比较, 干预组(LL+FNF)小鼠整体状态明显改善, 精神良好、反应较为灵敏, 毛发顺滑光泽; 肝脏红润, 表面相对光滑, 边缘锐利; 体质量、肝脏湿重及肝脏指数均显著降低($P<0.01$)。见图1。



A~C: 肝脏大体形态。D~F: 体质量、肝脏湿重及肝脏指数。ns, $P>0.05$; **$P<0.01$; ***$P<0.001$。

A-C: macroscopic appearance of the liver. D-F: body weight, body mass, liver wet weight, and liver index. ns, $P>0.05$; **$P<0.01$; ***$P<0.001$.

图1 持续光照对小鼠肝脏形态、体质量、肝脏湿重和肝脏指数的影响

Fig.1 Effects of continuous lighting on liver morphology, body weight, liver weight and liver index of mouse

2.2 持续光照对小鼠脂质代谢、肝脏及脂肪组织病理学影响

HE染色结果显示, LL组小鼠肝索排列紊乱, 细胞肿胀, 胞质呈典型泡沫形态。油红O染色见LL组肝细胞胞质中红色脂滴明显增多; 干预组肝细胞脂质沉积减轻, 胞质内红色脂滴减少、变小。与LD组相比, LL组小鼠肝脏和血清TG含量在ZT0时分别增加64%和52%, 在ZT12时分别增加53%和45%; 与LL组比较, 干预组小鼠肝脏和血清TG含量在ZT0时分别降低18%和25%, 在ZT12时分别降低13%和28%($P<0.001$)(图2)。

LL组小鼠脂肪细胞大小为LD组的1.40倍, 干预组脂肪细胞大小为LL组的0.74倍。ELISA法检测血清载脂蛋白ApoB含量, 结果显示, 与LD组相比, LL组小鼠血清ApoB含量在ZT0和ZT12时分别增加97%和73%; 与LL组相比, 干预组小鼠血清ApoB含量在ZT0和ZT12时分别下降24%和18%($P<0.001$)(图3)。

2.3 小鼠下丘脑*Atf4*及肝脏脂质代谢相关基因mRNA表达变化

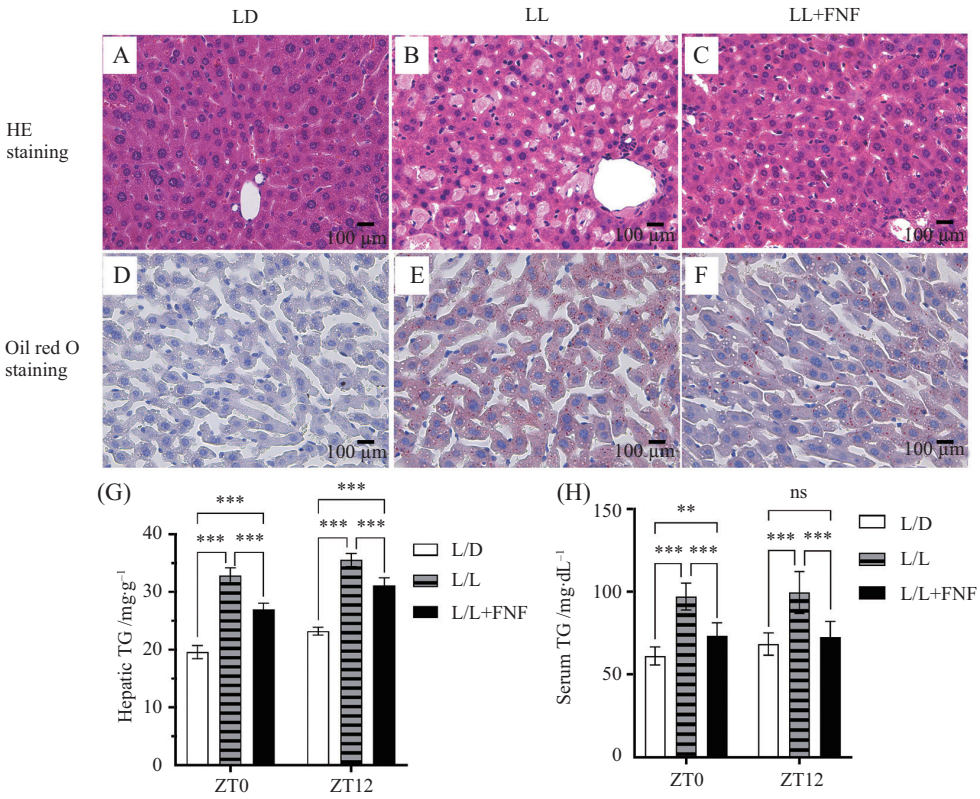
所提组织总RNA的D_{260}/D_{280}值, 均在1.9~2.1之间, 没有蛋白质和DNA污染, RNA浓度符合反转录要求。

采用RT-qPCR方法研究持续光照对下丘脑*Atf4*基因表达的影响, 结果显示, 在ZT0和ZT12, 与LD组比较, LL组小鼠*Atf4*被激活($P<0.05$), 干预组*Atf4*表达与LL组相比无显著性差异($P>0.05$)。

分析肝脏组织中脂质合成和分解代谢相关基因mRNA表达, 在ZT0和ZT12, 与LD组相比, LL组小鼠肝脏脂质分解代谢相关基因*Fgf21*、*Pgc1α*、*Pparα*及其下游靶基因*Cpt1a*和*Aco*表达显著下调($P<0.05$, $P<0.01$), 脂质合成代谢基因*Srebp1*及其下游靶基因*Fas*表达无显著性变化($P>0.05$)。干预组脂质分解代谢相关基因mRNA表达量基本恢复到正常节律特征, 并在ZT0和ZT12同步受到激活($P<0.05$, $P<0.01$)(图4)。

3 讨论

机体的生物节律受高度协调的内、外环境调节, 以维持正常的睡眠、血压和代谢等生理活动, 光是调节昼夜节律最重要的环境因素[21]。本研究结果显示, 夜间人造光可引起小鼠体质量、肝脏指数、血清和肝脏甘油三酯水平显著升高及肝细胞脂质沉积, 脂肪细胞体积增大, 提示异常光周期刺激小鼠肝脏脂质代谢紊乱, 过量血脂向脂肪组织运输, 导致小鼠肥胖。

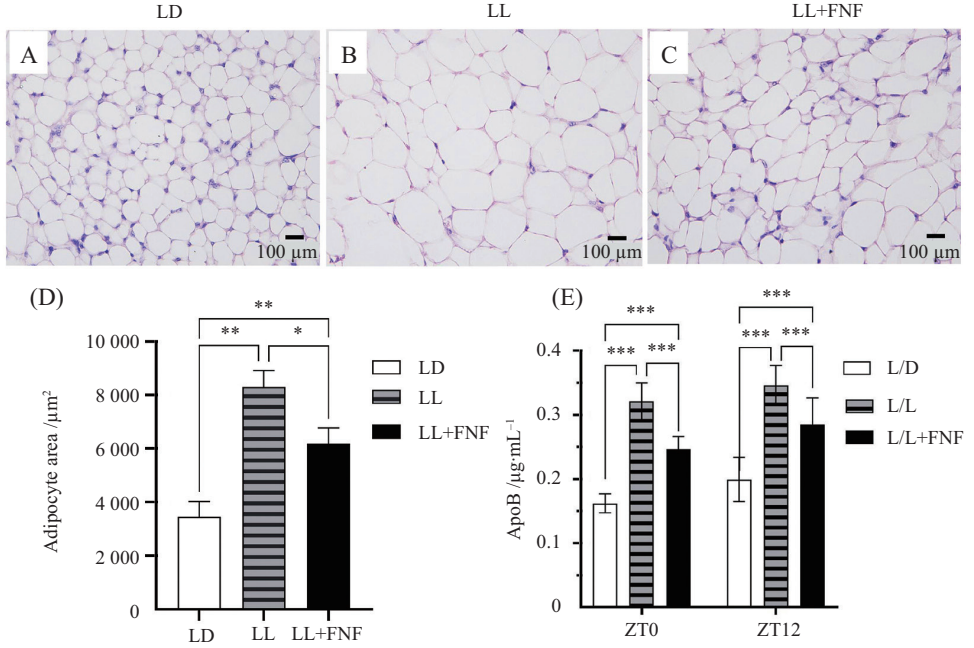


A~C: 肝脏组织HE染色; D~F: 肝脏组织油红O染色; G、H: 肝脏组织和血清TG含量。ns, P>0.05, **P<0.01, ***P<0.001。

A-C: HE staining of liver tissue; D~F: oil red O staining of liver tissue; G,H: hepatic and serum TG (triglyceride) content. ns, P>0.05, **P<0.01, ***P<0.001.

图2 持续光照对小鼠肝脏组织病理学、肝脏及血清中TG含量的影响

Fig.2 Effects of constant light on liver histopathology, TG content in liver and serum of mouse

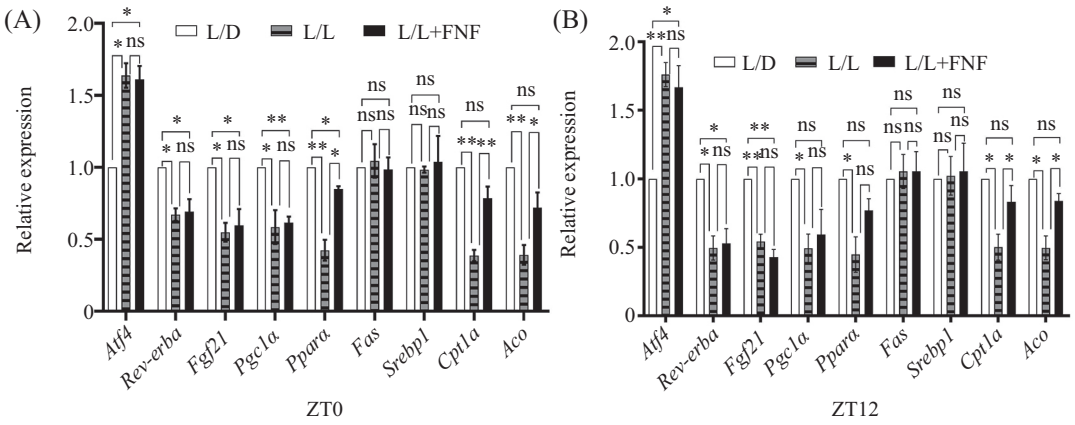


A~C: 脂肪组织HE染色; D: 脂肪细胞大小; E: 血清载脂蛋白B(ApoB)含量。ns, P>0.05; *P<0.05; **P<0.01; ***P<0.001.

A-C: HE staining of adipose tissue; D: adipocyte size; E: serum ApoB (apolipoprotein B) content. ns, P>0.05; *P<0.05; **P<0.01; ***P<0.001.

图3 持续光照对小鼠脂肪组织病理学及血清ApoB含量的影响

Fig.3 Effects of constant light on adipose histopathology and serum ApoB content of mouse



A: ZT0时脂质代谢相关基因表达。B: ZT12时脂质代谢相关基因表达。ns, $P>0.05$; *$P<0.05$, **$P<0.01$。

A: expression of lipid metabolism-related genes at ZT0. B: expression of lipid metabolism-related genes at ZT12. ns, $P>0.05$; *$P<0.05$; **$P<0.01$.

图4 持续光照对小鼠脂质代谢相关基因表达的影响

Fig.4 Effects of constant light on expression of genes associated with lipid metabolism of mouse

位于下丘脑的中央时钟视交叉上核, 可以通过视网膜接受光线, 协调外周组织中的振荡器以保持正常的昼夜节律[22]。肝脏是人体脂质代谢的中心器官, 近来研究表明, 下丘脑内质网应激可通过神经途径调控肝脏的糖脂代谢, 诱导葡萄糖耐受不良和胰岛素抵抗[23-24]。ATF4是一种内质网应激响应蛋白, 在调控能量代谢中具有重要作用[25-26], *Atf4*基因敲除小鼠可抵抗高脂或高糖饮食诱导的脂肪肝形成[27]。

基于以上研究, 我们推测光照可能通过下丘脑ATF4蛋白调控外周肝脏脂质代谢, 因为持续光照可诱导大鼠海马内质网应激[28]。本研究发现, 与对照组相比, 持续光照组小鼠下丘脑*Atf4*表达水平显著升高, 而肝脏*Fgf21*的表达水平显著降低。*Fgf21*主要由肝脏产生, 对机体多种组织的代谢具有重要调控作用[29-30]。已有研究证实, 交感神经通过Atf4/Rev-erbα/Fgf21信号轴将将下丘脑的信号传递到肝脏[31-32]。*Rev-erbα*作为生物钟基因, 其缺失会导致小鼠昼夜节律紊乱, 并通过调控代谢基因表达将昼夜节律与细胞代谢相耦联[33]。*Rev-erbα*主要在睡眠期高表达, 其活性与脂肪和糖代谢密切相关, *Rev-erbα*基因敲除小鼠活动周期延长, 脂肪利用率降低, 甘油三酯水平升高[34]。在肝脏中, *Fgf21*诱导*pgc-1α*表达, 后者广泛参与线粒体生物合成、能量代谢和糖脂代谢过程[35]。本研究结果显示, 持续光照组小鼠肝脏中*Rev-erbα*表达水平显著升高, 升高的*Rev-erbα*募集组蛋白去乙酰化酶3(histone deacetylase 3, HDAC3), 而HDAC3通过使PPARα共激活因子PGC-1α去乙酰化, 抑制其转录活性。与此一致, 我们发现持续光照组小鼠肝脏中脂肪酸分解代谢基因*Pgc-1α*、*Pparα*及其靶基因*Cpt1a*和*Aco*表达水平均显著降低。然而, 脂肪酸合成代谢基因*Srebp1*和*Fas*的表达在两组间无显著性差异。综合以上结果, 持续光照导致肝细胞脂质沉积的原因可能在于PPARα介导的脂肪酸氧化分解代谢水平降低, 而非脂肪酸从头合成增加。此外, 其他机制也可能参与其中, 如熬夜或高脂饮食已被证明可破坏生物节律并促进脂肪酸向肝脏的转运[36], 而有规律的体育活动则能加速脂肪分解, 改善脂质代谢[37]; 肝炎或酒精性肝损伤相关的脂质沉积则常源于甘油三酯输出障碍[38-39]。 这些因素在持续光照致肝脏脂质沉积中独立作用还是协同作用, 仍需进一步研究阐明。值得注意的是, 持续光照组小鼠血清ApoB水平升高, 提示更多的血脂被转运至脂肪组织存储, 这一发现与小鼠体质量增加、肝脏及血清TG水平上升相一致。

使用PPARα激动剂非诺贝特进行干预, 光照组小鼠肝脏及血脂水平显著降低, 体质量下降, 进一步明确了PPARα在脂质氧化分解代谢中的作用[40]。与LD组相比, 干预组小鼠下丘脑*Atf4*与肝脏*Rev-erbα*表达在ZT0和ZT12时均有显著性差异, 可能在于*Atf4*与*Rev-erbα*是*Pparα*的上游基因, 非诺贝特通过激活*Pparα*促进脂肪酸氧化分解, 抑制甘油三酯合成[41]; *Pparα*表达在ZT0和ZT12虽明显升高, 但在ZT0时有显著差异, 在ZT12时差异不显著, 可能是非睡眠期*Rev-erbα/β*表达水平降低, 抑制了肝脏*Pparα*活化, 非诺贝特对*Pparα*激活作用更大, 或者干预时间不够, 需进一步研究确认。

本研究揭示了持续光照激活小鼠视网膜上特殊的感光细胞，通过视神经传递信号至下丘脑视交叉上核(SCN)，激活了内质网应激响应蛋白ATF4，经交感神经传递抑制了PPARα依赖的肝细胞脂肪酸氧化。肝脏及血脂含量增加，血清载脂蛋白ApoB水平升高，更多的脂质通过血液运输到脂肪组织，这可能是异常光周期诱导小鼠肝脏脂质蓄积及肥胖风险增加的潜在机制。

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