下丘脑 AgRP 神经元调控食欲和体重研究进展

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摘要 食欲和体重稳态调控是动物维持生存的重要机制。中枢神经系统内的下丘脑是机体能量平衡调控的中心。下丘脑对外周的各种激素和营养素信号做出反应从而调控能量代谢。下丘脑弓状核内的AgRP神经元是饥饿敏感神经元, 在能量缺乏时被激活, 从而引起进食行为。AgRP神经元调控食欲和体重的分子机制较为复杂, 涉及到激素、神经递质和受体, 以及神经元内的多种调控分子(如炎症激酶IKK β)。此外, AgRP神经元与下丘脑及下丘脑外神经元之间形成复杂的神经环路, 从而调控食欲和体重。本文将从AgRP神经元的上游、下游和神经元内的分子调控机制, 以及相关神经环路作一回顾。

关键词 下丘脑, 弓状核, AgRP 神经元, 食欲, 体重, 肥胖

位于下丘脑内侧基底部的弓状核(arcuate nucleus, Arc)是调节食欲和能量平衡的关键区域^[1]。Arc靠近正中隆起, 由于没有完整的血脑屏障^[2], 可对多种外周激素信号作出响应。

1982年, Tatemoto等人^[3]在猪的大脑组织中发现一种与肽YY(Peptide YY, PYY)结构相似的新型神经肽, 将其命名为神经肽Y(Neuropeptide Y, NPY)。NPY后来被证明与食欲调控相关。最初人们将与刺豚鼠毛色特征相关的基因命名为Agouti基因。刺豚鼠相关蛋白(agouti-related protein, AgRP)是在寻找Agouti同源基因时发现的^[4]。1998年, Hahn等人^[5]通过荧光原位杂交的方法发现AgRP和NPY共表达于Arc内的神经元中, 因此将这种神经元命名为AgRP/NPY神经元, 也称作AgRP神经元。

AgRP神经元位于Arc的内侧下方, 紧临第三脑室, 与POMC(proopiomelanocortin)神经元相邻。AgRP神经元是“饥饿敏感神经元”。除了表达促食性神经肽AgRP和NPY, AgRP神经元能够释放抑制性神经递质

γ -氨基丁酸(γ -aminobutyric acid, GABA)。当机体缺乏能量时, AgRP神经元迅速被激活从而引发进食行为^[6,7]。损毁成年小鼠的AgRP神经元会导致进食行为停止, 甚至饿死^[8]。AgRP神经元调控食欲和体重的分子机制较为复杂, 本文将从AgRP神经元的上游、下游和细胞内分子机制, 以及相关神经环路作综述。

1 调节AgRP神经元的激素和神经信号

在不同的能量状态下, 机体内多种激素的水平也发生相应的变化。它们通过作用于下丘脑、脑干或自主神经系统等来调控食欲。同时, AgRP神经元也受到中枢神经系统内其他神经元的支配和调节。

1.1 激素

瘦素(leptin)是一种主要由脂肪细胞分泌的激素^[9], 其受体在下丘脑多个部位的神经元内表达。瘦素通过其受体发挥抑食作用。在胞内, 瘦素主要通过

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两种转录因子,即信号转导及转录激活因子3(signal transduction and activated transcription 3, STAT3)和叉头框蛋白O1(forkhead box protein O1, FoxO1)来调节AgRP和NPY的转录活性. FoxO1可显著增加AgRP的转录活性^[10];而STAT3则能够阻断FoxO1对AgRP启动子区的激活作用^[11]. 瘦素通过抑制FoxO1和激活STAT3从而下调AgRP的转录水平. 此外,对*ob/ob*小鼠的电生理研究表明,瘦素还能影响突触可塑性. 当瘦素缺乏时,支配AgRP神经元的兴奋性突触传入显著增加^[12]. 对于正常体重的动物,瘦素具有很强的抑制食欲的作用,但其作为减肥药物的研发却受到限制,原因是肥胖者常出现瘦素抵抗. 研究表明,炎症信号通路激酶IKK β (inhibitor of NF- κ B kinase β)/NF- κ B(nuclear factor- κ B)^[13],细胞因子信号转导抑制因子3(suppressor of cytokine signaling 3, SOCS3)^[14]和蛋白酪氨酸磷酸酶1B(protein tyrosine phosphatase-1B, PTP1B)^[15]在瘦素抵抗中发挥重要作用.

胰岛素是由胰岛 β 细胞产生的激素,在糖稳态调控中起着关键的作用. 研究表明,AgRP神经元表达胰岛素受体. 中枢给予胰岛素能够抑制AgRP和NPY神经肽的表达,从而显著抑制食欲.

饥饿素(ghrelin)是生长激素分泌素受体(growth hormone secretagogue receptor, GHSR)的内源性配体,主要由胃部和十二指肠等部位的细胞分泌. 免疫组化显示,下丘脑的Arc、VMH(ventromedial nucleus of the hypothalamus)、DMH(dorsomedial nucleus of the hypothalamus)和PVN(paraventricular nucleus)均表达饥饿素^[16]. 另外,GHSR在下丘脑表达丰富,尤其是Arc^[17]. 禁食、体重减轻和胰岛素诱导的低血糖都能够增加饥饿素的表达和分泌. 在Arc,饥饿素通过其受体激活AgRP神经元,同时抑制POMC神经元来发挥促进食欲的作用.

PYY是由肠道分泌的多肽,常以PYY₁₋₃₆和PYY₃₋₃₆两种形式释放到血液中. 血液中的PYY水平在禁食状态下很低,餐后快速增加. 直接将PYY₃₋₃₆注射到Arc能够使NPY mRNA水平降低,同时使动物的进食量减少^[18]. 将PYY₃₋₃₆注射至MC4R(melanocortin receptor 4)敲除小鼠仍然能够抑制动物的食欲,说明其抑食作用可能独立于黑皮质素系统^[19].

白脂素(asprosin)是一种由脂肪细胞产生的激素. 该激素由禁食诱导产生,能够促进肝脏葡萄糖的生成^[20]. 研究表明,外周白脂素可穿过血脑屏障,以

cAMP-PKA(protein kinase A)依赖的方式直接激活AgRP神经元,从而引起食欲和体重的增加^[21]. 白脂素受体是治疗肥胖的新靶点^[22].

糖皮质激素由肾上腺皮质分泌,对机体代谢以及免疫功能起重要的调节作用. 过量的糖皮质激素引起食欲过盛,而原发性肾上腺衰竭中导致的皮质醇缺乏最终引起厌食症^[23]. 糖皮质激素对食欲的调控主要通过黑皮质素系统. 对瘦素缺陷的*ob/ob*小鼠进行肾上腺切除,能够使AgRP和POMC的表达趋于正常,从而改善肥胖症状^[24].

1.2 神经信号

谷氨酸是脑内主要的兴奋性神经递质,在饥饿引起AgRP神经元激活的过程中起着重要的作用. 谷氨酸通过与谷氨酸能离子通道受体N-甲基-D-天冬氨酸受体(N-methyl-D-aspartate receptor, NMDAR)或 α -氨基-3-羟基-5-甲基-4-异噁唑丙酸受体(α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, AMPAR)结合发挥作用. Liu等人^[25]发现AgRP神经元上存在谷氨酸能的兴奋性输入. 这种兴奋性突触能够显著影响进食量和体重. 将AgRP神经元上的NMDAR敲除,小鼠的进食量和体重都显著降低,AgRP神经元的兴奋性突触后电位(excitatory postsynaptic potential, EPSP)频率和树突棘的数量明显减少. 因此,AgRP神经元上的谷氨酸能输入是激活AgRP神经元所必需的. 研究表明,饥饿素能够部分引起对于AgRP神经元的兴奋性输入,这一作用可被瘦素阻断^[26]. 对于支配AgRP神经元的谷氨酸能神经元的来源,Krashes等人^[27]的研究表明,下丘脑PVN中表达促甲状腺激素释放激素(thyrotropin-releasing hormone, TRH)和垂体腺苷酸环化酶激活肽(pituitary adenylate cyclase-activating polypeptide, PACAP)的神经元是AgRP神经元重要的兴奋性传入来源. 利用化学遗传学方法激活这些神经元可显著活化AgRP神经元并引发进食行为. 相反,如果抑制这些神经元,即使在饥饿状态下,小鼠的进食量也会明显减少. 下丘脑PVN一般被认为是一个抑制食欲的核团,但Krashes等人^[27]的结果显示其中某些类型的神经元是促进食欲神经环路的节点.

GABA是重要的抑制性神经递质,能抑制突触后神经元的活性. 众所周知,AgRP神经元活性在能量缺乏时迅速升高,而在食物摄入之后其活性又迅速

下降。近期多项研究表明这种活性下降甚至发生在食物摄入之前,即靠感官检测到食物存在时就能够使AgRP神经元的活性下降。这种快速的生理过程正是通过GABA作用于AgRP神经元而实现^[28-30]。下丘脑DMH中表达瘦素受体的神经元是AgRP神经元GABA输入的主要来源。瘦素可通过此通路抑制AgRP神经元活性从而抑制食欲^[31]。小鼠通过感官检测到食物存在时,DMH中表达瘦素受体的神经元迅速激活,通过释放抑制性的神经递质GABA使其下游的AgRP神经元活性迅速下降。

2 AgRP神经元调控食欲和体重的细胞内机制

2.1 受体

瘦素受体(Ob-R)是细胞因子受体家族的成员,至少存在6种亚型^[32]。其中,Ob-Rb在下丘脑和免疫细胞中表达丰富,在瘦素信号传导中起主要的作用。在能量代谢调控中,下丘脑Arc中AgRP和POMC神经元上的瘦素受体发挥着重要的作用。JAK2-STAT3是瘦素信号的主要传导途径。瘦素通过结合Ob-Rb的胞外段,引起受体募集JAK2使其胞内段的酪氨酸(tyrosine, Tyr)位点Tyr¹¹³⁸发生磷酸化,进而招募STAT3等信号分子使其磷酸化而激活。STAT3进入细胞核启动或者抑制其靶基因如POMC和CART (cocaine- and amphetamine-regulated transcript),或者AgRP和NPY的转录。SOCS3和PTP1B能抑制JAK2-STAT3信号通路的活性而引起瘦素抵抗。

嘌呤受体6(purinergic receptor 6, P2Y6)是一种G蛋白偶联的核苷酸受体,在Arc表达丰富。P2Y6主要被尿苷二磷酸(uridine-diphosphate, UDP)激活。Steculorum等人^[33]的研究表明,P2Y6受体在AgRP神经元激活中起着重要的作用^[33]。中枢神经系统中UDP的合成主要依赖于外周尿苷的供应^[34]。肥胖者外周血中尿苷水平升高,从而导致下丘脑中UDP含量增加。UDP作用于下丘脑AgRP神经元上的P2Y6,进而激活AgRP神经元,同时诱导ERK磷酸化和c-Fos的表达。

G蛋白偶联受体17(G protein-coupled receptor 17, GPR17)原是一种配体未知的孤儿受体,在分子进化上与核苷酸受体P2Y相关,可被其配体UDP激活^[35]。GPR17表达于神经元和少突胶质细胞的前体细胞^[36]。Ren等人^[37]的研究显示,下丘脑AgRP神经元中的

GPR17是转录因子FoxO1的靶基因。小鼠在禁食后其Arc内GPR17表达增加,恢复给食后表达水平下降。脑室内注射GPR17的激动剂促进动物的食欲,注射其拮抗剂则能明显抑制食欲。更为重要的是,这些效应在AgRP神经元中特异性敲除FoxO1后不复存在。后续研究发现,全身性敲除GPR17不改变进食量和体重^[38],但是AgRP神经元中特异性敲除GPR17的小鼠表现为进食量减少、体重降低,以及对胰岛素和瘦素敏感性增加^[39],说明AgRP神经元中的GPR17在食欲和体重调控中具有独特的作用。

2.2 离子通道

Na_v1.7是一种由Scn9a基因编码的电压门控钠离子通道,在疼痛中的作用已被广泛研究^[40,41]。作为大脑计算的基本单元,神经元通常能进行毫秒级的计算,从而高效地处理成千上万个由突触输入的电信号,并对这些信号进行整合以及作出合理的反应。不同类型的神经元整合突触信号所需的时间不尽相同,如大脑皮质神经元能在几十毫秒的时间内处理上千种快速变化的信息,而下丘脑AgRP神经元调节食欲的时间可持续数小时。Branco等人^[42]发现,正是由于Na_v1.7的存在,下丘脑AgRP神经元和POMC神经元对各种突触信号的整合时间延长,产生持续时间较长的EPSP,从而发挥各自在能量平衡调控中的作用。在AgRP神经元内特异性敲除Scn9a基因后,小鼠体重明显低于对照组。在POMC神经元内特异性敲除Scn9a基因则会导致肥胖。这些结果说明Na_v1.7在这两种功能相反的神经元中均具有作用。

小电导钙激活型钾通道(small conductance calcium-activated potassium channel, SK)由胞质内增加的钙离子激活,进而导致钾离子外流。相比于其他几种SK,SK3主要在Arc表达。最近的一项研究发现,小鼠禁食后,其AgRP神经元内SK3的表达显著低于正常进食组^[43]。SK3免疫荧光染色也得到了一致的结果,说明SK3可能是AgRP神经元内与营养水平相关的调节因子。He等人^[44]建立了在AgRP神经元中特异性敲除SK3的小鼠,结果发现敲除小鼠因食欲过剩和产热减少而发生肥胖。

2.3 激酶

IKK β 是NF- κ B抑制分子(I κ B)的激酶,可诱导NF- κ B的活化,从而调控相关基因的转录。中枢神经

系统尤其是下丘脑的慢性、低水平炎症在代谢性疾病的发生、发展中起重要作用,而IKK β 是该过程的关键调节分子. Zhang等人^[13]的研究发现,高脂食物诱导的肥胖小鼠下丘脑内IKK β /NF- κ B通路过度活化,且其激活与内质网应激相关. 同时,激活中下部下丘脑的IKK β 导致小鼠肥胖,抑制IKK β 则能显著减少体重的增加. 在AgRP神经元中敲除IKK β 后,肥胖表型明显改善,糖耐量和胰岛素敏感性显著增加. Benzler等人^[45]发现,无论是口服,腹腔注射还是中枢注射IKK β /NF- κ B通路的抑制剂紫铆因,都能显著增加糖耐量,进一步证实了Zhang等人^[13]的研究结果.

蛋白激酶A(protein kinase A, PKA)是一种依赖于cAMP的激酶. PKA R11 β 亚基的缺陷可以导致其活性下降. R11 β 在小鼠脑、棕色脂肪组织和白色脂肪组织中呈高水平表达,在其他组织中表达较少. 研究发现R11 β 敲除小鼠的白色脂肪组织减少,瘦素水平明显降低,瘦素敏感性增加,并对高脂食物诱导的肥胖和糖尿病具有保护作用^[46]. 在AgRP神经元中特异性抑制PKA的活性,能抑制能量缺乏导致的AgRP活性增加,从而改善高脂食物诱导的肥胖^[47].

AMP依赖性蛋白激酶(adenosine 5-monophosphate(AMP)-activated protein kinase, AMPK)是一种丝氨酸/苏氨酸激酶,也是重要的细胞能量感应器. 研究显示,AMPK活性受到瘦素的抑制. 当能量缺乏、钙离子浓度升高或饥饿素刺激时,其活性增加^[48,49]. 有研究表明,激活AMPK引起AgRP神经元的兴奋性突触传入增加,活性升高,从而促进食欲^[26,50]. 另外, Kong等人^[51]利用腺相关病毒介导的转基因技术构建了AgRP神经元特异性过表达或敲低AMPK的小鼠模型. 在能量缺乏状态下, AgRP神经元中的AMPK活性显著增加. 选择性激活AgRP神经元中的AMPK,可显著增加AgRP神经元树突棘的数量,小鼠的进食量和体重也显著增加. 相反,选择性抑制AgRP神经元中的AMPK活性,则能够抑制AgRP神经元的活化. 该研究还发现AMPK调控AgRP神经元突触可塑性的下游分子为p21激活激酶(p21-activated kinase, PAK). 此前, Yang等人^[26]的研究发现AMPK调节突触可塑性主要发生在突触前,即兴奋性神经元轴突末端内. Kong等人^[51]的研究则发现AMPK—PAK信号通路参与AgRP神经元中谷氨酸能神经传入的突触后调节,说明在调控能量平衡时, AMPK在突触前和突触后神经元中均有重要的作用.

2.4 内质网应激

内质网是由交织分布于细胞内的膜组成的扁平囊或腔状结构,负责蛋白质的合成、加工和运输. 各种病理因素可影响这一过程,导致未折叠或者错误折叠的蛋白质在内质网腔内聚集,以及钙离子平衡的紊乱,从而诱发未折叠蛋白反应(unfolded protein response, UPR),即发生内质网应激(endoplasmic reticulum stress, ER stress). 早期的体外和体内试验均显示内质网应激是肥胖相关的胰岛素抵抗和2型糖尿病的重要因素^[52]. 近年来,越来越多的证据表明内质网应激在瘦素抵抗中也起着关键的作用. 在食物诱导和遗传性肥胖模型中,下丘脑内质网应激反应均显著增强^[13,53,54]. 在普通食物饲养的小鼠中,用衣霉素(tunicamycin)诱导内质网应激会引起下丘脑内AgRP和NPY的mRNA水平升高,以及STAT3的激活途径被阻断,提示发生了瘦素抵抗^[54]. 颅内给予缓解内质网应激的化学伴侣分子,如4-苯基丁酸(4-phenylbutyrate, 4-PBA)或牛磺熊去氧胆酸(tauroursodeoxycholic acid, TUDCA)可显著改善肥胖小鼠的瘦素敏感性^[13,54,55]. 内质网应激是连接肥胖与瘦素抵抗的一个重要桥梁. 肥胖可以诱发内质网应激而导致瘦素抵抗,反过来,内质网应激也可以引起瘦素抵抗,促进个体肥胖,从而形成恶性循环.

高热量膳食如何诱导内质网应激,内质网应激又如何导致瘦素抵抗,具体机制仍未完全明确. 迄今为止,研究较多的是下丘脑脂肪毒在其中的作用^[56]. 下丘脑神经元,如AgRP神经元能够响应血液中的游离脂肪酸(free fatty acids, FFA)^[57,58]. 高脂食物饲养使小鼠下丘脑暴露于高浓度的FFA中,从而导致棕榈酰辅酶A(palmitoyl-CoA)和其他有害脂质堆积而产生下丘脑脂毒性^[59,60]. 体内和体外试验均证实过量的饱和脂肪酸可诱发下丘脑细胞发生内质网应激^[61,62],而内质网应激反应可通过降低STAT3的Tyr磷酸化水平而衰减瘦素信号的传导^[54].

内质网应激影响下丘脑AgRP和NPY的表达水平,但不影响POMC的表达水平^[54],其原因还需要进一步研究.

2.5 线粒体分裂与融合的动态

线粒体是为细胞提供能量的细胞器,能够对胞内环境做出响应而调整其形态和分布. 研究表明,线粒体的形态和数量与其分裂和融合有关,是在多种

蛋白质的精确调控下完成的^[63]。通常,线粒体的分裂和融合同时进行,处于动态平衡中。这种动态平衡的异常会影响线粒体正常的形态、数量和功能从而导致疾病^[64]。已知多种蛋白参与线粒体分裂和融合的动态调控,如线粒体融合蛋白1(mitofusin-1, Mfn1)和线粒体融合蛋白2(mitofusin-2, Mfn2)主要介导线粒体的融合^[65];动力相关蛋白-1(dynamin-related protein-1, Drp1)则参与线粒体的分裂^[66]。线粒体除自身的形态发生动态变化外,它与内质网之间也存在结构和功能上的联系。线粒体负责细胞的能量供应,而内质网是多肽合成与加工的主要场所。内质网与线粒体之间的联系能够加快细胞的工作效率^[67]。

Mfn2是一种跨线粒体膜且具有GTP酶活性的蛋白质,可介导线粒体融合^[65],并参与线粒体与内质网之间的联系^[68]。已有证据表明Mfn2参与肥胖和2型糖尿病的病理过程^[69,70]。Schneeberger等人^[71]的研究发现,POMC神经元中的Mfn2是联系内质网应激和瘦素抵抗的关键分子。Mfn2通过调节线粒体——内质网轴的功能,实现对全身能量平衡的调控。在肥胖小鼠的POMC神经元中,Mfn2表达水平降低,线粒体倾向于分裂而导致其密度增加。同时,线粒体——内质网之间的联系减少。POMC神经元中敲除Mfn2后,该神经元的线粒体动态和小鼠的代谢表型与高脂食物诱导的肥胖小鼠类似。POMC神经元中缺乏Mfn2引起线粒体形态和线粒体——内质网轴稳态异常,POMC前体肽加工障碍,最终导致内质网应激,进而引起瘦素抵抗和肥胖。颅内给予缓解内质网应激的化学药物4-PBA,能改善Mfn2敲除导致的代谢异常^[72]。总之,POMC神经元中Mfn2缺乏导致线粒体分裂和融合的动态平衡受到破坏。线粒体倾向于分裂而使线粒体与内质网之间联系减少,进一步发生内质网应激和瘦素抵抗,最终导致肥胖。

同时,Dietrich等人^[73]发现在不同的营养状态下,AgRP神经元中的线粒体也呈明显的动态变化,线粒体融合蛋白在此过程中发挥重要的作用。有趣的是,线粒体融合蛋白在AgRP神经元中的作用与在POMC神经元中明显不同。在肥胖小鼠中,POMC神经元的线粒体呈“分裂样”改变。但在AgRP神经元中,线粒体面积增大、密度变小,呈“融合样”改变,但线粒体与内质网之间的联系未发生显著的改变。这些现象表明,线粒体融合蛋白在调控线粒体动态时存在细胞特异性。此外,与POMC神经元中Mfn2敲除后导致

的内质网应激相反,AgRP神经元中敲除Mfn1或Mfn2能够抑制肥胖相关的内质网应激。同时,AgRP神经元活性降低,从而对高脂食物诱导的肥胖产生抵抗作用。

线粒体的动态变化为能量平衡调控和肥胖研究提供了新的思路和研究方向。这种动态变化是否涉及下丘脑其他核团或神经元,以及是否涉及其余相关的线粒体蛋白,需要进一步的研究。

3 AgRP神经元释放的神经递质

AgRP神经元的活性水平是影响摄食行为的重要因素。活性变化最直接的结果就是它释放的神经递质的改变。已知AgRP神经元共表达和释放AgRP, NPY和GABA,因此,其至少通过这3种神经递质发挥作用。

AgRP是促进食欲的神经肽,主要作用于下丘脑PVN等核团中表达MC4R的神经元^[74]。颅内注射AgRP或NPY都能促进小鼠的食欲^[75]。虽然由同一种神经元产生,但二者的作用机制并不相同。NPY直接通过NPY受体,如Y1和Y5发挥作用^[76];而AgRP则是通过竞争性结合黑皮质素受体3和4(melanocortin 3/4 receptor, MC3/4R),拮抗 α -促黑色素细胞激素(α -melanocyte-stimulating hormone, α -MSH)的抑食作用^[4]。此外,AgRP与NPY调节食欲的时程有所不同。NPY促进食欲的时间较短,而AgRP的作用时间较长^[75]。

除了AgRP和NPY神经肽,AgRP神经元还释放抑制性神经递质GABA。尽管AgRP和NPY都是很强的促食欲的神经肽,但是令人惊讶的是,同时敲除AgRP和NPY基因后,小鼠的体重几乎不受影响^[77]。因此,AgRP神经元中可能存在其他的、在能量平衡调控中发挥更为关键作用的分子。Tong等人^[78]发现,特异性敲除AgRP神经元中的GABA囊泡转运体基因VGAT(vesicular GABA transporter),能够抑制GABA的释放。由于传入POMC神经元的抑制性GABA信号减少,小鼠表现出能量消耗增加,从而对高脂食物诱导的肥胖产生抵抗。Wu等人^[79]利用腺相关病毒技术敲除Arc的谷氨酸脱羧酶基因Gad1,从而使GABA无法在Arc合成。这些小鼠表现出进食量明显减少。向中脑臂旁核内(parabrachial nucleus, PBN)注射GABA受体激动剂,能够使小鼠的食欲恢复,说明AgRP神经元可通过释放GABA抑制PBN神经元的活性,从而

维持正常的食欲. Campos等人^[80]的研究进一步发现, 这种抑制作用的靶细胞是外侧臂旁核内表达降钙素基因相关肽(calcitonin gene-related peptide, CGRP)的神经元. AgRP神经元通过抑制CGRP神经元的活性而促进食欲.

4 受AgRP神经元调控的受体及黑皮质素系统

黑皮质素受体家族(melanocortin receptor, MCR)共有5个亚型, 即MC₁₋₅R. 这些分子都是G蛋白偶联受体, 在中枢和外周的分布差别较大. 其中MC3R和MC4R主要在中枢神经系统内表达^[81]. MC4R突变导致的肥胖约占成人肥胖病例的0.5%到儿童肥胖的6%不等^[82]. 小鼠中MC4R的缺失引起明显的肥胖^[83].

AgRP和POMC神经元是中枢神经系统内调控食欲和体重的一级神经元. 它们都受到瘦素和胰岛素信号的共同调控. POMC神经元表达CART和POMC. POMC经酶切产生 α -MSH等多种成熟的多肽. α -MSH是黑皮质素受体3/4(MC3/4R)的天然配体, 主要通过结合PVN中的MC3/4R起抑制食欲和促进产热的作用. AgRP神经元则表达促食肽AgRP和NPY. AgRP通过与 α -MSH竞争性结合MC3/4R发挥促食作用. 在食欲和体重调控的研究中, 由AgRP, α -MSH和黑皮质素受体所构成的黑皮质素系统的作用一直占有重要的地位^[84].

早期的研究已证实MC4R通过与G蛋白偶联从而激活下游的cAMP-PKA信号通路^[85]. Ghamari-Langroudi等人^[86]的研究发现, α -MSH与AgRP对PVN中MC4R神经元活性的调节并非依赖于G蛋白信号通路, 而是通过调节Kir7.1离子通道的开闭而实现的. Kir7.1是一种内向整流钾通道, 主要作用是稳定膜静息电位和调节钾离子的跨膜转运. α -MSH结合MC4R, 使之与Kir7.1偶联使通道关闭, 从而使表达MC4R的神经元去极化而激活. 相反, AgRP与MC4R结合后使Kir7.1通道开放, 神经元出现超级化而被抑制.

5 AgRP神经元参与的神经环路

AgRP神经元与下丘脑及下丘脑外神经元之间存在广泛的突触联系, 形成复杂的神经环路.

5.1 下丘脑内神经环路

前面提到, AgRP神经元和POMC神经元是多种

激素和营养元素信号的整合部位. 它们均受到瘦素和胰岛素的调控, 并作用于下游PVN中表达MC3/4R的神经元从而调控能量代谢^[84]. 同时, AgRP神经元通过GABA抑制POMC神经元的活性, 但是这种抑制作用并不是AgRP神经元在急性诱发进食行为中所必需, 可能在长期调控中发挥作用^[87]. 反过来, POMC神经元通过 β -内啡肽抑制AgRP神经元的活性^[26]. 除了黑皮质素系统, AgRP神经元也通过神经递质GABA作用于PVN. 其中表达催产素(Oxytocin, OXT)的神经元是一个重要的作用靶点. OXT神经元功能缺失能导致食欲过剩和肥胖^[88,89]. AgRP神经元通过GABA抑制OXT的活性从而促进食欲^[87]. 另外, 研究表明, AgRP神经元对下丘脑外侧区(lateral hypothalamic area, LHA)的投射也足以引发进食, 但其作用机制还需进一步研究^[90].

此外, PVN中的TRH(thyrotropin-releasing hormone)神经元和PACAP(pituitary adenylate cyclase-activating peptide)神经元通过谷氨酸兴奋AgRP神经元, 而DMH中表达瘦素受体的神经元通过GABA抑制AgRP神经元的活性. 也就是说, TRH^{PVN}—AgRP和PACAP^{PVN}—AgRP的兴奋性神经环路在饥饿引起AgRP神经元的活化过程中起着重要的作用^[27], 而LepR^{DMH}—AgRP的抑制性神经环路在抑制AgRP神经元活性的过程中具有作用^[31].

5.2 下丘脑外神经环路

近年来, 下丘脑以外脑区对食欲和体重的调控引起了研究者的关注. 研究表明, 多个下丘脑外核团参与能量代谢的调控, 如终纹床核(bed nucleus of the stria terminalis, BNST)^[91]、中央杏仁核(central nucleus of the amygdala, CeA)^[92]、孤束核(nucleus of the solitary tract, NTS)^[93]和PBN等. 这些核团与下丘脑核团共同组成复杂的环路, 从而调控食欲和体重. Betley等人^[90]利用光遗传学技术研究AgRP神经元的投射部位, 发现其直接投射到PVN, LHA, BNST, CeA, PBN和中脑导水管周围灰质(periaqueductal gray, PAG). 通过光刺激AgRP神经元到PVN, LHA, BNST这几个脑区的轴突末端引起小鼠进食量增加, 但其具体机制还有待研究. 虽然光刺激AgRP神经元到PBN的轴突未观察到小鼠进食量增加, 但是多个研究发现激活PBN内神经元上的GABA受体能够恢复剔除AgRP神经元小鼠的进食量^[79,80].

PBN位于脑桥上部,与嗅觉和内脏感觉相关.越来越多的证据表明,PBN是一个参与食欲和体重调控的重要脑区^[79,80,94-96].进餐后,肠道内的胆囊收缩素(cholecystokinin, CCK)和胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)等将饱腹信号经迷走神经传至NTS^[97,98],NTS的轴突投射到PBN,通过谷氨酸激活PBN神经元,从而防止过度进食.PBN外侧部表达CGRP神经元(CGRP^{PBN})又通过谷氨酸投射到CeA,使CeA的神经元活化而抑制食欲.因此,NTS—CGRP^{PBN}—CeA之间形成一条非常重要的抑制食欲的神经环路^[80].同时,MC4R^{PVN}神经元也投射于PBN,通过谷氨酸激活PBN外侧部的神经元活性从而抑制食欲^[99].相反,AgRP神经元则通过GABA抑制PBN神经元活性从而促进食欲.Wu等人^[79]将GABA受体激动剂溴他西尼注射至多个核团,包括PBN,NTS和

PAG,发现只有注射至PBN能够避免AgRP神经元剔除小鼠的饥饿致死现象,说明AgRP神经元与PBN之间的神经投射对于食欲调控起到关键作用.AgRP神经元是引发进食行为所必需,而PBN则是一个非常重要的防止机体过度摄食的负反馈节点.

6 结语

AgRP神经元在食欲和体重调控中具有重要的作用,涉及复杂的神经环路及细胞和分子水平的机制.多种调控分子和信号通路,如激素、受体、离子通道、激酶、神经递质、内质网应激和线粒体动态等在AgRP神经元调控能量平衡中发挥着重要的作用.尽管如此,鉴于目前治疗肥胖的药物仍然极为有限,深入理解AgRP神经元在肥胖病理形成过程中的作用就具有重要的意义.

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Summary for “下丘脑 AgRP 神经元调控食欲和体重研究进展”

Hypothalamic AgRP neurons and the regulation of appetite and body weight: A review

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The maintenance of energy balance is essential for the survival of animals. The hypothalamus in the brain plays a central role in this process through the integration of neural, nutritional and hormonal signals. Multiple and distributed neuronal populations in the hypothalamus form complex circuits to regulate appetite and body weight. Located in the arcuate nucleus of hypothalamus, agouti-related peptide (AgRP)-expressing cells are known as the hunger-promoting neurons. Over the past three decades, extensive studies have been performed to understand the role of AgRP neurons in energy balance control. AgRP neurons are both necessary and sufficient to orchestrate feeding behavior. The AgRP neuron activity adapts to and thereby is regulated by the nutritional status in the body. Furthermore, we now know that this alternation is driven by various circulating hormones, such as Leptin and Ghrelin, as well as synaptic inputs from upstream neurons. Neurotransmitters (e.g. glutamate and GABA) play a vital role in the regulation of AgRP neuron activity. The excitatory glutamatergic input is required in fasting-related activation of AgRP neurons, whereas the inhibitory GABAergic inputs is crucial in the rapid reduction of AgRP neuron activity in response to food-related cues, and thus, to terminate a meal. In addition to these molecules, signaling molecules and pathways in AgRP neurons, such as receptors, ion channels, kinases (e.g. IKK β), endoplasmic reticulum stress (ER stress) and mitochondrial dynamic, are critically involved in the control of its activity. Moreover, AgRP neurons release neuropeptides AgRP and NPY, as well as neurotransmitter GABA to regulate neuronal activity. Both AgRP and NPY potently promote appetite. Although NPY is widely expressed in the central nervous system, it is mainly co-expressed with AgRP in the arcuate nucleus of hypothalamus. The appetite-promoting effect of NPY is mediated by Y1 and Y5 receptors, while AgRP exert its orexigenic effect mainly by antagonizing the central melanocortin system. Surprisingly, ablation of AgRP neurons in neonates has little effect on body weight, whereas these neurons are essential for the maintenance of appetite in adult mice. Moreover, accumulating evidences indicate that GABA released by AgRP neurons is required to retain animals' appetite. At the circuit level, AgRP neurons project to both intra- and extra-hypothalamic regions to regulate energy balance. For example, in arcuate nucleus, AgRP neurons innervate and inhibit POMC neurons via the inhibitory GABAergic synapses. Conversely, POMC neurons release β -endorphin, a μ -opioid receptor agonist, to inhibit the activity of AgRP neurons. In summary, AgRP neurons play a crucial role in the regulation of appetite and energy balance. Targeting hypothalamic AgRP neurons might be a relevant approach to treat common obesity.

hypothalamus, arcuate nucleus, AgRP neuron, appetite, body weight, obesity

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