神经肽PACAP对神经内分泌系统的调控

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摘要 神经肽类激素垂体腺苷酸环化酶激活多肽(pituitary adenylate cyclase-activating polypeptide, PACAP)最初从牛的脑垂体中被分离; 后续研究发现, PACAP及其受体广泛存在于机体的各个组织器官, 全面参与机体中枢和外周神经内分泌系统的功能调节。在中枢神经内分泌系统层面, PACAP通过促进下丘脑–垂体分泌各种上游激素, 正向调控下游神经内分泌组织和器官的分泌, 发挥神经内分泌网络的“指挥棒”功能; 在外周神经内分泌系统层面, PACAP通过分布在外周神经内分泌组织器官内的受体, 采用自分泌和旁分泌方式, 实现对各种下游激素分泌的精细调控, 发挥维持神经内分泌系统整体和谐平衡的“平衡器”作用。该文就PACAP对中枢和外周神经内分泌系统的调控作用进行整理, 分析得出PACAP对神经内分泌系统的双重调控功能, 为PACAP对神经内分泌系统功能的药用开发奠定理论基础。

关键词 垂体腺苷酸环化酶激活多肽; 神经肽; 激素; 神经内分泌系统; 调控

Regulation of Neuroendocrine System by Neuropeptide PACAP

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Abstract The neuropeptide hormone PACAP (pituitary adenylate cyclase-activating polypeptide) was originally isolated from the bovine pituitary gland. Subsequent studies have found that PACAP and its receptors are widely present in various tissues and organs of the body, and fully participate in the functional regulation of the central and peripheral neuroendocrine systems. At the level of the central neuroendocrine system, PACAP serve as the “baton” of the neuroendocrine network to regulate the secretion of downstream neuroendocrine tissues and organs by promoting the secretion of various upstream hormones from the hypothalamus-pituitary system. Moreover, at the level of the peripheral neuroendocrine system, PACAP works as the “balancer” to keep the neuroendocrine harmonize by fine adjustment on various downstream hormones secretion through its receptors distributed in the tissues and organs of the peripheral neuroendocrine system and in the way of autocrine and paracrine. This article collates the regulatory effects of PACAP on the central and peripheral neuroendocrine systems, infers the dual regulatory function of PACAP, and lays theoretical foundation for the drug development of PACAP in the neuroendocrine system.

Keywords pituitary adenylate cyclase-activating polypeptide; neuropeptide; hormones; neuroendocrine system; regulation

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神经肽垂体腺苷酸环化酶激活多肽(pituitary adenylate cyclase-activating polypeptide, PACAP)属于血管活性肠肽(vasoactive intestinal polypeptide, VIP)/胰高血糖素/生长激素释放激素/分泌素家族, 在机体各组织器官中广泛分布[1]。PACAP在体内有PACAP27和PACAP38两种形式, PACAP27是PACAP38的N-端截短肽; PACAP27与VIP有高达68%的同源性[2]。PACAP靶向3个B类G蛋白偶联受体: PAC1-R(pituitary adenylate cyclase 1 receptor)、VPAC1-R(vasoactive intestinal polypeptide receptor 1)和VPAC2-R(vasoactive intestinal polypeptide receptor 2), 其中VPAC1-R和VPAC2-R是PACAP和VIP的共同受体; PAC1-R与PACAP的亲和力是VIP的1 000倍, 也是PACAP的特异性受体[3]。作为特异敏感识别PACAP的受体, PAC1-R主要介导了PACAP对神经内分泌系统的调控功能。PACAP的不同基序发挥对PAC1-R活性不同调控作用; 其中, PACAP(1~5)负责正位激活PAC1-R[4]; 缺失PACAP(1~5)的PACAP(6~38)是PAC1-R的特异抑制剂[5]; 此外, PACAP(28~38)因能有效增强对PAC1-R的激活, 发挥了靶向PAC1-R的正向别构调节作用[6]。

PACAP进化过程极其保守, 人和青蛙的PACAP只有1个氨基酸的差异。PACAP及其受体广泛存在于机体神经内分泌系统的各个组织和器官; 已有的研究提示, PACAP不仅可以作为“指挥棒”调控下丘脑–垂体分泌上游激素, 调节下游神经内分泌系统相关的组织和器官的分泌; 还可以作为一种“平衡器”, 通过广泛存在于神经内分泌组织器官中的受体, 采用自分泌和旁分泌方式对下游神经内分泌进行精细调控; 本文就PACAP分别对中枢和外周神经内分泌系统的调节作用进行归纳和综述, 整理PACAP对神经内分泌系统的调控规律, 为PACAP对神经内分泌系统调控作用相关的药物开发奠定药理学研究的理论基础。

1 PACAP调控下丘脑–垂体激素分泌

1.1 生长激素(growth hormone, GH)

研究人员通过对动态灌流的大鼠垂体瘤细胞分泌GH的观测发现: PACAP38、PACAP27和VIP均可促进GH的释放; 在1 nmol/L浓度下, 三者作用效果相当, 但PACAP38有效作用时间显著较PACAP27和VIP延长; PAC1-R的特异抑制剂PACAP6-38和VIP拮抗剂可分别有效抑制PACAP38和VIP的促GH释放的活性[7-8]。在产生GH的垂体细胞, 如大鼠垂体瘤GH3细胞中, 检测到PACAP的多种受体的表达, 包括: PAC1-R的剪接变体PAC1-Hop[9]和VPAC2-R[10]。在绵羊和牛的垂体细胞中, 均发现PACAP可有效促进GH的分泌[11-12]。以上发现提示, PACAP通过受体PAC1-R和VPACR刺激生长激素分泌细胞释放生长激素, 且PAC1-R介导促生长激素分泌的效果更为显著。

1.2 催乳素(prolactin, PRL)

在大鼠垂体产PRL的GH3细胞中, PACAP可通ERK和cAMP/PKA信号通路增强PRL的合成和分泌[13]。用增强PAC1-R表达的载体转染GH3细胞后, PACAP诱导的催乳素基因表达的作用可随PAC1-R表达水平的增加而加强, 这提示是PAC1-R介导了PACAP促PRL分泌的作用。此外, PACAP还协助增强了促甲状腺激素释放激素(thyrotropin-releasing hormone, TRH)促进PRL分泌的作用, 而且PACAP协同TRH促PRL分泌的作用与PAC1-R密切相关[14]。

1.3 促性腺激素释放激素(gonadotropin-releasing hormone, GnRH)

1.3.1 GnRH 研究发现, PACAP可以通过PAC1-R上调GnRH受体的表达[15]; 同样GnRH可以诱导PACAP和PAC1-R的表达[16], 这表明了PACAP和GnRH之间存在交流(crosstalk), 可通过相互协同的作用, 以自分泌和旁分泌的方式上调促进性腺激素的表达。

1.3.2 促卵泡激素(follicle-stimulating hormone, FSH) 在大鼠垂体细胞体外培养系中发现, PACAP不仅增加了表达卵泡抑素(follistatin)的细胞数量, 而且增加了分泌FSH的垂体细胞内的颗粒数量; 而分泌卵泡抑素和FSH的垂体细胞均高表达PAC1-R[17]。体内研究则发现: 成熟大鼠间脑室旁核中PACAP与FSH的β亚基的表达之间的关联密切[18]; 另有机制研究则提示, PACAP通过MAPK/cFOS途径诱导FSH的β亚基的表达[19]。除了可以直接促进垂体细胞分泌FSH外[20], PACAP还被发现通过其特异PAC1-R有效增强GnRH对FSH表达的调控, 即PACAP对GnRH的调控具有协同作用[21]。

1.3.3 黄体生成素(luteinizing hormone, LH) 在雄性大鼠中发现, 脑室内注射PACAP会以剂量依赖的方式增加血浆中LH的水平[22]。同样地, 在垂体细胞

LβT2中发现, 一方面, 单独的PACAP可促进LHα和β亚基的表达; 另一方面, 细胞中PAC1-R的存在能够显著增强GnRH对LH表达的影响[23]。这些研究表明了PACAP可通过多个途径调控LH的分泌。

研究发现, PACAP对LH的调控与发情期和昼夜节律密切相关: 处于发情期的雌性或雄性大鼠的垂体中PACAP释放量显著高于发情间期, 并且在发情期的雌性大鼠中, PACAP促进LH分泌的作用在清晨与在中午或晚上相比显著增强; 而在发情间情期开始的前期10~12 h, PACAP会使LH的分泌降低, 在间情期后期(16 h) PACAP则不显著影响LH的释放[24]。

1.3.4 *促性腺激素*(gonadotropin, GTH) 整理发现, PACAP对下丘脑–垂体分泌GTH的调控作用存在明显的性别差异: 雄性大鼠下丘脑的PACAP对促性腺激素的调控作用主要是激动性的(正向); 而在雌性大鼠中, 它对促性腺激素分泌的调控作用具有激动(正向)和抑制(反向)的双向性[25], 而且作用的方向与雌性的生理周期密切相关; 这些发现与PACAP及其受体的表达有显著性别差异相吻合。

1.4 促肾上腺皮质释放激素(corticotropin-releasing hormone, CRH)和促肾上腺皮质激素(adrenocorticotropic hormone, ACTH)

PACAP在调控下丘脑–垂体–肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA)中发挥显著正向调节作用, 即PACAP能有效促进CRH和ACTH在下丘脑–垂体中的分泌。其中, CRH在调节HPA轴方面起着核心作用, 已发现PACAP可以通过cAMP/PKA信号通路[26]刺激*CRH*基因在下丘脑细胞中的表达[27]。而对于ACTH, 体内研究发现小鼠脑室单独给药PACAP, 就可有效促进ACTH分泌的增加[28]; 而利用大鼠垂体细胞克隆系ATT-20进行的研究, 则发现PACAP不仅单独用药就可以刺激分泌ACTH, 并且当CRH与PACAP共同作用ATT-20细胞时, ACTH的分泌更加显著[29]; 此结果提示PACAP对ACTH的正向调控可通过多个途径实现。

1.5 促甲状腺激素(thyroid-stimulating hormone, TSH)

在非哺乳动物中, 研究发现PACAP和VIP通过PAC1-R和VPAC2-R剂量依赖性刺激牛蛙垂体细胞释放TSH[30]。而在哺乳动物中, 数据较少, 只有早期的研究表明体内注射PACAP不影响大鼠[31]和人类[32]的血浆TSH浓度, 且共定位研究发现, 在垂体前叶细胞中, 只有少数细胞既表达TSH又结合PACAP[33], 即PACAP并不改变大鼠垂体前叶细胞TSH的分泌[34]。由于最新研究相关数据缺乏, PACAP对哺乳动物促甲状腺激素分泌的具体影响还需要更多的研究来证明。

1.6 促黑素细胞激素(melanocyte-stimulating hormone, MSH)

黑皮素原(proopiomelanocortin, POMC)是具有调控应激和抗炎作用的激素MSH的前体。在非洲爪蟾黑素细胞中, 发现PACAP通过显著刺激POMC表达进而促进MSH的分泌[35]。此外, PACAP被发现能够通过cAMP/PKA和PKC信号通路来增加小鼠垂体细胞[36]和神经中叶[37]中*POMC*的mRNA水平, 从而促进MSH的分泌; 在大鼠中也有相同的发现[38]。

2 PACAP调控松果体的分泌

PACAP很早已被发现在大鼠松果体中大量存在, 并且其分泌具有昼夜节律[39], 而且在松果腺中亦存在高密度的PACAP结合位点[40]。体外研究表明, PACAP可以有效刺激灌流的大鼠松果腺和培养的松果体细胞分泌褪黑素(melatonin, MT), 并参与调节视交叉神经活性的昼夜周期[41]。而体内的研究证明, PACAP有效参与大鼠和鸡的松果体中褪黑激素的释放[42], 即PACAP对松果体MT的释放具有显著正向调控作用。另外, 研究发现PACAP刺激松果体MT的释放是通过松果体自身细胞中的PAC1-R受体介导的; 并且具有与光照密切相关的作用特点, 表现于: 如果在黑暗条件下, MT的释放量不会随PACAP刺激的时间变化而发生规律性改变[43]。同样地, 有数据显示PACAP存在于鸡松果体的神经纤维中, 松果体细胞中含有PACAP的敏感受体, PACAP可规律性调节MT的释放但不改变松果体的固有生物钟[44]。这提示了松果体是可以通过自分泌PACAP在PAC1-R的介导下上调自身MT的释放, 并调节视交叉神经的昼夜节律的。

3 PACAP调控甲状腺的分泌

PACAP及其3个受体被发现在大鼠甲状腺和甲状旁腺中有分布[45]; 在小鼠甲状腺滤泡细胞中则发现存在有VPAC2-R[46]。在人的甲状腺细胞中发现存在PACAP和PAC1-R的表达[47]; 而在哺乳动物中, PA-

CAP27和PACAP38均可快速高效地增加猪甲状腺细胞中cAMP的产生量, 并高效增加小鼠体内甲状腺T4的产生量, 这两种PACAP均可抑制TSH与甲状腺膜的结合, 其中PACAP38的抑制效果更显著[48]。而最新的研究发现, 参与甲状腺激素(thyroid hormone, TH)代谢转化的2型脱碘酶(type 2 deiodinase, D2)可被PACAP上调, 提示PACAP直接参与介导了TH的代谢反馈[49]。

4 PACAP调控肾上腺的分泌

研究发现, PACAP38在大鼠的肾上腺髓质中高表达[50], 且PACAP38的浓度显著高于PACAP27[51]。此外, PACAP显著上调肾上腺儿茶酚胺(catecholamines, CA)的分泌在犬和大鼠中均有发现[52-53]; 并且其上调作用均可被PAC1-R特异拮抗剂以剂量依赖方式所抑制; 这提示PACAP是通过PAC1-R介导刺激肾上腺分泌CA的。已有的研究还表明, PACAP既可以作为肾上腺交感神经递质参与儿茶酚胺的调节[54], 又可以作为神经调节剂参与肾上腺的局部调节[55]。

关于PACAP上调CA的机制研究发现, 除PAC1-R介导PACAP刺激CA分泌外, 在大鼠肾上腺髓质细胞存在的VIP/PACAP共同受体VPAC1-R和VPAC2-R也能介导PACAP刺激CA的分泌; 其中, PAC1-R主要与腺苷酸环化酶级联耦合, VPAC1-R介导与腺苷酸环化酶和磷脂酶C依赖的级联耦合, VPAC2受体仅与磷脂酶C依赖级联耦合, 即PACAP刺激儿茶酚胺分泌的途径包括腺苷酸环化酶途径和磷脂酶C途径[56]。

另外, 值得注意的是, PACAP不仅通过促进上游激素CRH和ACTH的分泌, 调控肾上腺的分泌, 而且可以通过分布在肾上腺中的受体, 直接诱导去甲肾上腺素的释放, 这在利用PACAP27通过上胰十二指肠动脉局部输注到胰腺和肾上腺中观察去甲肾上腺素浓度的实验中已经得到了证明[57]。

5 PACAP调控多巴胺的分泌

已有的研究均显示, PACPA与多巴胺(dopamine, DA)的表达之间存在紧密联系, PACAP能够有效减缓DA随龄分泌的衰退; 例如: 在老年帕金森病的大鼠模型中, 脑室注射PACAP可减少老化大鼠脑部DA的随龄损失, 并提高具有神经保护作用的帕金森病蛋白7(parkinson disease protein 7, PARK7)的表达水平[58]。此外, PACAP在保护多巴胺能神经元方面也发挥显著积极作用, 例如: 在胚胎大鼠的原代培养物中, PACAP能够阻止6-羟基多巴胺诱导的多巴胺能神经元的死亡[59]; 在鱼藤酮(rotenone)诱导的蜗牛帕金森病模型和6-羟基多巴胺诱导的大鼠帕金森病模型中, 也同样发现了PACAP能够挽救多巴胺神经元, 改善6-羟基多巴胺诱导的帕金森症状大鼠运动能力损伤[60]。此外, PACAP还可以剂量依赖的方式, 减少内源性多巴胺代谢物Salsolinol所导致的多巴胺能神经元凋亡, 这种抗凋亡作用可以被PACAP特异性受体PAC1-R拮抗剂PACAP(6-38)所阻断[61]; 这提示了PACAP是在PAC1-R的介导下调控多巴胺神经元的保护作用的。

6 PACAP调控胰岛腺的分泌

PACAP27和PACAP38均可以显著刺激胰岛素分泌[52]。现已有研究发现, PAC1-R、VPAC1-R和VPAC2-R均存在于胰岛细胞中[62-63], 且PACAP38主要在PAC1-R的介导下通过cAMP及其下游效应的PKA途径增加胞内钙离子浓度刺激的胰岛素分泌[64]。PACAP在体内对葡萄糖诱发的胰岛素释放具有协同促进的作用; 表现在单独使用葡萄糖或PACAP进行胰腺局部注射, 均能引起胰岛素分泌水平的升高; 而当使用葡萄糖和PACAP共同进行注射时, 相比单独注射其中一者, 共同使用引起胰岛素分泌增加的效果更为显著[65]。总之, PACAP可以显著正向调控胰岛分泌胰岛素。

7 PACAP调控性腺的分泌

7.1 卵巢

研究表明, PACAP在下丘脑–垂体–性腺轴中发挥重要的调节作用, 既可以通过调节神经内分泌活动参与调节卵巢卵泡的发育过程, 也可以通过分布在卵巢中的受体, 采用自分泌和旁分泌的方式对卵巢的分泌功能进行精细调控。目前, 除在大鼠排卵前期的卵泡中检测到了PACAP的表达外, 在排卵期的卵巢细胞中也发现存在有PACAP, 包括有颗粒细胞、基质细胞, 甚至是支配卵巢的神经纤维也存在PACAP[66]。而在卵泡发育过程中, PACAP可以抑制原代卵泡细胞的转变并抑制其增殖[67], PACAP和VIP添加到FSH刺激的卵泡中, 可抑制卵泡生长[68]; PACAP可使未成熟卵泡细胞的雌二醇分泌增加[69]。另外, 在利用孕马血清促性腺激素和人绒毛膜促性

腺激素治疗后的大鼠卵巢颗粒细胞中, 均发现了PACAP以及其特异性受体PAC1-R的存在[70-71], 这表明了PACAP可能是在特异性PAC1-R的介导下发挥调控卵泡发育过程的, 但是其他受体是否参与介导PACAP作用, 这需要更多的研究证明。

最新的发现, PACAP与松弛素(relaxin)协同作用, 不仅可促进大鼠卵巢膜间质细胞和颗粒细胞分泌参与基质重塑的明胶酶(gelatinase), 并且PACAP通过cAMP通路, 可改变颗粒细胞和膜间质细胞的形状, 进而调节卵巢分泌功能[72], 而松弛素单独作用则不能改变颗粒细胞和膜间质细胞的形状。这也表明了PACAP调节卵巢的过程是通过cAMP相关的信号通路介导的, 也支持了PACAP本身可以作为卵巢响应促性腺激素的生理介质, 促进排卵过程的观点。

相关PACAP促进卵巢激素分泌的研究还表明, PACAP可以刺激大鼠卵巢中的cAMP积累和类固醇生成[73]; 在大鼠卵巢颗粒细胞中, PACAP不仅单独增加了雌激素、孕激素和20α-二氢黄体酮的生成, 而且还能够协同增强FSH诱导的黄体酮和20α-二氢黄体酮积累[74-75], 这表明PACAP在正向调节卵巢激素分泌方面也是可以通过多个途径实现的。

值得注意的是, 虽然单独PACAP会促进黄体酮和cAMP积累[76], 但是在LH存在时, 高浓度的PACAP则会抑制LH诱导的cAMP的积累和黄体酮的产生[70], 并且PACAP会抑制黄体细胞中LH受体的增加; 此研究提示PACAP对卵巢的分泌具有双向性, 既可通过PKA途径的参与刺激黄体酮的产生, 也参与对黄体酮分泌的负反馈调控, 从而发挥全面而精细调节卵巢激素分泌的功能。

7.2 睾丸

PACAP在睾丸中存在并被大量合成, 研究已经发现在大鼠的睾丸和附睾中存在有*PACAP* mRNA, 并且*PACAP* mRNA的表达也会受到睾丸内部温度的调控[77]。PACAP特异受体*PAC1-R*的mRNA也被发现存在大鼠睾丸中[78]。PACAP27和PACAP38均可刺激大鼠睾丸间质细胞睾酮及cAMP的产生, 而且PACAP38的作用比PACAP27更为显著[79], 这表明了PACAP单独作用即可刺激睾丸分泌睾酮。另外, 存在于睾丸中的PACAP及其受体PAC1-R在繁殖季的表达明显高于非繁殖季[80]。因此, 可以得出结论, 睾丸可以通过自分泌PACAP, 在PAC1-R的介导下刺激睾丸睾酮的产生, 且在繁殖季节PACAP刺激睾丸分泌睾酮可能比非繁殖季更显著。除此之外, 缺乏PACAP会导致精子发生中的信号受到干扰, 造成小鼠生育能力降低[81], 这也表明了PACAP具有一定改善雄性小鼠生育的能力。

然而关于睾丸中介导PACAP发挥作用的受体种类存在不同观点。有研究发现生殖细胞精子中不存在*PAC1-R* mRNA和*VPAC1-R* mRNA, 而VPAC2-R是可以很容易被检测到的[82], 表明PACAP是在VPAC2-R受体的介导下在睾丸中发挥作用的。还有研究表明了PACAP、PAC1-R、VPAC1-R、VPAC2-R在麝鼠的胚芽和体细胞睾丸中均有广泛的表达[80]。那么睾丸中介导PACPA发挥作用的是哪一种受体, 这还需要更多研究来证明。

总之, 上述的整理清楚地表明了PACAP对性腺激素具有多方面的调控, PACAP既可以在下丘脑–垂体–性腺轴中通过促进GnRH、FSH和LH的分泌来对性腺分泌性腺激素进行调控, 也可以通过分布在性腺中的受体, 通过自分泌和旁分泌, 或直接促进性激素释放, 或对FSH和LH在性腺中作用进行精细调节。

8 PACAP调控脂肪组织的分泌

PACAP及其3种受体均在脂肪细胞中被发现; 并且PACAP与VIP均可以诱导大鼠脂肪细胞的脂肪分解[83]。对于介导脂肪分解的受体类型, 有研究通过利用3种受体的拮抗剂和激动剂, 发现只有VPAC2-R的激动剂在脂肪分解方面介导和PACAP、VIP相似的活性[83]; 研究发现, 主要由VPAC2-R介导了PACAP和VIP的促脂肪分解作用[83-84]。除此之外, PACAP也被报道参与了脂肪细胞分泌的、具有抗炎、抗糖尿病和抗动脉粥样硬化作用的脂联素(adiponectin)的分泌调控[85]。另有研究发现, VPAC1-R激动剂在降低脂肪增长方面也起着一定作用, 使用VPAC1-R激动剂治疗的小鼠, 其因高脂肪饮食诱导的体重和白色脂肪组织(附睾和背侧)重量的增加被抑制, 高脂肪饮食诱导的血浆葡萄糖、胆固醇和甘油三酯水平的增加也因使用VPAC1-R激动剂被下调[86]。这说明了VPAC1-R激动剂可能有助于抑制高脂肪饮食诱导的肥胖相关代谢疾病的发病率。

9 PACAP调控胃肠道组织的分泌

PACAP27和PACAP38及其3类受体在胃肠道的表达均已得到证实[87]。通过对*PACAP*$^{-/-}$突变小鼠和

PACAP野生型小鼠分别给药葡聚糖硫酸钠诱导其发生结肠炎, 研究人员发现, PACAP可有效抑制葡聚糖硫酸钠所诱发的促炎细胞因子的产生[88]。另外, PACAP和VIP均可以放松大鼠平滑肌, 减少胃肠道的基础平滑肌收缩, 且PACAP的作用是VIP的100倍[89]。

PACAP可通过抑制胃泌素分泌, 从而抑制胃酸的分泌[90]。促胰液素、生长抑素和前列腺素E2也被报道参与了PACAP对大鼠胃酸分泌的抑制作用[91]。但是, 与此存在争议的是, 有研究认为, PACAP通过刺激能够调节胃酸分泌的肠嗜铬样细胞释放组胺, 进而诱导大鼠分泌胃酸[92], 并且在PAC1-R介导下的PACAP比胃泌素能够更加有效地调节肠嗜铬样细胞的增殖, 这也说明了PACAP对胃酸分泌有正向调节作用。那么, PACAP对胃酸分泌的调控作用到底是刺激还是抑制, 或者是先抑制再刺激, 或先刺激再抑制, 这需要更多的深入研究来探索证明。

除此之外, PACAP还可以对胃十二指肠碳酸氢盐的分泌产生影响, PACAP可由cAMP介导十二指肠碳酸氢盐的分泌, 但不介导胃中碳酸氢盐分泌[93]; 这些研究表明了PACAP能够对十二指肠起到一定的保护作用。

10 PACAP调控脑肠肽的分泌

已知大脑和肠道之间存在的脑肠轴是由神经内分泌介导的双向应答系统, 脑肠轴通过“脑–肠互动”进行调控。脑肠肽及其受体在大脑和胃肠道中双重分布, 是具有神经递质和激素双重功能的小分子多肽物质, 是脑肠轴发挥作用的重要物质基础。

已有研究发现, PACAP对多种脑肠肽的分泌具有显著的调控作用[94]。

10.1 胃泌素释放肽(gastrin releasing peptide, GRP)

GRP及其受体广泛分布于哺乳动物的大脑和胃肠道中, 在下丘脑、海马、杏仁核等区域表达较高。目前, 已有研究发现, PACAP对GRP存在正向的调控作用: 在离体的、孤立的猪胃窦组织中, PACAP的免疫反应定位于黏膜层和黏膜层下肌肉; PACAP38(10^{-9} mol/L)即可有效促进孤立的胃窦组织分泌GRP、物质P和VIP[94]。

10.2 胆囊收缩素(cholecystokinin, CCK)

CCK作为脑肠肽, 既调节胃肠道, 也作用于中枢神经系统[95]。在小鼠肠肿瘤细胞系 STC-1中发现, PACAP能够通过PKA途径调控*CCK*基因的转录, 从而促进CCK的分泌[96-97]。

10.3 降钙素基因相关肽(calcitonin gene-related peptide, CGRP)

脑肠肽CGRP广泛分布于人体的中枢和外周神经内分泌系统, 参与调节胃黏膜血流、胃肠道平滑肌收缩、胃肠道蠕动和迷走神经调控的胃肠黏膜分泌作用[98]。有研究发现, PACAP38可有效诱导CGRP从三叉神经核的释放[99]; 以及PACAP作为神经元的营养因子, 可有效调节背根神经节中CGRP的表达[100]。

10.4 瘦素(leptin)

已有研究发现: 在PAC1-R的介导下, PACAP27和PACAP38均可导致小鼠摄食量明显减少[101]。在下丘脑–垂体中, PACAP介导的信号转导在瘦素控制进食行为和脂质代谢交感神经流出方面起着关键作用; PAC1-R特异抑制剂PACAP(6-38)可抑制瘦素对脂质代谢交感神经的调控[102]; 因此, 可以得出结论, PACAP主要通过PAC1-R来调控瘦素分泌进而影响机体食物摄入与肥胖的发生发展, 这也为利用PACAP或PAC1-R激动剂治疗肥胖病症提供了可能。

10.5 神经肽Y(neuropeptide Y, NPY)

NPY是一种广泛存在于中枢和外周神经内分泌系统, 维持内环境稳态的脑肠肽。PACAP对NPY存在正向调控作用: 有研究发现VIP、PACAP27和PACAP38都对交感神经分泌NPY表现出持续有效的刺激作用; 且PACAP27和PACAP38的作用比VIP更强[103], 其中PACAP38可以使NPY分泌速率增加7至9倍[104]。关于介导PACAP的刺激作用的受体类型, 有研究发现大部分的NPY神经元表达*PAC1-R*或*VPAC2-R* mRNA[105], 而且NPY相关颈上交感神经节神经元高表达PACAP特异性受体PAC1-R; 研究提示, 在PAC1-R的介导下, PACAP刺激NPY的分泌过程主要与PKA/PAC途径有关[103]。

此外, CGRP、VIP、PACAP和NPY都在偏头痛的发病机制中起着关键作用。利用电刺激三叉神经节诱导建立偏头痛大鼠模型中, 经过单次电刺激后, 三叉神经节中的CGRP、VIP、PACAP和NPY在不同时间点的表达显著升高并达到峰值, 在反复连续电刺激后, CGRP、PACAP和NPY水平升高更加显著[106]。这表明了这些神经肽可能在偏头痛的发病机制中起重要作用, 也将为今后的偏头痛的药物研发提供帮助。

以上研究整理发现, PACAP及其受体不仅在神

经内分泌系统表达, 而且在胃肠道内也高密度表达; PACAP不仅作为神经递质, 通过自主神经系统促进脑肠肽的分泌, 而且作为神经调质, 通过分布在肠道内的受体, 采用自分泌或旁分泌, 对脑肠肽的分泌进行精细调控。

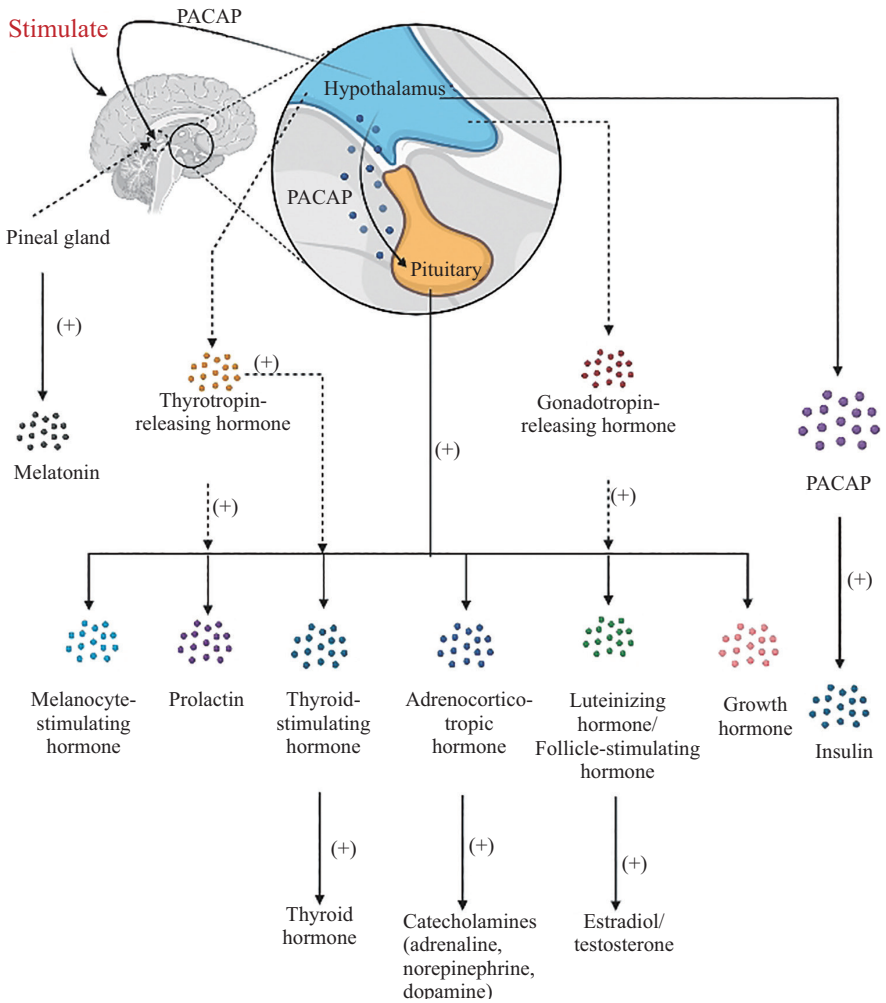
11 其他

脑啡肽(enkephalin), 是中枢神经系统的类吗啡性神经递质, 可有效抑制疼痛。在大鼠的脑室下区和相邻新皮层区域, 发现PACAP(主要是PACAP38)可显著提高脑啡肽的mRNA水平[107]。另外, 在牛脑的嗜铬细胞中, 研究人员也发现PACAP提高了甲基脑啡肽和原脑啡肽mRNA水平[108]。此外, PACAP调控的脑啡肽分泌过程主要是与PAC1-R和钙离子有关, 在PAC1-R的介导下, 其通过激活钙离子通路, 限制钙流入以促进脑啡肽分泌水平[107]。

12 总结与展望

总的来说, PACAP对神经内分泌系统的调控具有双重性: 一方面, 在中枢神经内分泌系统层面, 下丘脑–垂体分泌的PACAP既可以通过刺激下丘脑–垂体分泌各种上游和上上游激素来调控下游的外周神经内分泌组织器官的分泌(图1); 另一方面, 在各个外周神经内分泌组织和器官层面, 通过分布在广泛机体各个组织和器官的受体, PACAP以自分泌和旁分泌的方式, 参与各类下游激素分泌的精细调控(图2)。由此可见, PACAP对内分泌的调控具有全面性和精准性的特点。

由以上整理发现, 从整体上看, PACAP作为“指挥棒”, 可通过促进中枢内分泌的垂体分泌各类促激

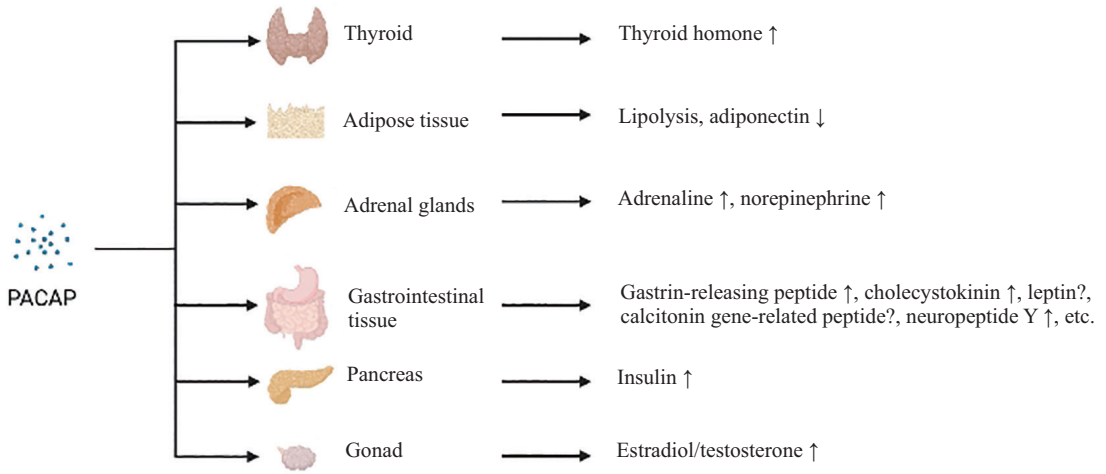


(+): 表示上调激素。

(+): indicates up-regulated hormone.

图1 PACAP对中枢神经内分泌系统的调控

Fig.1 Regulation of PACAP on the central neuroendocrine system



↑: 表示上调激素; ↓: 表示下调激素; ?: 表示未有文献说明激素上调还是下调。

↑: indicates up-regulated hormone; ↓: indicates down-regulated hormone; ?: indicates that there is no literature on whether the hormone is up-regulated or down-regulated.

图2 PACAP对外周神经内分泌系统的调控

Fig.2 Regulation of the peripheral neuroendocrine system by PACAP

素, 进而调控垂体–松果体轴、垂体–甲状腺轴、垂体–肾上腺轴、垂体–性腺轴等分泌激素; 也作为“平衡器”, 通过分布于外周内分泌系统中的受体, 发挥对各种激素分泌的精准调控作用; 使机体的激素分泌和相互作用达到一种和谐平衡的状态, 从而发挥了神经肽PACAP既作为神经递质又作为神经调质、既调控机体响应应激又维护机体代谢平衡的双重生理功能。

本文对PACAP在神经内分泌系统中的作用及其特点进行整理, 不仅为PACAP在神经内分泌系统调节功能的相关生物学机制的研究提供理论基础, 也将为PACAP及与PACAP相关的活性分子, 在神经内分泌系统的相关药用开发方面的提供理论依据。

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