

消化道营养物质吸收代谢昼夜节律性调控机制的研究进展

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摘要: 昼夜节律是指在生物体内存在的以近似24 h为周期的生物节律。昼夜节律的重要性质之一是内源节律的周期性, 哺乳动物的生理和代谢节律受昼夜节律的控制。昼夜节律的振荡导致下游分子通路和生理过程发生节律性变化, 对营养物质的消化、吸收和代谢有一定的调控作用。本文主要综述了消化道蛋白质、糖、脂类等营养物质吸收代谢的节律性及其调控机制, 以为生物钟调控动物营养物质利用机制的研究提供参考资料。

关键词: 昼夜节律; 营养物质; 消化道

中图分类号: Q493.99, S852.2

文献标识码: A

文章编号: 1007-7847(2021)04-0327-06

Advances in Mechanism of Intestinal Nutrient Absorption and Metabolism Regulated by Circadian Rhythm

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Abstract: Circadian rhythm refers to the biological rhythm that exists in the body with a period of approximately 24 hours. One of the important properties of circadian rhythm is the periodicity of endogenous rhythm. The physiological and metabolic rhythms in mammals are controlled by circadian rhythm. The oscillation of circadian rhythm leads to rhythmic changes in downstream molecular pathways and physiological processes, and has some regulatory effects on the digestion, absorption and metabolism of nutrients. Herein, the rhythms and regulation mechanism of the absorption and metabolism of nutrients such as protein, sugar and lipid in the digestive tract were summarized, so as to provide references for the study on the mechanism of biological clock regulating nutrient utilization in animals.

Key words: circadian rhythm; nutrient; digestive tract

(*Life Science Research*, 2021, 25(4): 327~332)

昼夜节律存在于生物体内多种生理生化过程中, 调节机体环境与生理过程之间的相互作用, 使生物体能更好地适应外界环境的节律改变^[1]。研究表明, 昼夜节律能够调控生物体对营养物质的吸收代谢, 并影响各种营养物质的功能^[2-3]。例如: 大鼠的体内实验显示, 葡萄糖摄取具有明显的24 h节律^[4]; 小鼠肠道中肽转运蛋白1 (peptide transporter 1, PEPT1)的表达具有节律性^[5]; 芳香烃受体

核转位蛋白样1 (*brain and muscle ARNT-like 1, Bmal1*)基因被证明可以调节肠道脂质吸收的节律^[6]。昼夜节律调节多种胃肠功能, 包括细胞增殖、免疫稳态、肠道通透性及微生物的平衡和代谢^[7-12]。昼夜节律的破坏会造成多种生理功能的失调, 对生物体的健康产生极其严重的影响。比如: *Bmal1*突变的小鼠和 *Clock* (*circadian locomotor output cycles kaput*)突变的小鼠的胃肠都表现出细胞增殖的

收稿日期: 2020-07-28; 修回日期: 2020-09-15

基金项目: 国家自然科学基金面上项目(31672446); 江苏省优势学科项目(PAPD)

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紊乱^[8-9]; *Per1* (*Period1*)和 *Per2* (*Period2*)基因敲除小鼠的肠道微生物的节律消失,昼夜节律被打乱,导致肠道菌群失调^[10-12]。此外,昼夜节律紊乱会增加消化系统疾病的易感性,如肠道炎症、十二指肠溃疡、肠应激疾病和胃肠癌症^[13-14]。相关研究报告,结肠癌组织中存在 *Clock* 基因的突变^[15]; 在小鼠中,昼夜节律紊乱损害肠道屏障的完整性^[16]; 敲除 *Clock* 或 *Cry* (*cryptochrome*)基因的小鼠比野生小鼠产生更多的促炎细胞因子^[17]; 与白班工人相比,夜班工人感染胃炎和消化性溃疡的风险较高^[18]。因此,昼夜节律在胃肠中发挥重要作用,进一步研究生物钟与消化道营养物质吸收代谢之间的关系,对调控机体健康有一定的参考意义。

1 消化道昼夜节律系统及其对消化循环的影响

沿胃肠道布的营养传感器可释放大量影响胃肠功能、营养稳态和能量平衡的信号肽^[19]。Furuya 和 Yugari 首先在 1974 年证明了肠道吸收在大鼠中表现出昼夜节律^[20-21]。与早餐后的消化率相比,晚餐后的消化率和肠吸收率要低^[22]。研究表明,消化道存在生物钟基因,这些生物钟基因参与胃肠功能和活动,如胃排空、结肠蠕动、胃液分泌和酶的活动^[7, 23]。*Bmal1* 通过调节应激反应,促进肠上皮 24 h 节律的产生^[8]。敲除 *Per1* 或 *Per2* 会改变结肠的运动节律,同时敲除 *Per1* 和 *Per2* 可使小鼠结肠活动的昼夜节律消失^[24]。有研究发现,啮齿动物的生物钟基因在胰腺中也以昼夜节律的方式表达。针对缺乏生物钟基因 *Bmal1* 的小鼠胰腺进行的研究发现,实验小鼠存在严重的葡萄糖不耐受和胰岛素分泌缺陷^[25-26]。目前,胰酶淀粉酶和胰蛋白酶分泌的昼夜节律变化在人类受试者中已被报道^[27]。此外,胰岛素分泌率也被证明有昼夜节律性,其中血浆胰岛素水平在清晨增加,下午达到峰值,晚上下降^[28]。由此可见,消化道的生物钟基因以昼夜节律的方式表达,它们可能是胃肠活动的重要调控因子。

2 昼夜节律与消化道营养物质吸收代谢

昼夜节律系统在营养吸收方面起着重要作用,正常的生物钟系统有利于营养物质的吸收利用。肠道生物钟的破坏会影响营养物质的吸收与节律性, Pan 等^[29]研究发现,在小鼠小肠中,转运营养物质水解产物的转运蛋白的 mRNA 表达具

有昼夜节律,而这些营养转运蛋白的昼夜节律在 *Clock* 突变小鼠中消失,并且 *Clock* 突变小鼠吸收营养物质的量也发生了改变,这说明生物钟调控着肠道内多种营养物质的转运。

2.1 葡萄糖吸收代谢的节律性和调节机制

碳水化合物主要由单糖(葡萄糖、果糖和半乳糖)、二糖(乳糖和蔗糖)和多糖(淀粉和纤维素)组成。多糖通过小肠刷状缘水解酶的作用分解为单糖,肠腔中的单糖被肠上皮细胞吸收,这些单糖通过肠上皮细胞基底外侧的转运蛋白从浆膜侧输出到肠上皮细胞外,进入血液循环^[30]。钠葡萄糖协同转运蛋白 1 (sodium/glucose cotransporter 1, SGLT1)、葡萄糖转运蛋白 2 (glucose transporter 2, GLUT2)和 GLUT5 是存在于啮齿动物小肠中的主要己糖转运蛋白,它们协同促进肠道中葡萄糖的吸收^[31]。

大鼠体内实验显示,无论是在实验前 1 h 禁食还是按照预定的喂养方案喂食,葡萄糖摄取都表现出明显的 24 h 节律^[4],这表明在正常喂养条件下,葡萄糖摄取的昼夜节律与进食模式无关,可能由视交叉上核(suprachiasmatic nucleus, SCN)中的昼夜节律系统调节。有研究发现, *Sglt1* 的 mRNA 表达具有明显的昼夜节律^[32-33]。此外, *Glut2* 和 *Glut5* 的表达也具有节律性^[34-35]。染色质免疫沉淀(chromatin immunoprecipitation, ChIP)实验发现, *Bmal1* 与己糖转运蛋白编码基因的启动子结合^[35]。以上信息提示, *Bmal1* 可能直接调节基因 *Sglt1*、*Glut2* 和 *Glut5* 的表达,己糖转运蛋白的调控直接受时钟基因的控制。

O'brien 等^[19]在研究鼠胃肠道糖传感器相关基因和蛋白质的表达水平时发现,甜味受体(*Tas1r2*, *Tas1r3*, *Gnat3*, *Gnat1*)、糖转运蛋白(*Sglt1*, *Glut2*, *Glut5*)和特定糖传感器(*Slc5a4a*, *Slc5a4b*)基因的表达水平分别在舌头、近端与远端小肠中最高,生物钟基因(*Cry2/Bmal1*)在所有研究区域均可检测到活动,尽管 SGLT3 蛋白的表达未检测到节律性,但是 *Slc5a4a* 和 *Slc5a4b* 基因的表达分别在小肠和胃中显示出明显的昼夜节律性,同时, *Tas1r2*、*Tas1r3* 和 *Gnat1* 在近端小肠中也表现出明显的表达节律。这说明,胃肠道糖传感器基因可能受生物钟基因调控,生物钟基因与营养素相互作用。

2.2 脂质吸收代谢的节律性和调节机制

生物钟在调节肠细胞的脂质吸收中也起重要作用,越来越多的研究表明,昼夜节律紊乱会增

加脂质积累的风险, 导致脂质吸收受损^[36-37]。脂肪从肠腔摄取到肠细胞的主要步骤是胆汁乳化、脂肪酶水解和转运体摄取^[38-44]。脂肪酸通过脂肪酸结合蛋白在细胞内转运, 在内质网中, 脂肪酸用于合成三酰基甘油、磷脂和胆固醇酯, 这些脂质被包装成称为乳糜微粒的脂蛋白^[45-46]。乳糜微粒是非常大的富含三酰基甘油的球形颗粒, 含有磷脂和胆固醇, 这些颗粒的表面覆盖有磷脂单层、游离胆固醇和几种载脂蛋白。乳糜微粒组装需要两种蛋白质: 载脂蛋白 B (apolipoprotein B, ApoB) 和微粒体甘油三酯转移蛋白 (microsomal triglyceride transfer protein, MTP)。

有研究表明, 脂质的吸收在 24 h 内差异显著, *Clock* 的过表达会显著降低 *Mtp* 的表达^[29, 47]。CLOCK:BMAL1 异二聚体有节奏地激活小异二聚体伴侣 (small heterodimer partner, SHP), 从而抑制 *Mtp* 的表达^[47]。相关研究报道, 小鼠在夜间吸收的甘油三酯和胆固醇含量明显高于白天, 并且甘油三酯和胆固醇的吸收与 ApoB 和 MTP 的表达表现出相关的昼夜波动^[48]; 小鼠小肠中有昼夜节律因子 *Noc* (nocturnin) 的表达, 与 *Noc*^{+/+} 小鼠相比, *Noc*^{-/-} 小鼠吸收更少的甘油三酯和胆固醇^[49-50]; *Noc* 的转录起始位点上游具有 E-box, 而 CLOCK:BMAL1 异二聚体可与这些序列直接结合^[51]。这些研究表明 *Clock* 参与脂质转运的日常调控。

此外, Pan 等^[29]在正常昼夜循环和自由获取食物的条件下, 还研究了其他参与脂质合成和吸收的基因的表达, 发现二脂酰基甘油酰基转移酶 2 (*diacylglycerol acyltransferase 2, Dgat2*)、脂肪酸结合蛋白 (*fatty acid-binding protein, Fabp*)、硬脂酰辅酶 A 去饱和酶 1 (*stearyl coenzyme A dehydrogenase 1, Scd1*) 和脂肪酸合成酶 (*fatty acid synthase, Fas*) 的 mRNA 呈现日变化。本实验室前期研究发现, 生物钟基因参与瘤胃上皮挥发性脂肪酸 (volatile fatty acid, VFA) 代谢的调控, *Clock*、*Bmal1*、*Per2* 和 *Per3* 与单羧酸转运蛋白 1/4 (*monocarboxylate transporter 1/4, Mct1/4*) 存在显著的相关性^[52]。综上所述可知, 昼夜节律参与调节脂质合成和吸收。

2.3 蛋白质吸收代谢的节律性和调节机制

生物钟基因已被证明可以调节肠道肽转运蛋白的节律^[53]。蛋白质在消化道中被消化成氨基酸、二肽和三肽, 其中, 二肽和三肽由 PEPT1 转运。PEPT1 是质子依赖的肽共转运蛋白, 能够将 H⁺ 和肽转运到肠上皮细胞中, 肽的转运与 H⁺ 浓度相

关, 而与细胞内肽的浓度无关。为了能够有效进行肽的转运, 细胞内的 H⁺ 浓度被 Na⁺/H⁺ 转运蛋白 3 (Na⁺/H⁺ exchanger 3, NHE3) 维持在较低水平。该转运蛋白将 H⁺ 泵入肠细胞, 并交换出 Na⁺, 使细胞内 Na⁺ 浓度保持较低水平, 同时 K⁺-ATP 酶泵出 Na⁺, 输入 K⁺。机体通过这些转运蛋白的共同作用促进肠上皮细胞对肽的摄取。所有的肽在肠上皮细胞的细胞质中被水解为氨基酸, 并通过氨基酸转运蛋白跨过基底外侧转移到血液循环中^[54-55]。

大鼠结肠中 *Nhe3* 的表达具有昼夜节律性^[54]。研究报道, *Cry1* 和 *Cry2* 敲除小鼠与 *Clock* 突变小鼠中 *Nhe3* 的 mRNA 表达均降低^[54]; *Nhe3* 的启动子含有一个 E-box 序列, 该序列可被 CLOCK:BMAL1 异二聚体反式激活, 提示 *Nhe3* 的这种有节奏的表达可能是由结肠生物钟驱动的^[5, 54]。

PEPT1 的表达在 24 h 内也会发生节律性变化。Pan 等^[5]检测了自由进食糖基肌氨酸并保持 12 h : 12 h 光暗周期的大鼠小肠中 PEPT1 的每日节律, 发现 PEPT1 的蛋白质水平和 mRNA 水平在 20:00 时最高, 在 08:00 时最低。但是, Saito 等^[55]发现, 决定 *Pept1* 表达的转录因子 SP1 和 CDX2 在 24 h 内没有表达变化; 此外, 调节 *Pept1* 的另一种转录因子过氧化物酶体增殖物激活受体 α (peroxisome proliferator-activated receptor α , PPAR α) 的缺乏虽然会降低 *Pept1* 的基础表达水平, 但对其每日表达没有显著影响^[56], 这表明它们可能不参与 *Pept1* 的昼夜节律调节。Okamura 等^[56]发现, *Dbp* (*D site of albumin promoter binding protein*) 的 mRNA 水平的日常节律与 *Pept1* 的 mRNA 的节律相似。此外, 该研究团队确定了 *Pept1* 远端启动子区域中的 DBP 结合位点, 并得出结论: DBP 可能有助于 *Pept1* 表达的节律性变化。另外有研究发现, 小鼠胃蛋白酶原的分泌在 24 h 内呈周期性变化, 在休息期间达到高峰^[57]。同样, 胰液的分泌在大鼠和猪中都有昼夜节律性^[58-59]。

2.4 离子吸收代谢的节律性和调节机制

结肠介导的电解质稳态受昼夜节律调节^[60]。结肠的主要功能是吸收水和电解质, Na⁺ 和 Cl⁻ 的吸收主要反映了两种转运体的活性, 一种是 Na⁺/H⁺ 交换器 (NHE), 另一种是 Cl⁻/HCO₃⁻ 交换剂 (anion exchanger protein, AE)。研究表明, *Nhe3* 和 *Ae1* 的表达具有昼夜节律, 此外, 参与 NaCl 吸收的其他关键转运蛋白和通道蛋白也受生物钟基因的调控, 如大鼠结肠黏膜钠钾 ATP 酶蛋白 A1 (*Atp1a1*)、

上皮钠离子通道蛋白 γ (*epithelial sodium channel gamma*, γ Enac)、下调式腺瘤载体(*downregulated in adenoma*, *Dra*)的 mRNA 表达均表现出昼夜节律变化^[61]。研究报道, 血浆醛固酮和 γ Enac 转录本之间的峰值水平具有相关性^[61], 这表明醛固酮可能在 γ Enac 的调节中发挥作用。此外, 参与 NaCl 吸收

的转运蛋白的表达可能直接受昼夜节律的控制, 有研究发现, CLOCK:BMAL1 异二聚体调控 *Nhe3* 启动子区域内的 E-box^[54]; 小鼠中 *Cry1* 和 *Cry2* 的双重敲除或 *Clock* 的突变均会使 *Nhe3* 的 mRNA 表达降低^[54]。总而言之, 生物钟参与肠道 NaCl 吸收, 对肠道运输具有重要作用。

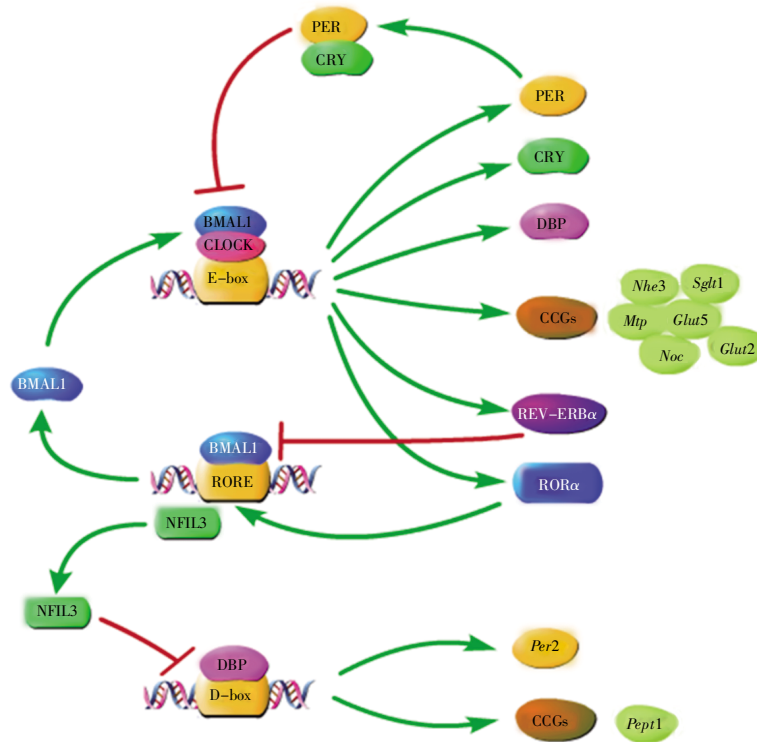


图 1 调节营养物质代谢的生物钟机制

CLOCK:BMAL1 异二聚体与启动子中的 E-box 元件结合激活 *Per* 和 *Cry* 基因的转录。PER 蛋白和 CRY 蛋白形成复合物并抑制 CLOCK:BMAL1 异二聚体的活性, 从而抑制其自身表达。CLOCK:BMAL1 异二聚体也激活核受体 REV-ERB α (reverse erythroblastosis virus α) 和视黄素受体相关的孤儿受体 α (retinoid-related orphan nuclear receptor α , ROR α) 的转录, 这些转录因子竞争性地结合 *Bmal1* 和核因子白介素 3 (*nuclear factor interleukin 3*, *Nfil3*) 启动子中的 RORE 反应元件 (RORE 激活 BMAL1 和 NFIL3 的表达, 而 REV-ERB α 抑制 BMAL1 和 NFIL3 的表达)。NFIL3 和 DBP 共同调节 D-box 启动元件 (NFIL3 负向调节, DBP 正向调节), 这两种因子协同 D-box 调控 *Per2* 基因的表达, 也调节时钟控制基因 (clock-controlled genes, CCGs), 使 CCGs 的表达具有昼夜节律。此外, CLOCK:BMAL1 异二聚体还调节参与营养物质代谢的 CCGs 的昼夜节律表达。例如: BMAL1 与己糖转运蛋白编码基因 *SglT1*、*Glut2* 和 *Glut5* 的启动子结合, 参与糖代谢; CLOCK:BMAL1 异二聚体有节奏地激活 SHP, 从而使 SHP 抑制 *Mtp* 的表达, 参与脂代谢; CLOCK:BMAL1 异二聚体与 *Noc* 转录起始位点上游的 E-box 结合, 参与脂代谢; CLOCK:BMAL1 异二聚体反式激活 *Nhe3* 启动子中的 E-box 序列, 调节机体蛋白质代谢。

Fig.1 The biological clock in nutrient metabolism regulation

CLOCK:BMAL1 heterodimer combines with the E-box element in the promoter to activate the transcription of *Per* and *Cry* genes. PER and CRY proteins form complexes and inhibit the activity of the CLOCK:BMAL1 heterodimer, thus inhibiting its own expression. CLOCK:BMAL1 heterodimer also activate transcription of the reverse erythroblastosis virus α (REV-ERB α) and retinoid-related orphan nuclear receptor α (ROR α), which competitively bind the RORE response elements in the promoters of *Bmal1* and *nuclear factor interleukin 3* (*Nfil3*). RORE activates the expression of BMAL1 and NFIL3, while REV-ERB α inhibits their expression. NFIL3 and DBP adjust the D-box element (NFIL3 negative adjustment, DBP positive adjustment). These two factors cooperate with D-box to regulate the expression of *Per2* gene, and also regulate clock-controlled genes (CCGs), so that CCGs have the circadian rhythm of expression. Furthermore, CLOCK:BMAL1 heterodimer also regulates the expression of circadian rhythm of CCGs involved in nutrient metabolism. Here are some examples: BMAL1 binds to the promoters of *SglT1*, *Glut2*, and *Glut5*, participating in glucose metabolism; CLOCK:BMAL1 heterodimer activates SHP rhythmically, making SHP inhibit *Mtp* expression and participating in lipid metabolism; the heterodimer binds to the upstream E-box of *Noc* transcription start site, participating in lipid metabolism; the heterodimer transactivates the E-box sequence in the *Nhe3* promoter, regulating protein metabolism.

3 小结与展望

营养素的吸收代谢与昼夜节律联系密切, 昼夜节律可调控消化道多种营养素的吸收及其相关转运蛋白的表达(图 1)。从目前研究结果来看, 生物钟与消化道营养代谢的互作调控机制没有形成网络联系, 主要体现在以下几个方面: 1) 影响机体生物钟节律的营养水平、营养代谢产物及参与营养吸收代谢的酶还需进行探索; 2) 节律基因调控营养物质吸收代谢相关因子的位点鉴定尚不能确定; 3) 生物钟基因在转录、翻译等不同水平上对消化道的调控机制还不清楚; 4) 不同动物上的研究尚不系统。因此, 未来应从以上几个方向着手进行深入研究, 以了解更多营养物质吸收代谢过程中昼夜节律调节的分子机制。

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