·综述·

昼夜节律紊乱对星形胶质细胞功能的影响

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摘要 星形胶质细胞是中枢神经系统分布最广泛的一类细胞,具有神经支持、维持血脑屏障稳定、调节脑脊液循环及参与神经炎症等功能。研究表明,星形胶质细胞具有极强的昼夜节律,并参与自身功能的调节。本文总结了昼夜节律紊乱对星形胶质细胞功能的影响,重点讨论昼夜节律紊乱情况下,内淋巴循环障碍、神经元氧化应激与炎症、神经递质代谢异常以及突触功能改变,及其与神经退行性疾病之间的可能存在的联系。

关键词 昼夜节律;星形胶质细胞;神经退行性变

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Effects of Circadian Rhythm Disorder on Astrocyte Function *XU Ji-yan, PENG Liang-yu, GU Xiao-ping. Affiliated Drum Tower Hospital of Medical School of Nanjing University, Nanjing 210008, China*

Abstract Astrocytes are the most widely distributed cells in the central nervous system, which have the functions of neuronal transmission, nerve support, maintaining the stability of blood-brain barrier, regulating endolymphatic circulation and nerve inflammation. Recent studies have shown that circadian rhythms are involved in the regulation of these functions. Circadian rhythm disorder of astrocytes can lead to disturbance of endolymphatic circulation, abnormal accumulation of neurotransmitters and pro-inflammatory mediators, this in turn leads to impaired cognitive function and rhythm disorder.

Keywords circadian rhythm; astrocytes; neurodegeneration

昼夜节律又称近日节律,是指生命活动以24 h左右为周期的变动,哺乳动物的核心昼夜节律起搏器被确定为下丘脑视交叉上核(suprachiasmatic nucleus,SCN),以驱动行为节律[1]。在分子水平,昼夜节律振荡是由一组形成转录自动调节反馈环路的基因产生的,这些基因几乎在哺乳动物所有细胞中均有表达,包括:*Clock*、*Bmal1*、*PER1*、*PER2*、*Cry1*和*Cry2*,以及其他一些候选基因。反馈环路的核心是转录激活因子*Clock*和*Bmal1*,它们可以正向调节*Per/Cry*基因的表达,*Per/Cry*基因产物积累并形成复合物,该复合物再与细胞核中的*Clock*和*Bmal1*相互作用,抑制它们自身的转录[2]。最近有研究表明,星形胶质细胞表现出极强的昼夜节律,影响神经递质代谢、神经炎症反应和脑脊液循环[3]。

1 星形胶质细胞昼夜节律

仓鼠SCN中星形胶质细胞标志物胶质纤维酸性蛋白(glial fibrillary acidic protein,GFAP)分布的日变化是首次观察到的星形胶质细胞昼夜节律表现[4],随后,体外培养的星形胶质细胞表现出明显的*Per2*基因昼夜振荡,且与SCN共培养后可以协调其表达节律[5]。腺苷三磷酸(adenosine triphosphate,ATP)在星形胶质细胞外的积累也显示出昼夜节律[6],这种昼夜节律性的ATP释放依赖于星形胶质细胞*Clock*、*Per1*和*Per2*基因表达[7]。随着研究的深入,最近发现小鼠SCN区星形胶质细胞在夜间的时候明显活化,此时大量分泌的谷氨酸盐(glutamate,Glu)与N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid,NMDA)受体NR2C亚基结合,抑制神经元兴奋和SCN节律输出[8],并且在缺乏有效的神经元昼夜节律的调控作用下,星形胶质细胞可独自维持机体的昼夜节律[9]。特异性*Bmal1*敲除破坏了SCN星形胶质细胞的昼夜基因表达节律,并明显影响小鼠的行为节律[10]。此外,SCN中星形胶质细胞特有的酪蛋白激酶1ε(casein kinase 1 epsilon,CK1ε)突变也可导致星形胶质细胞每日节律丧失,并延长SCN昼夜节律周期[11]。肿瘤坏死因子-α(tumor necrosis factor alpha,TNF-α)通过调控星形胶质细胞*Per2*的表达引起昼夜节律。

2 星形胶质细胞昼夜节律影响脑脊液循环

神经退行性疾病的典型特征为β-淀粉样蛋白(amyloid β-protein,Aβ)、Tau蛋白等毒性蛋白在脑中聚集。Tau蛋白的堆积与阿尔兹海默症早期发病有关[13],其过度磷酸化和细胞内积聚,引起突触丢失,并最终导致神经退化和认知能力下降[14]。睡眠觉醒周期似乎可以调节脑脊液中Aβ和Tau蛋白的水平,在睡眠剥夺的小鼠脑脊液中Tau蛋白水平升高[15]。

传统观点认为脑内缺乏淋巴循环,后来证明大脑里存在一种称为“类淋巴系统”的液体转运途径,用于清除包括Aβ在内的代谢废物[16]。尽管动脉搏动、血压[17]和心率[18]都会影响类淋巴系统的功能,但研究发现星形胶质细胞终足上富含的水通道蛋白4(aquaporin 4,AQP4)才是维持该系统正常运行的关键,这些水通道集中在血管壁侧膜域,可以支持血管

周围液体和溶质沿类淋巴系统运动[19,20]。最先的研究认为睡眠状态可以引起类淋巴系统功能增强，是睡眠-觉醒状态本身决定了淋巴流动的快慢，昼夜节律并未参与其中[21]。但最近一项研究推翻了这个观点，该研究证实在恒定光照的条件下，小鼠的淋巴流入、溶质清除和脑脊液引流的昼夜差异持续存在；小鼠大脑皮质血管周围的AQP4极化存在昼夜振荡现象，且AQP4特异性敲除的小鼠丧失了脑脊液分布的昼夜调节[22]。此外，在Bmal1基因敲除的星形胶质细胞中，AQP4过度表达[23]。因此，昼夜节律对星形胶质细胞在类淋巴系统中功能起调节作用，节律紊乱可影响AQP4表达，进而引起代谢废物清除障碍。

此外，AQP4的表达极性在各种病理情况下明显改变。与认知功能正常老年人相比，AD患者血管周围AQP4的定位减少，并且这种减少与Aβ病理的增加密切相关[24]。脂多糖（lipopolysaccharide，LPS）诱导活化的星形胶质细胞上也发现了AQP4的表达极性受到明显影响[25]。另外，在促炎介质（TNF-α或LPS）的作用下，星形胶质细胞产生大量的基质金属蛋白酶3（matrix metalloproteinase 3，MMP3）[26,27]，而MMP3可以分解对维持AQP4表达极性极为重要的聚集蛋白[28,29]。由于昼夜节律紊乱除了是神经变性的症状外，还可能是患AD和其他神经退行性疾病的潜在风险因素[30]，改变AD患者AQP4表达极性的因素更加难以明确。

3 星形胶质细胞昼夜节律紊乱促进神经元氧化应激与炎症

神经元氧化代谢旺盛，产生大量有害的活性氧（reactive oxygen species，ROS），与神经退行性疾病密切相关。Keap1-Nrf2信号通路-通过中和ROS、控制线粒体氧化磷酸化等来发挥抗氧化作用[31,32]；但神经元转录因子E2相关因子2（NF-E2-related factor 2，Nrf2）活性较弱，需要依靠星形胶质细胞的Nrf2通路来调节自身谷胱甘肽的水平[33]。特异性敲除*Bmal1*基因可以诱导大脑活化的星形胶质细胞显著增多，引起抗氧化酶表达受损，进一步加重神经元氧化损伤[34]。此外，星形胶质细胞上神经营养素受体P57的表达存在昼夜波动，可以调节下游Nrf2信号和抗氧化酶的表达[35]。

神经炎症同样也是引起认知功能受损的重要因素。昼夜节律和炎症反应相互调节，首先，机体的炎症反应受到昼夜节律的调控，在小鼠活跃期开始时给予LPS诱导的细胞因子反应比在休息期给予的LPS更为严重[36]；相反，昼夜节律也受到炎症介质的影响，如TNF-α可以调控Per2的表达节律[37]。星形胶质细胞作为中枢神经系统主要免疫细胞之一，其免疫功能也受到昼夜节律调节。星形胶质细胞白细胞介素-1（interleukin-1，IL-1）、TNFα的分泌存在昼夜节律振荡[38]。时钟基因*Per1*的缺失可以引起脊髓星形胶质细胞趋化因子2（chemokines 2，CCL2）和IL-6表达增加[39]，而Bmal1缺失可以诱导皮质星形胶质细胞IL-6、IL-2的表达[23]。昼夜节律时钟成分Rev-erbα的缺失也可以通过小胶质细胞激活，引起继发性星形胶质细胞增生，加重神经炎症[40]。在神经退行性疾病背景下出现的昼夜节律紊乱，可能会加剧神经炎症引起的认知功能障碍，因此星形胶质细胞免疫和抗氧化系统的正常节奏振荡对于大脑健康运行至关重要。

4 星形胶质细胞节律紊乱引起神经递质代谢异常

在突触水平上，星形胶质细胞对神经递质（如Glu、ATP和GABA）代谢起关键作用，且可以通过胶质递质和神经递质与神经元进行交流，这种局部微结构被称为“三方突触”[41]。星形胶质细胞对Glu的摄取受到*Clock*和*Per2*基因的调节，虽然摄取没有表现出昼夜变化，但通过抑制*Per2*或*Clock*的表达，星形胶质细胞膜上Glu转运体EAAT1/2的表达明显受到抑制[42]。小鼠SCN中谷氨酰胺合成酶（glutamine synthetase，GS）的活性则表现出了明显的昼夜节律，在白天GS活性达到高峰，为神经元合成Glu提供更多的谷氨酰胺（glutamine，Gln）[43]。

如前所述，不管是SCN区还是体外培养的SCN星形胶质细胞外ATP的积累均呈现明显的昼夜节律性[6]，钟基因突变或IP3通路抑制可导致ATP释放节律改变[7]。此外线粒体Ca^{2+}信号也介导了节律性星形胶质细胞外ATP积累，线粒体内$[Ca^{2+}]_i$与细胞外ATP积累振荡节律一致[44]。

作为SCN主要神经递质之一，GABA对神经元同步和协调SCN背区和腹侧的昼夜节律信息起关键作用[45]。GABA及星形胶质细胞上GABA转运体（GAT3）在SCN区的表达均具有节律性[46]。敲除星形胶质细胞钟基因*Bmal1*可以导致GAT3表达减少，细胞间隙GABA增多，从而影响昼夜节律和认知功能[10]。随后的研究表明，*Bmal1*敲除小鼠表现出年龄依赖性星形胶质细胞变性，能量平衡改变及脑脊液中Glu和GABA水平升高，而抑制GABA信号传导可以恢复Glu水平，延缓星形胶质细胞活化并延长寿命[47]。

此外，星形胶质细胞对Glu、ATP和GABA的调节相互关联。当神经元过度兴奋释放大量的Glu时，星形胶质细胞上谷氨酸转运体被大量激活，将谷氨酸盐和Na^+一同转运至细胞内，增加的$[Na^+]_i$促使GABA转运体兴奋，将GABA放入细胞间隙，通过抑制作用防止神经元过度兴奋[48]。另外，GAT3的功能增加的时候，GABA大量转运入细胞内，引起Na^+/Ca^{2+}转运体兴奋，增加的$[Ca^{2+}]_i$促进ATP释放进入细胞间隙。后者则在ATP酶的作用下快速分解为腺苷，从而兴奋神经元上突触前A1受体，导致突触前Glu释放减少，抑制兴奋性突触后电流[49]。

5 昼夜节律调节星形胶质细胞对突触的塑造

星形胶质细胞与突触的日常相互作用对发育和疾病至关重要，星形胶质细胞可以将突触信息处理并整合到不同的可塑性反应中[50]。缺血性脑病中的星形胶质细胞参与了血管生成、神经发生、突触形成和轴突重塑，从而促进神经系统的恢复[51]。针对大鼠的研究发现，与夜晚相比，白天SCN中VIP神经元的星形胶质细胞覆盖率降低，这可能依赖于神经元亚型和BDNF/TrkB信号机制[52,53]；另一项研究表明，海马CA1区星形胶质细胞在昼夜节律的黑夜阶段精细突起的数量减少，并且星形胶质细胞突起与突触后致密区（postsynaptic density，PSD）之间的距离增加了两倍[54]。Bmal1缺失的年轻小鼠，覆盖在海马苔藓纤维

突触上的星形胶质细胞细小突起的体积分数减少，这些形态学改变可能导致突触功能改变，造成与节律紊乱有关的认知障碍[55]。另外AD患者β-淀粉样蛋白也可以损害星形胶质细胞对营养不良突触的吞噬作用[56]。因此，星形胶质细胞对突触的覆盖、吞噬是可塑的，可能受昼夜节律控制。

星形胶质细胞作为一类重要的神经支持细胞，多种疾病的发病机制均与其相关。本文总结了星形胶质细胞昼夜节律紊乱对自身功能的影响，这涉及到对神经元功能极为重要的神经递质和胶质递质的缓冲调节、AQP4分布异常导致的内淋巴系统功能障碍、协助神经元抗氧化障碍、促进神经炎症以及星形胶质细胞突起对突触覆盖率降低等。在神经退行性疾病中，昼夜节律紊乱导致的以上功能障碍扮演了极为重要的角色。因此，更充分地了解昼夜节律对星形胶质细胞的影响将会为神经退行性疾病提供更多治疗思路。

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（本文编辑：王晶）

（上接第139页）

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