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评 述

色氨酸代谢调控昼夜节律的作用机制研究进展

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摘要 昼夜节律对于调节生物体的行为、器官和细胞正常运行具有至关重要的作用. 当昼夜节律紊乱时, 可能会导致抑郁、严重失眠和狂躁等一系列疾病的发生, 从而危害人类健康. 许多研究表明, 色氨酸及其代谢物对生物昼夜节律紊乱导致的精神疾病、肝功能以及代谢功能障碍等慢性疾病具有良好的疗效. 本文简要综述色氨酸及其代谢物与生物昼夜节律的联系, 并重点解析色氨酸代谢调控生物昼夜节律的作用机制以及其在昼夜节律紊乱中的潜在作用, 以期为色氨酸及其代谢物防治常见昼夜节律相关疾病提供新的思路和依据.

关键词 色氨酸, 昼夜节律, 生物钟, 色氨酸代谢物

1729年, 法国科学家de Mairan利用暗箱观察含羞草24小时的持续变化, 发现内源时钟的存在[1], 并提出昼夜节律是一种内源性自我维持的模式[2]. 20世纪30年代, 德国生物学家Erwin也确定植物的光周期时间为24.4小时, 进一步证实内源时钟的存在[3]. 1971年科学家们利用黑腹果蝇等模式动物对昼夜节律开展经典遗传研究, 发现基因*per*可影响果蝇的生物钟[4]. 但直到1994年通过对小鼠采用正向遗传学方法才发现第一个哺乳动物生物钟基因-CLOCK, 并于1997年在哺乳动物上发现*Per*基因, 随后系统分析其对哺乳动物昼夜节律的调控作用[5~7]. 近年来, 昼夜节律功能障碍所引发的一系列健康问题越来越受到广泛的关注, 特别是对其引发的代谢综合征、心血管疾病、糖尿病和癌症[8]以及伴随着的人类睡眠障碍、重度失眠和重度抑郁症(major depressive disorder, MDD)等相关疾病[9]进行大量研究. 在临床治疗上, 强光治疗和外源性褪黑素(melatonin, MT)给药被认为是昼夜节律紊乱的首选治疗方法[10]. 强光治疗的持续时间很短, 而且会出现眼部疲劳和头痛[11], 而外源性MT给药耐受性良好, 但其效果可能会因患者持续产生内源性MT而降低[12]. 目前有许多研究表明, 可通过改善强光治疗的持续时间或研发新的MT受体激动剂及新药物来治疗昼夜节律紊乱[13,14], 但还需在临床实践上进一步验证.

色氨酸(tryptophan, Trp)作为MT前体物质, 是一种重要的必需氨基酸[15], 机体可通过不同的代谢途径在调控肠道免疫功能、维持肠道微生物稳态和促进神经系统发育等方面发挥重要作用[16~19]. 研究发现无Trp

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饮食会扰乱昼夜节律功能[20]，也有研究表明Trp/大中性氨基酸比率对睡眠和昼夜节律有一定的影响[21]. Trp代谢可通过调节肠道微生物群影响肠道健康[15,22]，而肠道微生物群又可作为Trp代谢和摄食的传感器进而调节动物昼夜节律[23]. 由此可见，Trp及其代谢物在维持昼夜节律和改善昼夜节律紊乱上有着重要作用. 然而，目前鲜有Trp调节昼夜节律相关研究的综述. 因此，本文对Trp及其代谢物与昼夜节律的联系进行综述，重点阐述其对昼夜节律的调控作用及相关分子机制，以期为在防治昼夜节律紊乱相关疾病中的药物开发和应用提供理论参考.

1 昼夜节律系统及其紊乱对机体的危害

1.1 昼夜节律调控系统

昼夜节律是生物钟的一种表现形式，是生物体在24小时周期内生理和行为活动的重复变化. 这些变化包括睡眠-清醒周期、体温调节、激素分泌、饮食行为等, 它们与外部环境的昼夜变化密切相关. 这种节律可保障生物功能规律与可预测的环境模式保持一致, 使生物适应不同环境且具有灵活性，并更好地利用不断变化的环境资源，以优化功能和健康[24]. 地球上的生物为适应这一过程演化出一个重要的调控系统，即生物钟[25].

哺乳动物昼夜节律系统是由位于下丘脑的视交叉上核(suprachiasmatic nucleus, SCN)和众多生物钟一同构成的，生物钟通过内部基因的表达和反馈来进一步调节昼夜节律系统(图1)[26]. 昼夜节律的生物钟调控系统是基于一组时钟基因*CLOCK*/*BMAL1*构建的转录-翻译反馈环路[27]，*BMAL1*与*CLOCK*形成异二聚体，它们通过与E-box增强子基元结合，共同驱动三个*Period* (*Per1*，*Per2*和*Per3*)和两个*Cryptochome*基因(*Cry1*和*Cry2*)的转录[28]. *Per*和*Cry*基因被翻译后形成二聚体，当*Per*和*Cry*蛋白积累过多时，会反过来抑制基因*CLOCK*和*BMAL1*介导的转录[29]. 当*Per*和*Cry*开始降解时，对转录的抑制作用开始减弱，整个生物钟的循环便再次开启[30]. 除这种核心时钟，还有其他调节机制，其中一个是通过类维生素A相关孤儿受体(ROR*a*, *b*，*c*)的转录激活和核受体REV-ERB(*α*，*β*)的抑制产生[1,31]. REV-ERB通过与*BMAL1*启动子区域中的受体相关孤儿受体反应元件ROR结合，再通过RORE元件以竞争方式调控*BMAL1*的表达，以确保昼夜节律系统的微调[32]. 研究表明，动物的许多行为、生理和生化过程，如睡眠-觉醒周期、运动活动节律、体温波动以及免疫和内分泌功能[33]等均与昼夜节律息息相关，因此昼夜节律系统的稳定与生物体组织器官代谢的正常运行具有很强的互作效应.

1.2 昼夜节律紊乱对人体健康的危害

在人类生理学和病理学中，昼夜节律的稳定越来越重要. 但由于人们习惯性地参与到诸如夜间工作安排、跨时区旅行以及异常光周期等扰乱内源性节律及相关生物过程的情况中[34]，从而导致昼夜节律紊乱. 昼夜节律紊乱已被证实有损人体健康，甚至患相关神经性疾病的几率也会增加[35]. 患有神经性疾病或精神障碍的病人，还可能因昼夜节律异常而病情加剧[36]. 双向情感障碍(bipolar disorder, BD)等神经疾病与昼夜节律系统的不稳定息息相关，且还可能导致肥胖与神经认知障碍[37]; 在BD患者中, 还发现异常睡眠与昼夜节律紊乱之间存在重叠，睡眠异常导致昼夜节律不稳定和社会心理功能恶化[38].

昼夜节律紊乱可引起一系列代谢和免疫功能紊乱, 从而引发糖尿病、肥胖等代谢性疾病的发生, 甚至促进肿瘤的发展[39]. 例如，当敲除小鼠的肝细胞特异性功能基因*Clock*时，小鼠葡萄糖糖稳态失衡，出现过度肥胖症状[40]，这可能是由于昼夜节律紊乱引起的睡眠结构改变，包括夜间后半段快速动眼期睡眠持续时间相对较短，进而导致皮质醇浓度升高和胰岛素敏感性降低[41]，从而使体重飙升. 作为昼夜节律调控系统主体之一的*BMAL1*可以调节线粒体能量代谢，维持正常的胰岛素分泌[42]，当*BMAL1*缺失时会增加线粒体解偶联，这反过来又损害葡萄糖诱导的线粒体膜电位产生、ATP合成和胰岛素分泌，从而诱发糖尿病[43]. 在临床调查中发现，轮班工人发生代谢综合征、骨折和骨质疏松症等疾病的几率增加[44]，这也是因为昼夜节律紊乱导致葡萄糖代谢受损，从而引起骨骼能量代谢减少，最终抑制骨骼的发育和生长[45]. 夜间光照引起的昼夜节律紊乱可能还会对肿瘤的发展产生不利影响，其中昼夜节律调控系统的基因功能受损可能是主要原因[46,47]. 动物实验也证实，昼夜节律生物钟的生理扰动和遗传破坏都会促进肿瘤的生长和进展[48,49]. 也有研究表明，长期从事夜班工作(即超过8年)会使乳

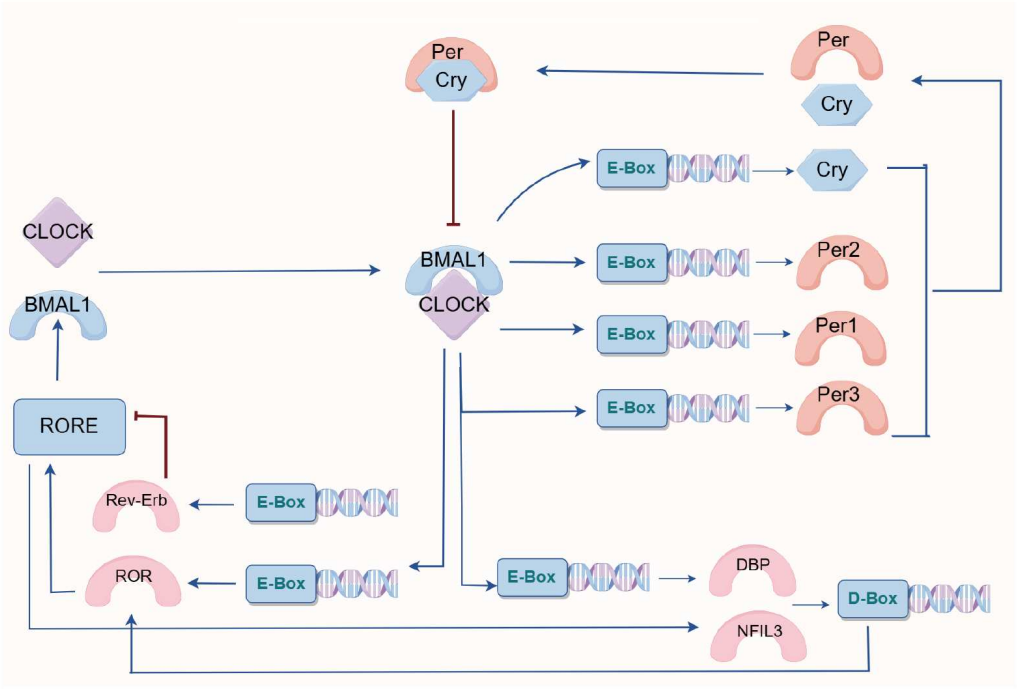

图 1 哺乳动物体内昼夜节律分子机制
Figure 1 Molecular mechanism of circadian rhythm in mammals

腺癌发病率提高114.15%[50]，且还可能导致男性的生育能力下降[51]. 在产后早期出现的母乳喂养时间较短的问题也是基于昼夜节律系统的紊乱，并且还对荷尔蒙的代谢产生负面影响[52]. 最新研究还发现血压与内源性昼夜节律系统耦合并同步，血压昼夜节律紊乱可诱发左心室肥厚和左心房扩大[53]，这或许是老年人夜间易产生高血压的原因之一[54].

2 色氨酸及其代谢物与昼夜节律的联系

Trp在生物体内的代谢途径大致分为三种: 犬尿氨酸(kynurenine, KYN)途径、5-羟色胺(5-Hydroxytryptamine, 5-HT)途径和微生物途径(图2)[16]. 其中生物体内大多数的Trp主要通过KYN途径，在色氨酸2,3-双加氧酶和吲哚2,3-双加氧酶(indoleamine 2,3-dioxygenase, IDO)的作用下分解为犬尿酸、喹啉酸(quinaldinic acid, QA)和烟酸等物质, 这既是Trp的降解途径也是合成途径. 5-HT途径则是Trp在色氨酸羟化酶(tryptophan hydroxylase, TPH)的作用下转化为5-羟基色氨酸(5-hydroxytryptophan, 5-HTP), 5-HTP然后被L-芳香族氨基酸脱羧酶转化成5-HT[55]. 芳基烷基胺-N-乙酰转移酶在血清素向N-乙酰血清素的转化中起着关键作用，最后在N-乙酰血清素O-甲基转移酶催化N-乙酰血清素下产生MT[56,57]. 此外，可能有部分未被完全消化吸收掉的Trp通过微生物途径, 在肠道菌群的作用下分解为吲哚一类的物质[58].

昼夜节律与Trp代谢是相互影响的. 研究表明，脑脊液中的Trp浓度随昼夜节律变化而变化, 其浓度在晚上11点至午夜之间达到最高, 之后在早上稳定下降, 最低水平出现在下午[59]. 吡啶甲酸(picolinic acid, PIC)是L-Trp通过KYN途径的侧支合成, 在中枢神经系统中具有神经保护和抗增殖作用[60]，其合成和分解代谢受日常生物节律的影响, 浓度变化与脑脊液中的Trp波动一致[61]，而PIC的昼夜波动也可能减弱炎症介导的KYN途径的活化[62]. 昼夜节律的中枢生物钟SCN可调节松果体中MT合成以及各种生理、内分泌和行为功能[63]. 当体内5-HT含量降低时, 睡眠-觉醒周期和运动活动的昼夜节律消失, 并被分成几分钟的超常交替, 导致产生睡眠障碍、抑郁和焦虑[64]，而由5-HT转化而来的MT可影响海马体中5-HT神经传递的昼夜节律[65].

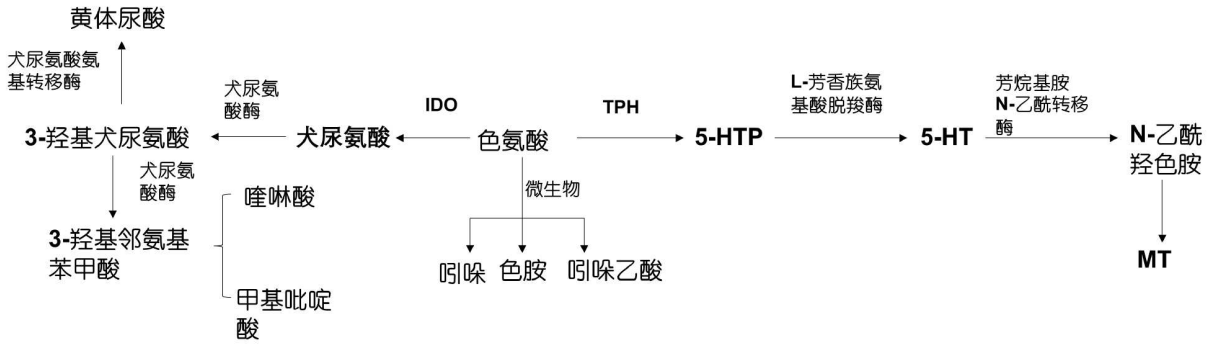

图 2　色氨酸代谢途径
Figure 2　Tryptophan metabolic pathway

3　色氨酸代谢对昼夜节律的调控机制

3.1　犬尿氨酸途径对昼夜节律的调控机制

KYN途径对昼夜节律的调控机制如图3所示. 6-甲酰吲哚醇[3,2-b]咔唑(6-Formylindolo [3,2-b] carbazole, FICZ)作为Trp的光产物之一，对芳香烃受体(aryl hydrocarbon receptor, AhR)具有高亲和力, 并被假定为内源性配体[66]. AhR被证明是昼夜节律计时系统的一部分，在昼夜节律中发挥着重要作用[67]，这是因为生物钟基因*BMAL1*的剪切模式与AhR十分地接近，两者在一定条件下可形成新的二聚体[68]. Trp的光产物FICZ增加的细胞色素P4501A1酶(cytochrome P450 1A1 enzyme, CYP1A1)的表达可以通过触发AhR信号来调节昼夜节律的光依赖性[69]，而光照的扰乱会使生物昼夜节律紊乱, 导致生物睡眠时间和质量下降[70]，表明Trp光产物可以影响因光照引起的昼夜节律紊乱. AhR和芳香烃受体核转位因子(aryl hydrocarbon receptor nuclear translocator, ARNT)以及BMAL1和CLOCK蛋白, 都是PAS结构域家族的成员[68,71]. 异二聚体AhR/ARNT和CLOCK/BMAL1复合物是规范复合物，但AhR蛋白可以通过其PAS结构域与 BMAL1 蛋白结合形成其他的复合物[72]. 当*Per*基因遭受破坏时，会改变乳腺中的AhR信号通路[73]，说明AhR信号通路与昼夜节律存在一定的联系，AhR信号可以干扰昼夜节律, 生物钟也能调节AhR蛋白的表达. 研究表明, 用β-萘黄酮处理小鼠肝癌细胞可诱导AhR/BMAL1复合物的形成降低CLOCK/BMAL1复合物的水平，当AhR信号激活时，诱导剂β-萘黄酮也会抑制SCN和肝脏中*Per1*基因的光诱导转录[74]. 所以AhR信号的激活可以使CLOCK蛋白从*Per1*基因的启动子中移开，从而抑制CLOCK/BMAL1诱导的*Per1*启动子的反式激活[75]. Ah受体是一种配体调节的转录因子，是多种环境毒素的主要环境传感器，例如2,3,7,8-四氯二苯并对二噁英(2,3,7,8,-tetrachlorodibenzo-p-dioxin，TCDD)和多环芳烃(polycyclic aromatic hydrocarbon，PAH)化合物[76]. 当AhR信号受到TCDD刺激开始传导时，TCDD会抑制*BMAL1*, *Per1*, *Per2*和*Cry1*基因的表达, 降低昼夜节律的频率[77]. TCDD的使用还会抑制小鼠卵巢中*BMAL1*转录本的表达，而当AhR蛋白与BMAL1蛋白相互作用, TCDD处理后抑制相互作用增强[78]. 最新研究证明AhR蛋白在其启动子序列上会与昼夜节律驱动的E-box结合，从而抑制昼夜节律，进而抑制许多脂解基因的转录[79].

昼夜节律还会受到动物炎症状态的影响，在KYN整个途径中，Trp在IDO的作用下分解为次级代谢物, 并激活AhR通路[80]. 而IDO本身便是一种炎症激活剂, 当KYN途径激活时，IDO信号通路也会导致炎症. 最新的研究也表明昼夜节律 IDO1介导的犬尿烯的产生有助于在一天中的特定时间促进免疫抑制机制，从而调节宿主免疫反应[81].

促炎细胞因子白细胞介素-1 (interleukin-1，IL-1)会通过核因子κB (nuclear factor kappa-B, NF-κB)依赖性通路破坏软骨中的昼夜节律基因[82]. 当小鼠发生炎症时会促进血清促炎细胞因子的表达，从而抑制肝时钟基因的表达[83]. 研究表明CLOCK蛋白可用作激活NF-κB途径的正调节因子[84]. 当受外界刺激，动物体内发生炎症时，昼夜节律时钟基因*CLOCK*, *BMAL1*, *Per1*和*Cry1*mRNA水平降低[85]，导致昼夜节律紊乱.

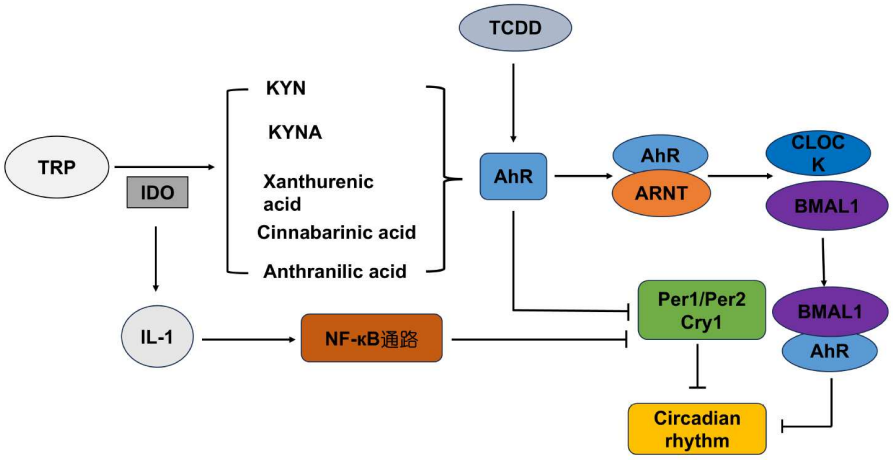

图 3 犬尿氨酸途径对昼夜节律的调控机制
Figure 3 Regulation mechanism of kynurenine pathway on circadian rhythm

同时炎症的发生会抑制*BMAL1*的转录, 促进*Clock*的释放, 后者会进一步加强炎症反应, 破坏昼夜节律[86]. 所以KYN通路可能还会通过IDO信号通路的激活导致炎症反应, 从而影响昼夜节律.

总之, AhR信号通路的激活通过干扰昼夜节律生物钟核心时钟蛋白和抑制其反式激活功能和影响与昼夜节律相关的调控系统, 从而使昼夜节律紊乱; KYN途径产生的大量代谢物是Ah受体的有效内源性激动剂[87,88], 并且该途径上的分解酶IDO也能促进炎症的发生, 通过NF-κB通路来使昼夜节律紊乱. 最新的实验结果也证明KYN途径的Trp代谢物能调节小鼠SCN和肝脏中生物钟的节律性[89]. 即KYN途径的Trp代谢物能通过IDO1-KYN-AhR信号通路来调控昼夜节律.

3.2 5-羟色胺途径对昼夜节律的调控机制

神经递质5-HT又名血清素, 其可通过Trp羟化酶2酶(Tryptophan hydroxylase 2, TPH2)在大脑中产生, 并转化为MT. MT可主要作为神经递质参与昼夜节律、喂养、性行为以及情绪调节[90]. 中脑中缝复合体(mid-brain raphe complex)是SCN的主要传入投射, 而中脑中缝核分别由中缝背核(dorsal raphe nucleus, DRN)和中缝中核(median raphe nucleus, MRN)组成[91]. 有研究表明, 这个部位是大脑中最密集的5-HT神经丛之一[92], 而SCN又是昼夜节律的主体之一, 因此, 5-HT调控系统被认为是哺乳动物中枢神经系统结构中最复杂和最广泛的[93]. SCN通过接受来自MRN的直接血清素能神经支配, 以及来自突触间的间接DRN驱动的神经肽Y输入, 进而通过下丘脑背内侧投射向这些中脑血清素能核进行多突触输出[94]. 此时, 5-HT便可与神经肽Y一起调节昼夜节律系统对光的反应, 以及通过行为唤醒和来自运动活动的反馈分别调节中央时钟的周期和相位变化[95]. 这表明5-HT既可在突触前作用于视网膜传入神经末梢, 又可在突触后作用于SCN神经元, 来抑制视网膜对中枢生物钟的输入, 从而调节生物的昼夜节律[96].

研究表明, 来自血清素信号网络的信号分子, 如5-HT_{1B}, 5-HT_{1A}和5-HT_{2C}受体等[95], 它们会在SCN核中表达, 通过引起膜的超极化以及动物细胞的去极化来促进觉醒和抑制快速眼动睡眠[97], 从而介导血清素调节昼夜节律功能. 反过来, 生物钟基因网络也可以在5-HT的中缝神经元中表达, 并且昼夜节律还可调节关键5-HT基因的活性[98]. 作为5-HT产物之一的MT也早已被证明是调节昼夜节律的主要因子之一[99]. MT主要通过激活MT1受体调节*Per*基因来增强生物钟振荡幅度和MT2受体实现生物钟同步来增加睡眠倾向以及维持昼夜节律[100,101]. 体外研究表明, 小鼠松果体中的mPER1蛋白是在去甲肾上腺素-环腺苷酸(cylic amp, cAMP)-cAMP反应元件结合蛋白(cAMP response element-binding protein, CREB)级联反应这一信号通路激活后诱导的, 并且mPER1可能在小鼠松果体中参与体内调节节律性细胞反应[102]. 在这个基础上, Lorsung等

人[103]发现MT与MT1和MT2的结合通过抑制腺苷酸环化酶使cAMP含量下降, 从而降低蛋白激酶A (Protein Kinase A, PKA)的水平来间接调节时钟基因表达. 此外, MT1和MT2的结合还会抑制CREB的磷酸化[104], CREB抑制同样导致时钟蛋白PER1和PER2的表达降低, 减弱生物钟的光导引[105]. 这也是哺乳动物在夜晚体内MT释放增加, 从而引发睡眠倾向的原因之一[104]. 也有研究表明, MT还可以激活γ-氨基丁酸(γ-aminobutyric acid, GABA)合成酶, 增加下丘脑GABA的含量[106]. GABA作为哺乳类动物中枢神经系统的一种重要的神经递质, 可以缩短哺乳动物的睡眠潜伏期, 同时延长哺乳动物睡眠持续时间[107], 故MT可以通过GABA受体来调节动物的睡眠与觉醒[108], 但目前关于动物体内GABA影响昼夜节律的作用机制尚不清楚, 需要后期进一步地深入探索.

3.3 微生物途径

当部分未被吸收完全的Trp在经过大肠的微生物群时, 被分解为吲哚及其衍生物[17]. 虽然微生物途径调节昼夜节律的机制还不太明确, 但已有很多研究证明Trp涉及的微生物途径拥有调节并维持昼夜节律的功能[109~112]. Trp通过肠道微生物群代谢产生的一些吲哚分子具有神经保护和抗氧化等特性[113], 不但可保护微生物群稳态的同时, 还能有助于调节与年龄相关的衰老和神经衰退性疾病的发生发展[114]. 吲哚是脑肠轴的重要介质, 并且在中和自由基方面, 部分吲哚物质的效率至少是褪黑激素的两倍, 所以在调节昼夜节律这一方面可能效果更显著[115].

Trp代谢也可直接或间接调节肠道微生物的组成[17,116], 如通过不同饮食改变肠道微生物群可以影响动物的中枢和外周生物钟功能, 从而调节昼夜节律[23]. 在无菌小鼠的体内, *REV-ERBα*的表达会增加, 从而降低其竞争性时钟调节器RORα与RORE的结合并影响*BMAL1*时钟基因的微调[117], 且肝脏昼夜节律基因*BMAL1*和*Per1*的表达还受微生物衍生的短链脂肪酸(Short chain fatty acid, SCFA)丁酸盐的调节[118]. Ghare等人[119]研究发现, Trp可通过保护肠道屏障功能来调节肠道微生物群组成, 促进短链脂肪酸的合成[120], 且发现丁酸盐的含量还与Kyn/Trp比率呈负相关. 这些结果表明, 一方面, Trp可以通过调节肠道微生物的组成来调节肠道功能, 另一方面, 肠道微生物所产生的Trp及代谢物、神经递质和细胞因子等亦可通过迷走神经或免疫系统作用于相应的神经元, 从而影响昼夜节律[8], 最近的研究也直接证明色氨酸代谢细菌显示出昼夜节律性[121]. 但是Trp-肠道微生物-昼夜节律这一信号通路是如何相互作用的还未可知, 需要进一步深入研究.

4 色氨酸代谢对昼夜节律紊乱的潜在应用

Trp及其代谢物对昼夜节律的调节作用是一把双刃剑, 虽然能在一定程度上改善昼夜节律, 但是也会在某些情况破坏昼夜节律的稳定. 因此, 研究者需要根据Trp代谢在这两个相反的作用中深入挖掘其潜在的调控靶点和剂量效应, 为治疗昼夜节律紊乱提供更多的科学依据. KYN途径的代谢物可以调节谷氨酸能神经传递, 也能通过N-甲基-D-天冬氨酸受体(N-methyl-D-aspartic acid receptor, NMDAR)的拮抗剂/激动剂活性发挥神经毒性/神经保护作用[122]. KYN途径的一些代谢物也具有促炎功能, 例如QA、3-羟基犬尿氨酸和3-羟基邻氨基苯甲酸[123], 会导致生物神经中枢系统遭受破坏, 轻度会使生物失眠和精神紊乱, 重则可能导致MDD. 而当老年人体内KYN/Trp的比例增加时, Trp的降解率也增加, 使大脑中的IDO含量增加, 从而导致炎症的发生[124], 这也是老年人易患精神疾病的原因之一. 有研究指出, MT和5-HT在调节食欲行为和情绪方面发挥着重要作用, 不仅可调节昼夜节律、行为、免疫反应和生殖功能[125], 还对BD患者的情绪症状有改善作用[126,127]. 因此外源MT可作为临床上治疗人类相关疾病的潜在药物[128].

Trp可以改善睡眠质量和减少睡眠潜伏期[129]. 补充1~5 g/d的Trp可降低睡眠潜伏期, 因其不会产生精神表现下降和不耐受等有害副作用, 所以可以作为慢性失眠症的催眠药[130]. 通过对小鼠的试验研究发现Trp代谢可以作为一种昼夜节律调节剂, 调节并维持昼夜节律[89]. 而且Trp代谢可以独特地调节多种认知障碍, 其代谢稳态对昼夜节律紊乱和免疫功能十分重要[131]. 总之, Trp在BD, MDD和注意缺陷多动障碍(attention deficit hyperactivity disorder, ADHD)这一类精神疾病中具有一定的效果, 这为治疗精神疾病提供一种新的思路[132]. 此外, IDO的小分子抑制剂可以重新编程生物炎症环境, 将“冷”肿瘤(非T细胞炎症性肿瘤)转变为“热”(T细胞炎症性肿瘤), 成为治疗癌症的新方

法[133]，这可能与IDO1抑制剂可以通过抑制KYN通路削弱免疫抑制功能，从而克服相关的免疫抵抗，并增强肿瘤免疫治疗相关[134].

5 总结与展望

昼夜节律对生物体生理稳态和健康至关重要. Trp作为机体必需氨基酸，一方面可以通过KYN途径调控AhR的活性和调节生物体内炎症反应进而调节昼夜节律；另一方面通过5-HT途径产生的MT来维持昼夜节律系统；也可以通过微生物途径来影响肠道微生物组成进而维持生物昼夜节律系统稳态. 目前大量研究重点关注5-HT途径产生的MT在昼夜节律中的作用. 然而, Trp及其他代谢产物与昼夜节律的关系及其调控机制尚不明确. 例如，Trp微生物代谢途径及其产物与昼夜节律系统的互作关系到底如何进行的？其直接或间接作用的分子机制又是什么？Trp及其代谢产物是否直接靶向生物钟振荡器而参与昼夜节律输出的调控，以及介导这一调控的具体分子机制是什么？对昼夜节律产生的众多积极影响是由Trp本身直接介导的还是由其代谢物介导的？昼夜节律与Trp相互调节、相互作用的靶点是什么？Trp及其代谢物作为靶向药物缓解昼夜节律紊乱的具体分子机制是什么，其优缺点又是什么？总而言之，对于Trp及其代谢物作为昼夜节律功能障碍进行靶向调控或防治将会成为未来研究的重点方向，以期为开发Trp及其代谢物作为防治常见昼夜节律相关疾病的药物提供新的科学思路和理论依据，从而改善人类健康.

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Research progress on the mechanism of tryptophan metabolism regulating circadian rhythm

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Circadian rhythms are essential for regulating the behavior of organisms and ensuring the proper functioning of organs and cells. Disruptions in circadian rhythms can lead to various disorders, including depression, severe insomnia, and mania, which pose significant risks to human health. Numerous studies have demonstrated that tryptophan and its metabolites are effective in treating chronic conditions associated with circadian rhythm disruptions, such as psychiatric disorders, liver dysfunction, and metabolic disturbances. This review provides an overview of the relationship between tryptophan and its metabolites and circadian rhythms, focusing on the mechanisms by which tryptophan metabolism regulates circadian rhythms and its potential role in circadian disorders. The aim is to offer new insights and evidence for the prevention and treatment of common circadian rhythm-related diseases using tryptophan and its metabolites.

tryptophan, circadian rhythm, circadian clock, tryptophan metabolite

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