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下丘脑星形胶质细胞与代谢稳态

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摘要 下丘脑作为中枢神经系统调控能量代谢的核心, 在维持机体代谢稳态中扮演着至关重要的调控角色. 星形胶质细胞是中枢神经系统中最主要的神经胶质细胞, 具有多种关键生理功能, 在神经系统的发育、稳态维持和功能调控中发挥核心作用. 而下丘脑星形胶质细胞在神经代谢调控中呈现出双重特性: 一方面参与生理性代谢调节, 另一方面介导神经元功能障碍与代谢性疾病(如肥胖)之间的病理联系. 最新研究发现, 下丘脑星形胶质细胞具有精密的营养感知系统, 能够灵敏地响应外周代谢信号(包括激素波动和营养状态变化), 并通过释放神经活性物质精细调节下丘脑神经元网络功能, 从而精确调控全身代谢平衡. 值得注意的是, 在营养过剩状态下, 下丘脑星形胶质细胞会发生显著的功能重塑, 成为触发下丘脑低度炎症反应并促进肥胖发生发展的关键效应细胞. 本文基于最新研究进展, 系统阐述了下丘脑星形胶质细胞在代谢调控中的生理和病理生理学机制, 重点探讨了该类细胞在代谢稳态维持和代谢紊乱进程中的双向调控作用及其潜在的分子机制.

关键词 下丘脑, 星形胶质细胞, 神经元, 代谢稳态, 肥胖

中枢神经系统, 特别是下丘脑在调控机体代谢稳态方面起着关键作用[1]. 全基因组关联研究显示, 绝大多数与极端肥胖相关的基因均与下丘脑中密切相关[2,3]. 下丘脑可感应由脂肪组织、肝脏、胰腺和胃肠道等外周器官释放的循环营养物质、代谢物和激素, 将这些代谢信息整合并传递至下游神经环路, 调节食物摄入、葡萄糖代谢和血压等生命活动的动态平衡, 以维持机体的能量和代谢稳态[4]. 下丘脑由多个核团组成, 其中位于下丘脑基底部的弓状核(arcuate nucleus, ARC)位置靠近血脑屏障(blood-brain barrier, BBB)较为薄弱的正中隆起(median eminence, ME)[5]. ME是一种具有特殊血管结构的室周器官(即缺乏血脑屏障的有孔微血管), ME的有孔毛细血管允许外周信号转运到下丘脑的核团[6], 因此靠近ME的ARC能够较早感知循环中营养素与激素的变话, 进而整合信号并协调全身能量平衡[7,8]. ARC中存在两个特征明确、相互关联且功能拮抗的神经元群体协同调节食欲和稳态进食: 表达神经肽Y和刺鼠相关蛋白(neuropeptide Y/agouti-related protein, NPY/AgRP)的神经元, 其激活可促进食欲并减少能量消耗[9,10]; 以及表达前阿片素和可卡因-苯丙胺相关转录物(pro-opiomelanocortin/cocaine and amphetamine-regulated transcript, POMC/CART)的神经元, 其激活可以抑制食欲并增加能量消耗[11,12]. 下丘脑POMC/CART神经元可加工生成α黑素细胞刺激素(α-melanocyte-stimulating hormone, α-MSH), α-MSH可以作用于表达黑素皮质素4受体(melanocortin 4 receptor, MC4R)的神经元, 特别是位于室旁核(paraventricular hypothalamus nucleus, PVH)的神经元, 进而抑制食欲并促进产热[13]. AgRP神经元释放AgRP神经肽可以与MC4R结合, 拮抗α-MSH与MC4R的结合[14]. AgRP神经元同时可以释放γ-氨基丁酸(γ-aminobutyric acid, GABA)以抑制POMC神经元的活性[15]. 由POMC、α-MSH、AgRP

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以及MC4R构成的黑素皮质素系统在能量平衡中具有重要的作用[16]. POMC与MC4R突变是单基因型肥胖的常见原因[17], 并与人类早发性严重肥胖有关, 这突显了黑素皮质素依赖性控制进食的重要进化作用.

星形胶质细胞作为中枢神经系统(central nervous system, CNS)中数量最庞大的胶质细胞群体, 传统上被认为主要发挥结构性支持及神经保护作用. 然而, 近年来的研究进展彻底革新了这一认知, 揭示其在神经系统中具有极其广泛的功能多样性. 大量证据表明, 星形胶质细胞不仅参与神经发生、神经元发育和神经保护等基础过程, 还在突触形成、突触可塑性调节以及神经递质动态平衡等高级神经活动中发挥关键作用[18,19]. 这些功能的实现依赖于其表面表达的多种激素受体、生长因子受体及神经肽受体系统[20~22]. 在代谢调控方面, 星形胶质细胞具有双重功能: 一方面作为血脑屏障的重要组成部分, 调控营养物质和生物活性分子的跨屏障转运; 另一方面通过糖原储存与代谢维持CNS的能量稳态[23,24]. 特别值得注意的是, 下丘脑ARC区域的星形胶质细胞与局部神经元及血管系统形成高度特化的功能单元. 这种独特的解剖学定位使其能够实时监测机体的代谢状态, 并通过动态调节血管通透性来控制外周代谢信号的选择性中枢传递, 从而成为神经内分泌调控的关键节点[25,26]. 研究表明, 下丘脑星形胶质细胞能够精确感知循环中的激素和营养信号, 并通过与神经元的协同作用调控代谢应答[21,27,28]. 但在营养过剩的病理状态下, 细胞会经历显著的功能重塑, 直接参与代谢紊乱的早期发生过程[26,29,30]. 饮食诱导的肥胖模型研究显示, 下丘脑星形胶质细胞会出现明显的反应性增生现象. 虽然这种增生最初可能代表一种神经保护性适应反应, 但长期持续则可能诱发下丘脑低度炎症, 最终导致不可逆的代谢调控障碍[31,32]. 这些发现为理解代谢性疾病的神经机制提供了新的理论视角.

鉴于下丘脑星形胶质细胞在代谢稳态调控中兼具生理性和病理性双重作用, 本文拟从以下维度展开系统性综述: 首先, 探讨星形胶质细胞介导的下丘脑炎症反应机制及其在代谢紊乱中的关键作用; 其次, 解析该类细胞感知外周激素和营养信号的分子途径及其代谢调控网络; 再次, 阐明星形胶质细胞通过神经递质释放调控神经元活性的细胞间通讯机制; 最后, 整合现有证据, 深入剖析星形胶质细胞-神经元功能耦联失调在代谢性疾病发生发展中的病理生理学意义. 通过多角度整合分析, 旨在为代谢调控的神经胶质机制提供新的理论框架和研究方向.

1 星形胶质细胞与下丘脑炎症

肥胖不仅是脂肪组织的异常堆积, 更是一种慢性低度炎症状态, 与多种代谢性疾病的发生发展密切相关. 研究发现, 肥胖个体的脂肪组织(尤其是内脏脂肪)中存在显著的免疫细胞浸润, 它们分泌大量促炎因子, 如肿瘤坏死因子α (tumor necrosis factor-α,TNF-α)、白细胞介素6 (interleukin-6, IL-6)、单核细胞趋化蛋白-1 (monocyte chemotactic protein 1, MCP-1), 导致系统性炎症反应. 值得注意的是, 肥胖引起的中枢神经系统炎症因子上调会先于脂肪组织等外周部位出现, 肥胖发展的病理生理机制之一是高脂饮食(high-fat diet, HFD)所诱导下丘脑微炎症, 高脂饮食喂养可显著增加啮齿动物下丘脑中IL6、白细胞介素1β (interleukin-1β, IL1β)和转化生长因子-β (transforming growth factor-β, TGF-β)等炎症因子的信使核糖核酸(messenger RNA, mRNA)表达. 这些炎症因子在下丘脑的增加均被证明可直接影响代谢信号传导. 小鼠在使用肥胖诱导炎症中观察到的水平相似的剂量给予TNF-α会促进食欲亢进并减少能量消耗[33,34]. 中枢给予TNF-α抗体可减少体重增加、脂肪酸诱导的IL-1β表达以及饮食诱导的胰岛素抵抗[35]. 阻断下丘脑IL-1β的表达增加可改善高脂饮食相关的葡萄糖代谢损伤[36]. 向下丘脑或中枢神经系统给予IL-6可减少食物摄入、体重和体脂, 并增加能量消耗. 敲低下丘脑的TGF-β表达可降低体重和下丘脑炎症标志物[37]. 其中下丘脑神经元中的核因子κB (nuclear factor-κB, NF-κB)级联反应是代谢综合征的关键促炎信号通路, 可响应TNF-α、白细胞介素1 (interleukin-1, IL-1)、白细胞介素4 (interleukin-4, IL-4)等多种细胞因子[38]. 下丘脑神经元中NF-κB通路的缺失可抑制细胞因子信号传导抑制因子3 (suppressor of cytokine signaling 3, SOCS3)通路, 进而增加瘦素与胰岛素的敏感性, 改善高脂诱导的肥胖[30,39,40]. 与此相似的是, TNF-α、IL-1β等促炎细胞因子可激活神经元c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)通路[41]. 在中枢神经系统, 特别是下丘脑区域, JNK信号通路的异常激活与多种代谢紊乱密切相关, 包括食欲亢进、胰岛素抵抗和葡萄糖耐受不良等病理过程. 研究发现, 条件性敲除大脑特异性JNK1基因能够有效预防高脂饮食诱导的肥胖相关的外周组织胰岛素抵抗[42]. 而下丘脑AgRP神经元JNK信号的激活可诱发食欲亢进[43]. 炎症

引起的下丘脑神经元内质网应激在肥胖进展中也发挥了重要的作用. TNF-α和IL-1β等可抑制内质网(endoplasmic reticulum, ER)伴侣蛋白的表达, 减少对蛋白质错误折叠的修正, 进而导致内质网应激[44]. 下丘脑神经元内质网应激在肥胖和瘦素抵抗的发生发展中起核心作用. 在内质网应激化学诱导剂(如衣霉素和毒胡萝卜素)作用下, 下丘脑中瘦素受体信号通路的负调控因子表达增加, 进而引起瘦素抵抗[39,45]. 内质网应激会损害下丘脑POMC的加工, 导致能量稳态的中枢调节因子α-MSH的产生减少[46], 这均可导致食欲旺盛与肥胖的产生. 在HFD情况下, 这些细胞因子的增多与下丘脑Toll样受体4 (toll-like receptor 4, TLR4)信号通路密切相关. HFD会激活TLR4信号通路并促进肥胖. TLR4作为模式识别受体, 可识别革兰氏阴性菌释放的脂多糖(lipopolysaccharide, LPS). 脑室注射TLR4抗体能显著降低下丘脑IL-6、IL-1β和TNF-α基因表达并减轻体重[47]. 但神经元并非驱动TLR4介导神经炎症的主要因素, 因为神经元(特别是AgRP和POMC神经元)并不表达TLR4[47], 这一现象更可能由非神经源性胶质细胞协调完成(图1).

近年来一系列的研究表明, 神经元炎症可能是高脂饮食诱导代谢紊乱的下游事件, 而下丘脑神经胶质细胞的募集和激活是对HFD暴露的更早期反应[32]. Thaler在肥胖啮齿动物模型中观察到反应性胶质增生, 表现为下丘脑星形胶质细胞数量和体积增加, 胶质细胞标志基因表达上调. 反应性神经胶质增生的标志物结构蛋白胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)在早期HFD喂养期间明显增多, HFD诱导的反应性星形胶质增生的特征是GFAP的上调、促炎性表型的增加(产生和释放细胞因子标志物)以及形态肥大[48]. 有趣的是, 仅一天HFD喂养即可使星形胶质细胞标志物GFAP水平升高. 高脂饮食会诱导下丘脑反应性星形胶质增生, 伴随着的是星形胶质细胞的形态发生了明显变化, 细胞胞体肥大, 分支延长且数量增多, 与神经元的物理相互作用发生了变化, 导致下丘脑神经元的突触结构发生改变[31,32]. 这些星形胶质细胞的形态变化以及下丘脑中细胞因子产生的增加, 发生在任何全身炎症或体重增加的迹象之前[49]. 最近的一项单细胞测序研究探讨了星形胶质细胞在下丘脑弓状核的解剖定位及空间分子分布如何决定其对高热量饮食的细胞应答[50]. 在单细胞分辨率下对ARC多种细胞群体进行RNA测序发现, 相较于海马, 皮层等部位, 下丘脑弓状核的星形胶质细胞在高脂高糖(high-fat/high-sucrose, HFHS)饮食后, 星形胶质细胞调控脑内营养与激素感知的信号通路的变化更加显著. 同时与弓状核的神经元和小胶质细胞相比, 星形胶质细胞对5天HFHS饮食的基因表达变化最为显著. HFHS饮食会增加两种星形胶质细胞特异性分子标记GFAP和/或乙醛脱氢酶1家族成员L1 (aldehyde dehydrogenase 1 family member L1, Aldh1L1)的表达. 对ARC中表达GFAP与Aldh1L1的星形胶质细胞进行了拓扑学和分子特征解析, 发现HFHS饮食不仅显著增加这些细胞的数量, 还改变了其空间分布和分子特征. 高热量饮食主要促进ARC内复杂神经环路的异常活动, 因此该区域GFAP和Aldh1L1阳性星形胶质细胞的增加可能导致这些胶质细胞对不同神经元和突触亚型改变的适应性反应. 在临床上, 内侧基底下丘脑核磁共振T2弛豫时间延长已被用作小鼠[51]和人类[32]反应性胶质增生的替代标志物, 且与脂肪量和葡萄糖耐受不良显著相关. 另一研究也发现T2弛豫时间与身体质量指数(body mass index, BMI)、空腹胰岛素水平和胰岛素抵抗稳态模型评估(homeostatic model assessment for insulin resistance, HOMA-IR)评分相关[52].

髓样分化因子88 (myeloid differentiation primary response protein 88, MyD88)/NF-κB炎症通路参与下丘脑星形胶质细胞对代谢稳态的调控作用, 炎症状态下MyD88/NF-κB被明显激活. 星形胶质细胞中Myd88的条件性缺失可以抑制细胞内的炎症通路, 如NF-κB通路, 改善慢性HFD诱导的反应性星形胶质细胞增生和神经炎症, 抵抗HFD诱导的肥胖[53]. 而在HFD时星形胶质细胞NF-κB-核因子κB激酶亚基β抑制因子(inhibitor of nuclear factor kappa B kinase subunit β, IKKβ)通路的缺失可以抑制食物摄入并增加能量消耗, 最终抵抗高脂诱导的肥胖, 同时还伴随着葡萄糖耐量和胰岛素敏感性的改善[26]. 且HFD喂养的星形胶质细胞IKKβ敲除小鼠的下丘脑炎症和反应性星形胶质增生均明显减少[26](图1). 而星形胶质细胞中IKKβ/NF-κB信号的激活可改变星形胶质细胞的形态, 并提高了细胞外GABA水平, 同时降低了下丘脑中基底部脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)的表达, 进而导致代谢紊乱[54].

反应性星形胶质细胞增生的原因可能与饱和游离脂肪酸也密切相关, 营养过剩会导致血浆和大脑的游离脂肪酸水平增加[55]. 此外, 饱和脂肪酸的富集会导致

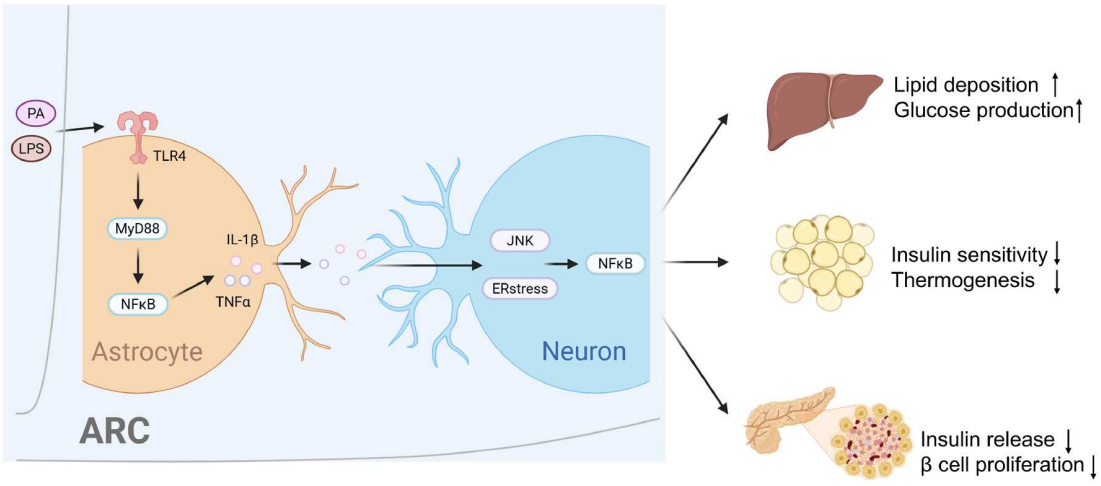

图 1 星形胶质细胞与下丘脑炎症的关系. 高脂饮食可促使棕榈酸、脂多糖等物质释放入血, 通过激活星形胶质细胞TLR4受体及其下游Myd88/NF-κB信号通路, 引发炎症因子释放并作用于下丘脑神经元. 这些炎症因子可进一步激活神经元内的NF-κB、JNK等信号通路或诱发内质网应激反应, 导致神经元功能障碍, 进而影响代谢组织的正常功能, 最终引发肥胖等代谢性疾病. 图片使用BioRender绘制

Figure 1 Crosstalk between astrocytes and hypothalamic inflammation. A high-fat diet leads to the release of palmitate, LPS and other pro-inflammatory mediators into the bloodstream. These molecules activate the TLR4 receptor on astrocytes, triggering the MyD88/NF-κB signaling pathway, which promotes the release of inflammatory cytokines. These cytokines act on hypothalamic neurons, stimulating the NF-κB signaling, JNK signaling or ER stress pathways and disrupting neuronal function. Consequently, this dysregulation impairs metabolic homeostasis in peripheral tissues, contributing to obesity and other metabolic disorders. Created with BioRender

下丘脑中的脂质积聚[56,57]. 体外研究表明, 饱和游离脂肪酸(如棕榈酸、月桂酸和硬脂酸)可激活培养的星形胶质细胞中的炎症信号传导, 诱导培养的星形胶质细胞释放IL-6、IL-1β和TNF-α[58]. 从机制上讲, 饱和脂肪酸通过TLR4激活MyD88/NF-κB通过进而释放炎症因子, 导致代谢紊乱[58](图1).

2 星形胶质细胞对激素与营养素的感应与代谢

下丘脑星形胶质细胞表达参与代谢控制的多种激素和神经肽受体, 并通过调节代谢因子的转运/摄取、神经递质的摄取和代谢, 以及神经递质、生长因子、代谢物、细胞因子和趋化因子的释放来响应这些信号[18](图2). 这些激素和营养素可以改变星形胶质细胞形态及其与神经元的物理联系, 以调节代谢平衡.

2.1 瘦素

瘦素作为脂肪组织分泌的重要脂肪因子, 通过中枢神经系统调控能量代谢过程, 在食欲抑制和能量消耗调节中发挥关键作用. 临床研究表明, 瘦素缺乏或功能缺陷可导致严重肥胖表型[59]. 星形胶质细胞中, 瘦素受体(leptin receptor, LepR)在瘦素跨越血脑屏障的运输以及对成年后发病的肥胖症的调节中扮演着重要角色[60], 同时肥胖会迅速增加星形胶质细胞中LepR的表达, 影响星形胶质细胞瘦素诱导的钙信号传导[61]. 脑室进行急性瘦素注射可促使下丘脑中GFAP迅速下降[62], 而长期接受瘦素处理则能够显著减轻体重并增加下丘脑GFAP的表达量[62]. 此外, 瘦素还快速刺激谷氨酸-天冬氨酸转运体(glutamate-aspartate transporter, GLAST)的表达以及谷氨酸的摄取, 最终影响葡萄糖摄取进而影响POMC神经元的功能[63]. 进一步研究显示, 敲除星形胶质细胞中的瘦素受体后, 星形胶质细胞对POMC神经元的细胞膜覆盖减少[64]. 虽然星形胶质细胞瘦素受体缺失的小鼠在体重稳态方面没有明显变化, 但该小鼠对瘦素诱导的摄食减少不敏感, 并且在禁食后会出现明显的饮食增加[64].

2.2 胰岛素

胰岛素作为胰腺β细胞分泌的核心代谢调节激素, 在协调摄食行为和全身能量代谢平衡中起着中枢性调控作用. 大量研究表明, 胰岛素通过作用于下丘脑神经元网络参与肥胖和2型糖尿病(type 2 diabetes mellitus, T2DM)的病理生理过程[65,66]. 近年研究发现, 下丘脑星形胶质细胞的胰岛素信号通路在脑葡萄糖代谢调控中

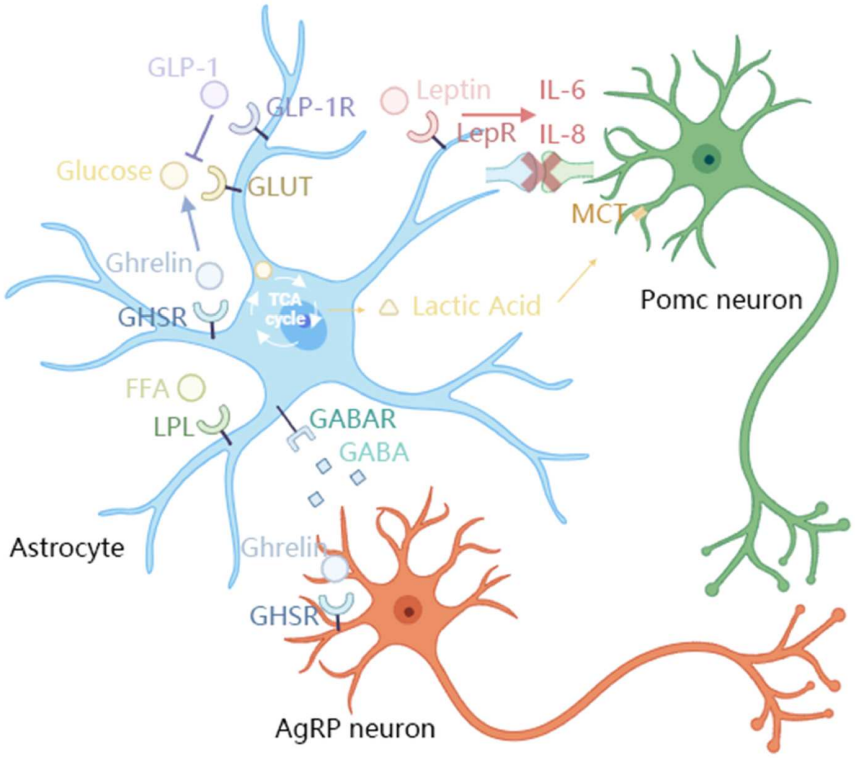

图 2 星形胶质细胞对激素与营养素的感应. 星形胶质细胞整合外周营养和激素信号以调节神经元活动和功能. 星形胶质细胞除了通过提供代谢底物和神经递质再摄取来调节神经元活动外, 还通过感应外周激素, 如瘦素、胰岛素、饥饿素、胰高糖素样肽-1参与对摄食与血糖的调控. 星形胶质细胞还可以通过感应营养素, 如葡萄糖, 脂肪酸等调控机体代谢稳态. 图片使用BioRender绘制

Figure 2 Sensing of hormonal and butritional signals in astrocyte. Astrocytes integrate peripheral nutritional and hormonal signals to modulate neuronal activity and function. In addition to regulating neuronal activity by recycling of metabolic substrates and neurotransmitter, astrocytes participate in feeding behavior and glucose homeostasis by sensing peripheral hormones such as leptin, insulin, ghrelin, and GLP-1. Furthermore, astrocytes contribute to systemic metabolic homeostasis by detecting nutrients, including glucose and fatty acids. Created with BioRender

具有特殊地位, 是连接外周葡萄糖波动与中枢代谢应答的关键分子枢纽[27]. 星形胶质细胞胰岛素信号通路的完整性对维持脑葡萄糖摄取效率至关重要. 当该通路功能受损时, 会导致下丘脑葡萄糖感应机制障碍, 进而破坏中枢对全身葡萄糖稳态的精确调控. 实验证据表明, 在GFAP阳性细胞中特异性敲除胰岛素受体(insulin receptor, IR)的成年小鼠模型中, 星形胶质细胞和POMC神经元均表现出显著的葡萄糖代谢适应不良. 在高血糖刺激下, 这些突变小鼠的下丘脑星形胶质细胞呈现明显的线粒体动力学异常, 表现为线粒体数量减少和形态学改变. 值得注意的是, POMC神经元也出现类似的线粒体功能障碍, 包括受损线粒体的累积和内质网-线粒体接触位点的结构紊乱. 从功能层面来看, 星形胶质细胞IR缺失导致下丘脑神经胶质网络活动异常, 尤其是POMC神经元电活动显著抑制. 这种细胞水平的缺陷在整体代谢表型上体现为: 突变小鼠既丧失了在空腹状态下抑制食欲亢进的能力, 又表现出明显的葡萄糖耐量受损和胰岛素抵抗. 这些发现充分证明, 星形胶质细胞胰岛素信号系统构成了中枢葡萄糖感知与外周代谢调控之间的关键桥梁, 对维持系统葡萄糖稳态具有不可替代的生理功能.

2.3 饥饿素

饥饿素(ghrelin)是一种从胃肠道合成和释放的促进食欲的激素, 通过生长激素促分泌素受体亚型1a (growth hormone secretagogue receptor 1a, GHS-R1a)来刺激食欲并诱导肥胖[59]. 胃饥饿素刺激AgRP神经元, 促进其将GABA释放到附近的POMC神经元上, 从而降低POMC活性并促进进食[67]. 饥饿素可调节下丘脑星形胶质细胞中谷氨酸和葡萄糖转运蛋白的水平[68]. 饥饿素还可诱导AgRP神经元释GABA作用于邻近星形胶质细胞, 进而导致星形胶质细胞的线粒体适应, 线粒体

形态学发生变化, 增加AgRP神经元周围的神经胶质覆盖和AgRP神经元的兴奋性, 且星形胶质细胞衍生的前列腺素E2 (prostaglandin E2, PGE2)通过前列腺素E2受体(prostaglandin E receptor 2, EP2)直接激活AgRP神经元[69]. 这些发现揭示了饥饿素通过“神经元-星形胶质细胞-神经元”的级联信号通路调控摄食行为的新机制, 为理解中枢食欲调控的神经胶质基础提供了重要理论依据.

2.4 胰高血糖素样肽-1

胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1)是一种主要由肠道L细胞所产生的激素, 可以抑制食欲、减轻体重并降低血糖[70]. 脑干孤束核(Nucleus tractus solitarius, NTS)的星形胶质细胞可能介导了GLP-1的厌食作用, GLP-1激动剂可以激活星形胶质细胞环磷酸腺苷(cyclic adenosine monophosphate, cAMP)通路、进而激活星形胶质细胞. 同时, 通过药理学途径抑制星形胶质细胞可以减弱NTS内GLP-1受体(glucagon-like peptide-1 receptor, GLP-1R)介导的厌食和体重抑制作用[71]. 下丘脑星形胶质细胞GLP-1信号在调节星形胶质细胞葡萄糖摄取以及全身葡萄糖代谢中发挥中作用. GLP-1抑制培养的星形胶质细胞对葡萄糖的摄取, 并促进脂肪酸β-氧化[72]. 相反, 在表达GFAP的星形胶质细胞中, 出生后GLP-1R的缺失会损害星形胶质细胞的线粒体完整性, 增加成纤维细胞生长因子21 (fibroblast growth factor 21, FGF21)的产生和大脑对葡萄糖的摄取. 相应地, 在星形胶质细胞中缺乏GLP-1R表达的小鼠中, 星形胶质细胞特异性FGF21失活会消除星形胶质细胞中缺乏GLP-1R所引起的葡萄糖耐受性和学习能力的改善[72].

2.5 葡萄糖

下丘脑星形胶质细胞感知循环葡萄糖并参与葡萄糖摄取, 以满足邻近神经元的高能量需求. 大脑对能量的需求极高, 而葡萄糖是其首选的能量来源. 与神经元不同, 星形胶质细胞能够以糖原沉积物的形式储存葡萄糖, 以便其通过乳酸穿梭运输来支持自身代谢. 星形胶质细胞摄取的葡萄糖通过糖酵解途径, 生成并释放乳酸. 随后, 乳酸通过单羧酸转运蛋白(monocarboxylate transporters, MCTs)转运至神经元, 再被转化为丙酮酸, 然后在神经元线粒体中用于氧化磷酸化供能[73,74]. 此外, 星形胶质细胞也表达乳酸受体-羟基羧酸受体1 (hydroxycarboxylic Acid Receptor 1, HCAR1), POMC神经元通过星形胶质细胞HCAR1对乳酸表现出兴奋性反应[75]. 基于葡萄糖转运蛋白2 (glucose transporter 2, GLUT2)的研究证实了下丘脑星形胶质细胞参与中枢葡萄糖感应, GLUT2主要在星形胶质细胞而非神经元中表达[76]. 全身敲除GLUT2的小鼠表现出血清胰高血糖素水平升高, 并且对全身葡萄糖波动的胰高血糖素分泌减少, 这种表型说明GLUT2对于低血糖的反调节反应至关重要[76]. 同时, 位于下丘脑中的星形胶质细胞也通过葡萄糖转运蛋白1 (glucose transporter 1, GLUT1)与链脲佐菌素(streptozotocin, STZ)处理的大鼠中的葡萄糖感应机制相关, 在STZ糖尿病大鼠的下丘脑星形胶质细胞中通过病毒过表达GLUT1可以使循环葡萄糖水平正常化并恢复大鼠中的下丘脑葡萄糖感应[77]. 因此, 以上数据表明下丘脑星形胶质细胞是葡萄糖感应机制的重要组成部分.

2.6 脂肪酸

星形胶质细胞通过包括脂蛋白脂肪酶(lipoprteinlipase, LPL)在内的脂质转运蛋白摄取脂质并以液滴的形式储存它们, 这对于控制大脑中的细胞脂质储存至关重要. 当星形胶质细胞中敲除LPL后, 小鼠会出现严重的食欲亢进与产热降低, 最终导致肥胖和葡萄糖不耐受. 进一步机制研究显示, 这些小鼠出现神经酰胺积累增加. 在原代培养的下丘脑星形胶质细胞中LPL缺失可以导致星形细胞的脂质储存减少, 糖酵解增强[78]. 血管生成素样蛋白4 (angiopoietin Like 4, ANGPTL4)是过氧化物酶体增殖物激活受体γ(peroxisome proliferator activated receptor γ, PPARγ)的反应基因, ANGPTL4通过抑制LPL的活性来控制脂肪酸对不同组织的可用性. 成年小鼠星形胶质细胞特异性消融ANGPTL4可以防止高脂饮食诱导的下丘脑星形胶质细胞线粒体变化和POMC神经元活性变化, 并增加下丘脑PPARγ的mRNA水平, 防止饮食诱导的肥胖. 相反, 星形胶质细胞特异性PPARγ缺失加剧了对HFD的易感性, 导致下丘脑POMC神经元活性减少和体重增加[28].

3 星形胶质细胞释放的递质

星形胶质细胞可以释放神经递质等物质作用于周围的神经元, 这与能量平衡的调节密切相关. 这些星形胶质细胞释放的递质通过囊泡介导的胞吐作用以及通道和转运体依赖性机制释放, 以响应邻近神经元的活

动(图3), 进而调控机体的代谢稳态, 具体情况如下:

3.1 腺苷

Yang等人[79,80]报道, 用特定药物激活的受体(designer receptors exclusively activated by designer drugs, DREADDs)和氯氮平N-氧化物(clozapine N-oxide, CNO)激活弓状核中的星形胶质细胞可导致基础摄食量和胃饥饿素诱导的摄食量减少, 而腺苷A1受体(adenosine A1 receptor, A1R)拮抗剂DPCPX可以减弱这些作用. 机制研究表明星形胶质细胞通过释放腺苷参与食物摄入调节, 腺苷是一种已知对突触前和突触后神经元都有抑制作用的神经胶质递质, 可抑制AgRP神经元的活性进而抑制食欲. 与这些结果相反, Wu等人[81]发现脑室注射腺苷可以促进小鼠食欲[82]. 这些相互矛盾的发现可能与实验设计的差异有关.

3.2 十八碳内啡肽(octadecaneuropeptide, ODN)

星形胶质细胞所分泌的一种神经胶质肽酰基辅酶A结合蛋白(acyl-CoA-binding protein, ACBP)及其产物ODN, 在调节下丘脑星形胶质细胞-神经元能量平衡中具有重要意义. ACBP基因的全脑缺失会导致小鼠食欲亢进和肥胖, 而在全脑ACBP缺失小鼠中星形胶质细胞ACBP过表达则能够抵抗这些表型. 机制研究表明, ODN通过G蛋白偶联受体(g-protein-coupled receptor, GPCR)而非GABA受体选择性激活POMC神经元, 并通过黑素皮质素系统抑制进食, 同时提高碳水化合物利用率[83]. 类似地, ARC星形胶质细胞中ACBP过表达也会减少进食和体重增加. 最后, ODN-GPCR激动剂能够

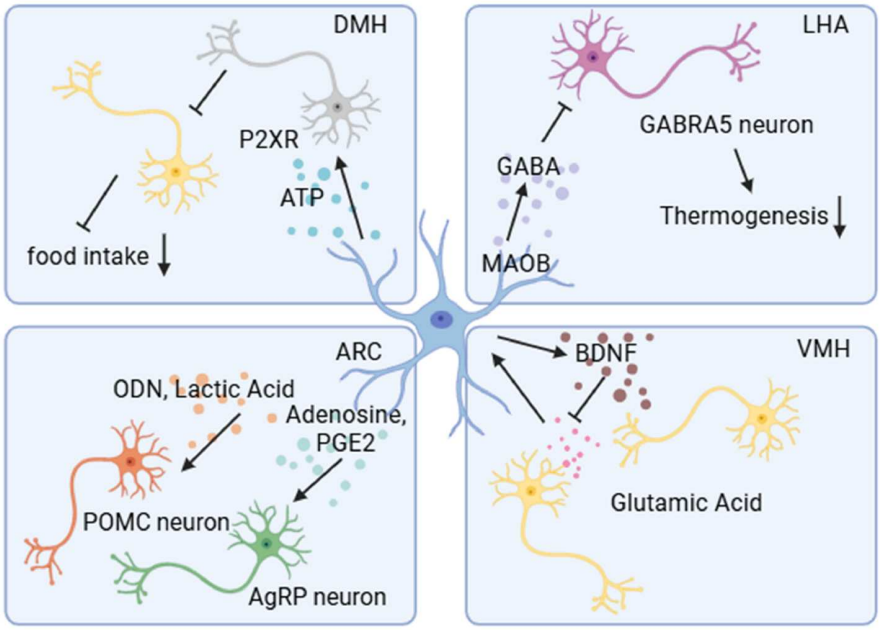

图 3 星形胶质细胞释放的递质. 星形胶质细胞可以释放神经递质等物质作用于周围的神经元, 这与能量平衡的调节密切相关. DMH中的星形胶质细胞可释放ATP, ATP通过P2XR受体刺激该区域的GABA能神经元, 最终作用于DMH中的食欲神经元, 进而抑制食欲. ARC中的星形胶质细胞可以释放ODN或乳酸作用于POMC神经元, 进而抑制食欲和减肥. 禁食和胃饥饿素诱导星形细胞释放PGE2, PGE2激活AgRP神经元, 增加食物摄入. 星形胶质细胞在化学遗传学刺激这些细胞后释放ATP后, 在细胞外空间迅速产生腺苷, 作用于突触前和/或突触后A1R, 以降低AgRP神经元的活性并减少食物摄入. VMH的星形胶质细胞可通过谷氨酸循环调控BDNF的释放, 进而调控摄食与代谢. 在LHA的星形胶质细胞通过腐胺降解途径调控GABA的释放, 进而作用于GABRA5神经元群体, 抑制产热导致肥胖. 图片使用BioRender绘制

Figure 3 Neurotransmitters released by astrocytes. Astrocytes can release neurotransmitters and other substances that act on surrounding neurons, which is closely related to the regulation of energy balance. In the DMH, astrocytes release ATP, which stimulates GABAergic neurons in this region via P2XR receptors, ultimately acting on appetite-regulating neurons in the DMH to suppress appetite. In the ARC, astrocytes release ODN or lactic acid to act on POMC neurons, thereby inhibiting appetite and promoting weight loss. Fasting and ghrelin induce astrocytes to release PGE2, which stimulates AgRP neurons in the ARC, thereby increasing food intake. After astrocytes release ATP upon chemogenetic stimulation, adenosine is rapidly generated in the extracellular space and acts on presynaptic and/or postsynaptic A1R to reduce AgRP neuronal activity and decrease food intake. In the VMH, astrocytes regulate the release of BDNF through glutamate cycling, thereby modulating feeding and metabolism. In the LHA, astrocytes regulate GABA release via the polyamine degradation pathway, which acts on the GABRA5 neuronal population, inhibiting thermogenesis and leading to obesity. Created with BioRender

减少瘦素缺陷小鼠的进食并促进体重减轻[83]. 这些发现揭示了ACBP是一种ARC胶质肽, 在能量平衡控制中起到关键作用, 并通过中央黑素皮质素系统发挥强烈的厌食作用.

3.3 乳酸

星形胶质细胞不仅将葡萄糖转运到大脑中, 还可以代谢葡萄糖并将乳酸释放到神经元中, 进而对神经元提供能量. 不仅如此, 乳酸除了具有能量作用外, 还具有信号分子的作用. 乳酸可以通过单核苷酸转运体转运到弓状核POMC神经元, 乳酸受体HCAR1特异性激动剂可使POMC神经元去极化, 进而激活POMC神经元抑制食欲[75]. 此外, POMC神经元亚群的去极化对乳酸转运蛋白阻滞剂α-氰基-4-羟基肉桂酸(α-Cyano-4-hydroxycinnamic acid, 4-CIN)敏感, 这表明L-乳酸诱导的去极化也可以通过直接的细胞内作用发生[84]. 但是在糖尿病小鼠模型中, 星形胶质细胞中的丙酮酸脱氢酶(pyruvate dehydrogenase, PDH)和丙酮酸脱氢酶激酶(pyruvate dehydrogenase kinases, PDK)介导星形胶质细胞中代谢从氧化磷酸化转变为糖酵解, 从而促进炎症反应. 星形胶质细胞特异性PDK2缺乏可抑制乳酸的产生, 并抑制乳酸作用于下丘脑POMC神经元以及AgRP神经元, 进而逆转糖尿病引起的食物摄入增加[85], 这些均凸显了下丘脑星形胶质细胞分泌的乳酸在代谢生理性与病理性下不同的作用. 星形胶质细胞通过连接蛋白形成相互连接和协调的网络, 星形胶质细胞连接蛋白(connexin, Cx) 30和Cx43在间隙连接处相对, 允许单个星形胶质细胞中的葡萄糖或乳酸在星形胶质细胞网络内传播, 使其可供活跃的神经元使用. 在高血糖下Cx43表达增加, 而在大鼠下丘脑内侧基底部(mediobasal hypothalamus, MBH)中使用RNA干扰对其进行短暂抑制会降低中枢葡萄糖感应, 从而减少大脑葡萄糖诱导的胰岛素分泌[86]. 星形胶质细胞中Cx43的缺失通过减弱星形胶质细胞网络的葡萄糖和乳酸运输, 使外侧下丘脑区域的促进食欲素神经元沉默, 导致小鼠夜间活动期过度嗜睡[87].

3.4 前列腺素E2

前列腺素E2 (PGE2)是另一种与AgRP神经元调节有关的星形胶质细胞衍生因子. 禁食或者饥饿素的作用可以刺激AgRP神经元释放GABA作用于星形胶质细胞, 星形胶质细胞可释放PGE2通过EP2受体特异性促进AgRP神经元的激活, 同时侧脑室注射EP2受体抑制剂可以减弱体内胃饥饿素全身递送的促进食欲作用[86].

3.5 胆囊收缩素

饱腹肽胆囊收缩素(cholecystokinin, CCK)在食欲调控中发挥重要的作用, CCK可以将下丘脑背内侧核(dorsomedial hypothalamic nucleus, DMH)的GABA突触可塑性从长期抑制转变为长期增强. 星形胶质细胞中代谢型谷氨酸受体5 (metabotropic glutamate receptor 5, mGluR5)和2型CCK受体的激活导致细胞内储存的Ca^{2+}释放, 随后星形胶质细胞释放三磷酸腺苷(adenosine triphosphate, ATP). ATP则与抑制性末梢上的嘌呤能受体(purinergic 2X receptor, P2XR)结合, 延长GABA释放到作用于DMH的食欲肽能神经元上, 进而抑制食欲[88].

3.6 γ-氨基丁酸

下丘脑外侧核(lateral hypothalamic area, LHA)有一群独特的γ-氨基丁酸A型受体亚单位Alpha5 (gamma-aminobutyric acid type A receptor subunit alpha5, GABRA5)阳性神经元群体, 这群神经元的激活可以调节棕色脂肪组织的活动, 并增加能量消耗. 长期高脂喂养情况下, 这群神经元的活性显著降低. 这些GABRA5阳性神经元被星形胶质细胞GABA强烈抑制, 该GABA由反应性星形胶质细胞中的单胺氧化酶-B (monoamine oxidase B, MAOB)合成, 进而释放作用到GABRA5阳性神经元群体, 导致GABRA5阳性神经元抑制, 脂肪堆积并引起肥胖. LHA中的星形胶质细胞特异性MAOB敲低可在不改变HFD喂养后食物摄入的情况下减少体重增加[89]. 此外, 在慢性HFD喂养的小鼠中, MAOB的药理学抑制在不改变食物摄入的情况下导致显著的体重减轻, 并减少LHA中的反应性星形胶质细胞增生[89].

3.7 谷氨酸

突触间隙中谷氨酸的清除是介导星形胶质细胞对兴奋性神经传递控制的主要机制之一, 并涉及代谢回路的调节. 细胞外谷氨酸主要通过星形胶质细胞兴奋性氨基酸转运蛋白(excitatory amino acid transporters, EAATs) GLT-1和GLAST去除[89], 它们调节突触处谷氨酸的浓度和时间进程. 此外, 它们防止神经递质溢出到相邻的突触, 确保突触传递的特异性. BDNF对维持中枢神经系统内的能量和葡萄糖平衡至关重要. 禁食或

中枢BDNF耗竭增强了星形胶质细胞突触谷氨酸的清除, 从而降低了小鼠的神经元活性[90]. 下丘脑腹内侧核(ventromedial hypothalamus, VMH)星形胶质细胞中选择性缺失原肌球蛋白受体激酶B (tropomyosin receptor kinase B, TrkB)-T1 (这些细胞表达的唯一TrkB同种型)的小鼠表现出GLT-1表达增加和VMH中星形胶质细胞突起的突触侵入[91]. 这种由星形胶质细胞BDNF信号减少引起的分子和结构改变, 增强了星形胶质细胞对突触谷氨酸的清除, 并降低了神经元的兴奋性和活动. 值得注意的是, 突变小鼠食欲亢进、肥胖、葡萄糖耐受不良, 并表现出产热减少、运动活动减少、对代谢组织的交感神经张力降低以及肥胖前对瘦素的反应减弱[91]. 而在下丘脑PVH中, 星形胶质细胞双向调控相邻神经元活动、自主神经输出、葡萄糖代谢和能量平衡. 这涉及星形胶质细胞对周围谷氨酸水平的控制在肥胖中受损. PVH星形胶质细胞Ca^{2+}信号的激活或者抑制分别恶化或改善饮食诱导的肥胖小鼠的代谢状态[92].

3.8 血管内皮生长因子(vascular endothelial growth factor, VEGF)

高血压是代谢综合征的重要组成部分. 肥胖患者的下丘脑中炎症、肾素-血管紧张素系统(renin-angiotensin system, RAS)激活、交感神经血管运动张力增加以及压力感受器反射受损等因素都可导致高血压[93]. 在此背景下, 尽管星形胶质细胞如何参与心血管疾病发病机制的确切机制尚需进一步阐明, 但其在肥胖相关高血压的发生和进展中起着关键作用. HFD喂养的小鼠在MBH中显示出血管长度和密度的显著增加, 以及血脑屏障完整性的缺乏[31]. 20周以上的慢性HFD诱导反应性星形胶质细胞形成, 影响血脑屏障的结构, 这使得POMC和NPY细胞体和树突难以进入血管. 小鼠喂食HFHS饮食会诱导下丘脑内快速发生微血管重塑, 这发生在系统动脉血压变化之前, 但同时伴有大量饮食诱导的体重增加和血清瘦素水平升高[31], 说明下丘脑星形胶质细胞在促进下丘脑微血管病变和与肥胖相关的系统性动脉高血压中的作用. ARC中的星形胶质细胞在慢性HFD喂养下分泌VEGF, 这种VEGF信号增加了血脑屏障的通透性, 进而通过调节交感神经输出对系统性血压进行控制, 提示星形胶质细胞在血压控制方面的重要作用[94].

4 展望

星形胶质细胞通过影响下丘脑炎症, 激素与营养素的感应与代谢, 递质释放, 突触谷氨酸的清除等影响代谢稳态. 星形胶质在代谢调控的作用下, 如何整合传入的信息以影响周围神经元, 进而调控代谢稳态仍需研究. 由于星形胶质细胞与神经元是相互作用、相互影响的, 前期的研究多集中于星形胶质细胞对神经元供能的影响, 但是在能量和葡萄糖平衡控制的背景下确定星形胶质细胞如何受到神经元衍生信号的调控以及影响仍十分重要. 鉴于下丘脑结构的复杂性, 在下丘脑不同核团的星形胶质细胞应该具有不同的功能, 随着单细胞RNA测序以及旨在研究特定星形胶质细胞群体定位的多重原位杂交的应用, 对星形胶质细胞异质性的理解应该会得到明显推进. 基于星形胶质细胞在代谢性稳态中重要的作用, 随着研究的进一步深入, 如何靶向星形胶质细胞, 探究代谢性疾病的预防与治疗也是未来的研究趋势.

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Summary for “下丘脑星形胶质细胞与代谢稳态”

Hypothalamic astrocytes and metabolism homeostasis

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As a key structure in the central nervous system for regulating energy balance, the hypothalamus plays a core regulatory role in maintaining metabolic homeostasis. Astrocytes are the most predominant type of glial cells. They not only constitute an important structural and functional unit of the synaptic microenvironment, but also exhibit dual characteristics in neurometabolic regulation. Astrocytes participate in basic physiological metabolic regulation and mediate the pathological association between neuronal dysfunction and metabolic diseases such as obesity. Recent studies have shown that hypothalamic astrocytes have a highly sensitive ability to perceive nutrition and dynamically respond to peripheral metabolic signals such as fluctuations in hormone and nutrient levels, thereby releasing neuroactive substances to maintain hypothalamic neuronal function and metabolic homeostasis. Particularly, under the pathological state of excessive nutrition, hypothalamic astrocytes undergo significant functional remodeling, becoming the key effector cells that induce low-level inflammation in the hypothalamus and further promote the occurrence and development of obesity. Based on the latest research evidence, we systematically elaborate the physiological and pathophysiological mechanisms of hypothalamic astrocytes in metabolic regulation, and focus on revealing the bidirectional regulatory role and molecular basis of this type of cell in maintaining metabolic homeostasis and the process of metabolic disorders.

HFD exposure elevates circulating free fatty acids that activate TLR4 signaling on hypothalamic astrocytes, inducing reactive astrogliosis marked by increased GFAP expression, cellular hypertrophy, and enhanced process arborization, accompanied by synaptic structural remodeling. This TLR4 engagement triggers intracellular MyD88-dependent NF-κB pathway activation, leading to the subsequent release of proinflammatory cytokines including IL-1β and TNF-α. These inflammatory mediators disrupt neuronal metabolic signaling through activation of NF-κB transcriptional activity, JNK phosphorylation, and ER stress responses, ultimately impairing central leptin and insulin sensitivity.

Hypothalamic astrocytes express an array of hormone and neuropeptide receptors critical for metabolic regulation, including receptors for leptin, insulin, ghrelin, and GLP-1. These astrocytes respond to metabolic signals by modulating transport and uptake mechanisms for metabolic substrates, neurotransmitter recycling and cellular metabolic processing, and regulating the release of neurotransmitters, neurotrophic factors, metabolites, cytokines and chemokines. Astrocytes also detect nutrient availability through GLUTs and fatty acid receptors, integrating these signals to maintain systemic metabolic homeostasis. Importantly, these metabolic cues induce structural plasticity in astrocytes, which physically modulates neuron-astrocyte interactions and synaptic efficacy within metabolic circuits.

Astrocytes modulate energy balance by releasing neurotransmitters and neuromodulators that act on surrounding neurons. Astrocytes exhibit functional heterogeneity across distinct hypothalamic nuclei. They modulate metabolic processes through targeted release of neuroactive substances including ATP, adenosine, PGE2, ODN, lactate acid, GABA and BDNF, which act on different neurons and thereby exert different neuroregulatory functions, ultimately regulating metabolic functions such as feeding behavior and thermogenesis.

Given the structural and functional complexity of the hypothalamus, astrocytes residing in distinct hypothalamic nuclei are postulated to exhibit specialized functional properties. The advent of single-cell RNA sequencing and multiplex *in situ* hybridization technologies enables precise molecular characterization and spatial mapping of astrocyte subpopulations, which is expected to significantly advance our understanding of astrocyte heterogeneity. Considering the well-documented role of astrocytes in maintaining metabolic homeostasis, future research directions will likely focus on developing astrocyte-targeted therapeutic strategies for the prevention and treatment of metabolic disorders, representing a promising avenue for translational investigation in metabolic medicine.

hypothalamus, astrocyte, neuron, metabolic homeostasis, obesity

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