胰高血糖素样肽-1受体显像定位诊断胰岛素瘤的研究进展

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摘要 胰岛素瘤的诊断和手术治疗依赖于准确的影像学检查定位. 以胰腺 β 细胞为靶点的胰高血糖素样肽-1受体 (glucagon-like peptide-1 receptor, GLP-1 receptor) 显像是近年来建立的定位诊断胰岛素瘤的核医学分子影像新技术, 有很高的诊断敏感性和特异性. 本综述回顾了GLP-1受体显像的建立和临床研究情况, 并展望了该技术的应用和研究前景.

关键词 胰岛素瘤, 胰高血糖素样肽-1受体, exendin-4

胰岛素瘤是起源于胰岛 β 细胞的神经内分泌肿瘤, 约占胰腺肿瘤的1%~2%, 发病率约0.4/10万^[1]. 其是引发非糖尿病患者出现器质性低血糖症最常见的病因, 临床表现为反复发作的高胰岛素血症性低血糖, 伴交感神经兴奋、中枢神经受抑制的临床症状和体征. 胰岛素瘤的治疗方式包括手术和非手术治疗, 外科手术是根治胰岛素瘤的唯一方法, 其远期有效率为77%~100%^[2]. 胰岛素瘤的诊断首先需要定性, 定性诊断依靠临床症状并确立内源性高胰岛素血症性低血糖; 然后是定位诊断, 影像学的定位诊断既是鉴别胰岛素瘤与其他引起内源性高胰岛素血症性低血糖的疾病的重要依据, 更是指导外科手术的关键.

1 胰岛素瘤简介

1927年, 美国Mayo临床中心Wilder等人^[3]报道了1例难治性低血糖的病例, 手术探查发现胰岛素瘤多发肝转移, 这是世界上报道的第一例胰岛素瘤. 2年后, 加拿大多伦多大学Howland等人^[4]报道了第一例经过手术切除成功治愈的胰岛素瘤病例. 4年后, 北京协和医院内科刘士豪等人^[5]确诊了我国第一例胰岛素瘤, 并由时任外科主任Loucks成功实施手术切除了肿瘤, 达到当时的国际先进水平. 此后的几十年中, 北京协和医院对胰岛素瘤的临床表现、各种辅助检查特征、围手术期血糖监测及管理、手术治疗、术后并发症防治和随访等进行系统研究, 创建了系统的诊断方法, 建立了综合的治疗体系, 使得北京协和医院胰岛素瘤的诊

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治水平一直在全国领先, 保持国际先进水平.

时至今日, 胰岛素瘤常用的影像学定位诊断方法包括增强CT、磁共振、超声内镜等. 在增强CT及磁共振中, 典型的胰岛素瘤表现为持续强化及高血流灌注, 但约1/4的胰岛素瘤在增强各期表现为等强化^[6], 约1/3表现为一过性强化^[7], 容易漏诊, 诊断准确率约60%~70%^[8,9]; 超声内镜对胰头和胰颈的胰岛素瘤敏感性可达80%~90%, 但对胰尾及异位的胰岛素瘤诊断困难, 并且其准确性与操作者经验相关^[9~11]. 因此, 即便在胰岛素瘤已被世界认识近一个世纪的今天, 其定位诊断仍然时常成为临床的难题.

核医学影像技术能够反映疾病的病理生理过程和分子生物学信息变化, 具有常规影像学技术难以企及的“功能影像”的优势. 例如, 生长抑素受体显像被认为是诊断胃肠胰神经内分泌肿瘤最敏感的影像学方法^[12], 因为胃肠胰神经内分泌肿瘤具有高度表达生长抑素受体的特征. 北京协和医院于20世纪90年代在国内最早将生长抑素受体显像的技术用于神经内分泌肿瘤诊断, 技术一直保持国际先进水平. 虽然胰岛素瘤也属于胰腺神经内分泌肿瘤, 但随着进一步的研究发现, 接近60%的胰岛素瘤不表达或仅低度表达生长抑素受体^[13], 所以生长抑素受体显像定位诊断胰岛素瘤的敏感性仅20%~60%^[12,14~16].

胰岛素瘤起源于胰岛 β 细胞, 近年来建立了以胰腺 β 细胞为靶点的胰高血糖素样肽1受体(glucagon-like peptide-1 receptor, GLP-1 receptor)显像技术, 用于胰岛素瘤的定位诊断. GLP-1受体在胰岛素瘤中的表达程度非常高, 是截至目前发现的胰岛素瘤表达程度最高的受体^[17,18]. 本综述回顾了GLP-1受体显像的建立、临床研究情况, 并展望了该技术的应用和研究前景.

2 GLP-1受体

在生理情况下, GLP-1受体在人体胰腺、十二指肠、神经垂体、小肠、乳腺、甲状腺、肾脏、肺等少数组织中有特异性表达, 大部分组织表达GLP-1受体的密度很低. 在胰腺中, 胰腺腺泡和胰岛均有GLP-1受体表达, 其中胰岛细胞的GLP-1受体表达密度明显高于胰腺腺泡^[19]. 曾有研究认为除胰岛 β 细胞以外, α 细胞和 δ 细胞也有GLP-1受体表达^[20,21], 但后来更多的研究否定了这一观点, 证明GLP-1受体的mRNA和蛋白

只在胰岛 β 细胞中存在^[22].

胰岛素瘤是GLP-1受体表达密度最高的肿瘤, GLP-1受体密度约为正常胰岛 β 细胞的6~12倍, 并且90%以上的胰岛素瘤都具有表达GLP-1受体这一分子特征^[18,19]. 除胰岛素瘤外, 其他几种神经内分泌肿瘤也表达一定程度的GLP-1受体, 如胃泌素瘤、VIP瘤、嗜铬细胞瘤、支气管类癌等, 但这些肿瘤表达GLP-1受体的密度较低, 表达概率低, 并且上皮来源的肿瘤、淋巴瘤不表达GLP-1受体^[18,19]. 因此, 以GLP-1受体为靶点的核医学分子影像对于胰岛素瘤可兼具良好的敏感性和特异性, 具有相当大的临床研究和应用价值; 此外, GLP-1受体也有可能成为胰岛素瘤的靶向核素治疗的靶点^[17].

3 GLP-1类似物: Exendin-4

GLP-1受体的天然配体是由小肠L-细胞分泌的GLP-1, 它是含36个氨基酸的多肽, 在进食后出现分泌高峰. GLP-1是重要的葡萄糖依赖性胰岛素促分泌剂, 它与胰岛 β 细胞的GLP-1受体结合后激活胞内第二信使, 可促使胰岛素合成与释放、抑制胰高血糖素分泌、抑制胃排空和糖原分解, 促进胰岛 β 细胞增殖并抑制其凋亡^[23,24]. 天然的GLP-1在体内迅速被二肽基肽酶IV裂解, 生物半衰期仅1~2 min^[25], 因此需要更加稳定的GLP-1类似物来制备示踪剂.

exendin-4是从毒蜥唾液中分离出的GLP-1类似物, 是GLP-1受体激动剂, 它含39个氨基酸并与GLP-1有53%的同源性^[26,27]. exendin-4具有和GLP-1类似的受体亲和力^[28], 与受体结合后能被细胞内化^[29~31], 并且其耐受二肽基肽酶IV的裂解作用, 在体内24 h仍有70%以上以完整分子结构存在^[32,33]. 除exendin-4之外, 研究也发现了其他exendin多肽, 如exendin-3, exendin(9~39)等^[34,35]. exendin-3和exendin(9~39)与GLP-1受体的亲和力、体内稳定性、细胞内化率均低于exendin-4^[29], 所以exendin-4是更为理想的靶向GLP-1受体的化合物.

4 GLP-1受体显像诊断胰岛素瘤的临床研究

4.1 GLP-1受体单光子发射断层显像的应用

¹²⁵I-GLP-1(7~36)酰胺和¹²⁵I-exendin-3是首个合成

的GLP-1受体示踪剂^[30]。由于GLP-1体内稳定性差, 并且exendin-4放射性碘化的效率低, 其进一步的应用受到限制。之后有研究者成功合成了¹¹¹In标记的exendin-4^[31,36], 其中¹¹¹In标记的[Lys⁴⁰(Ahx-DTPA)-NH₂]-exendin-4 (¹¹¹In-DTPA-exendin-4)是首个用于临床研究的靶向GLP-1受体的示踪剂。2008年, Wild等人^[37]在新英格兰医学杂志报道了2例隐匿性胰岛素瘤的病例, 这是GLP-1受体显像首次用于临床研究的报道。这2例胰岛素瘤在常规影像学检查中均未见异常, 而¹¹¹In-DTPA-exendin-4单光子发射断层显像(single photon emission computed tomography, SPECT)/CT准确定位了胰岛素瘤病灶, 之后外科手术成功切除了这2例隐匿性胰岛素瘤。

2009年, Christ等人^[38]报道了一项前瞻性、开放标签的GLP-1受体显像研究的结果, 研究用[Lys⁴⁰(Ahx-DOTA-¹¹¹In)NH₂]-exendin-4 (¹¹¹In-DOTA-exendin-4) SPECT/CT成功定位诊断了6例胰岛素瘤, 而CT, MR仅诊断了其中1例胰岛素瘤, 超声内镜诊断了其中4例。随后的外科手术借助术中 γ 探测仪的引导, 成功切除了这6例患者的胰岛素瘤病灶。2013年, Christ等人^[39]进一步报道了¹¹¹In-DTPA-exendin-4 SPECT/CT定位诊断胰岛素瘤的前瞻性、多中心的2期临床研究结果, 研究纳入了30例内源性高胰岛素血症性低血糖的患者, ¹¹¹In-DTPA-exendin-4 SPECT/CT定位诊断胰岛素瘤的敏感性为95%(95%CI 74~100), 阳性预测值为83%(95%CI 62~94), 其诊断敏感性显著高于CT/MRI(47%[95%CI 27~68], $p = 0.011$)。在这项研究中, 23%的胰岛素瘤患者的常规影像学检查阴性, 仅在GLP-1受体显像中探测到了胰岛素瘤病灶, 从而改变了临床治疗决策。

上述以¹¹¹In标记exendin-4的GLP-1受体显像的临床研究均来自瑞士。鉴于¹¹¹In的物理半衰期较长(67 h), 并且除发射 γ 射线外还发射俄歇电子和转换电子, 辐射剂量较高且SPECT成像的质量不如^{99m}Tc。2013年, 波兰的Sowa-Staszczak等人^[40]以^{99m}Tc标记exendin-4 (^{99m}Tc-HYNIC-exendin-4), 报道了11例临床拟诊胰岛素瘤患者的研究结果。这11例患者的常规影像学检查均正常, 而^{99m}Tc-HYNIC-exendin-4 SPECT/CT在8例患者中检出了胰岛素瘤病灶, 其中6例接受了外科手术。随后, 该研究团队进一步报道了在40例常规影像学检查阴性或无法诊断的高胰岛素血症性低血糖患者中, ^{99m}Tc-HYNIC-exendin-4 SPECT/CT检出了28例胰岛素

瘤, 其中18例经手术切除了肿瘤^[41]。2020年, Senica等人^[42]的研究也报道了类似结果。虽然上述研究显示, ^{99m}Tc-HYNIC-exendin-4 SPECT/CT对胰岛素瘤具有很高的诊断敏感性^[40~42], 但值得注意的是, 以上^{99m}Tc-HYNIC-exendin-4的研究中胰岛素瘤病灶的放射性摄取强度似乎低于¹¹¹In-DOTA-exendin-4, 这可能与^{99m}Tc-HYNIC-exendin-4的细胞内化程度较低有关^[28]。

4.2 GLP-1受体正光子发射断层显像

由于胰岛素瘤多体积较小(直径多<2 cm), 具有更高空间分辨率和图像信噪比的正电子发射断层显像(positron emission tomography, PET)成为进一步研究的方向。基于exendin的PET示踪剂先后被⁶⁸Ga^[33,43~46], ¹⁸F^[47~52], ⁶⁴Cu^[44,53~56], ⁸⁹Zr^[57]标记, 在这些正电子核素当中, 由发生器生产的⁶⁸Ga易于获得、价格低廉、半衰期适中($t_{1/2} = 68$ min), 适合进一步用于临床研究和转化。自2015年起, 先后有多个研究报道了⁶⁸Ga标记exendin-4的GLP-1受体显像用于定位诊断胰岛素瘤^[58~67]。北京协和医院自2014年起便开展了⁶⁸Ga标记exendin-4 PET/CT定位诊断胰岛素瘤的前瞻性临床研究, 有最大型的胰岛素瘤研究队列, 并且报道了最大宗病例的GLP-1受体PET/CT诊断胰岛素瘤的研究^[59~61,63,64,68]。2016年北京协和医院Luo等人^[61]发表的研究报道, 在52例临床拟诊胰岛素瘤的内源性高胰岛素血症性低血糖患者中, ⁶⁸Ga-NOTA-MAL-cys⁴⁰-exendin-4 (⁶⁸Ga-NOTA-exendin-4) PET/CT定位诊断胰岛素瘤的敏感性为97.7%(95%CI 87.7~99.9), 阳性预测值100%(95%CI 92~100), 明显优于胰腺灌注CT(敏感性74.4%[95%CI 58.8~86.5])、磁共振(敏感性56.0%[95%CI 34.9~75.6])、超声内镜(敏感性84.0%[95%CI 63.9~95.5])和^{99m}Tc-HYNIC-TOC生长抑素受体显像(敏感性19.5%[95%CI 8.8~34.9])(图1和2)。

为了进一步研究GLP-1受体PET/CT的诊断优势, Antwi等人^[58,65]采用随机交叉分组设计进一步比较了[Nle¹⁴, Lys⁴⁰(Ahx-DOTA-⁶⁸Ga)NH₂]exendin-4 (⁶⁸Ga-DOTA-exendin-4) PET/CT和¹¹¹In-DOTA-exendin-4 SPECT/CT的诊断效能, 发现⁶⁸Ga-DOTA-exendin-4 PET/CT定位诊断胰岛素瘤的准确性为93.9%(95%CI 87.8~97.5), 显著优于¹¹¹In-DOTA-exendin-4 SPECT/CT(诊断准确性67.5%[95%CI 58.1~76.0])。更重要的是,

图 1 胰岛素瘤病例。患者女性, 44岁, 发作性心悸、大汗、意识模糊5年。 ^{68}Ga -exendin-4 PET/CT (A: PET最大密度投影图; B: PET/CT融合图像横断层)见胰腺钩突摄取异常增高结节(绿箭头), 诊为胰岛素瘤; 正常胰腺可见弥漫均匀轻度摄取, 另可见肝、脾、肾、输尿管及膀胱正常摄取。胰腺灌注CT (C)、胰腺MR(图像未显示)未见异常。后行胰腺钩突部胰岛素瘤摘除术, 病理为胰岛素瘤(WHO 1级)(摘自文献[64])

Figure 1 A case of insulinoma. A 44-year-old woman presented with intermittent palpitation, hyperhidrosis and confusion for 5 years. ^{68}Ga -exendin-4 PET/CT (A: maximum intensity projection of PET; B: PET/CT axial fusion image) showed a focal lesion with intense radioactivity in the uncinate process of the pancreas (green arrow), suggesting an insulinoma. There was diffuse and mild uptake in the normal pancreas, and physiological distribution of radioactivity could also be noted in the liver, spleen, kidney, ureter, and bladder. Pancreatic perfusion CT (C) and MR (image not shown) was unremarkable. The surgical resection of the tumor confirmed the insulinoma (WHO grade I) in the uncinate process at histology. (Reproduced from ref. [64]).

与 ^{111}In -DOTA-exendin-4相比, ^{68}Ga -DOTA-exendin-4在循环中清除速度更快、肿瘤的靶本比更高, 加之PET的空间分辨率高于SPECT, 因此 ^{68}Ga -DOTA-exendin-4 PET/CT的报告结果更明确、阅片一致性更高、不能诊断的报告比例更少(阅片一致性89.5% vs. 75.7%)^[65]。

GLP-1受体显像有助于制定胰岛素瘤外科手术计划。2015年, Wenning等人^[69]报道了3例外科手术成功切除的胰岛素瘤病例, 由于术前GLP-1受体显像准确定位了肿瘤, 患者的手术创伤更小、手术安全性更高, 并且正常的胰腺组织得以更大程度的保留。除了术前定位诊断以外, GLP-1受体显像也可用于胰岛素瘤非手术治疗的疗效评价。北京协和医院Luo等人^[68]报道了一例超声内镜引导下无水酒精注射治疗的胰岛素瘤病例, 治疗后的 ^{68}Ga -exendin-4 PET/CT显示肿瘤的放

图 2 胰岛素瘤病例。患者男性, 10岁, 阵发性抽搐、意识不清4年。 ^{68}Ga -exendin-4 PET/CT (A: PET最大密度投影图; B: PET/CT融合图像横断层)见胰体摄取异常增高结节(长箭头), 手术切除证实为胰岛素瘤; 胰尾另一小结节未见放射性摄取(短箭头), 为胰腺内副脾结节。C: 胰腺灌注CT显示胰体部胰岛素瘤和胰尾部副脾结节均为动脉期明显强化(摘自文献[61])

Figure 2 A case of insulinoma. A 10-year-old boy presented with paroxysmal convulsion and confusion for 4 years. ^{68}Ga -exendin-4 PET/CT (A: maximum intensity projection of PET; B: PET/CT axial fusion image) showed focal intense radioactivity accumulation in the body of the pancreas (long arrow), consistent with surgically removed insulinoma. Another photopenic lesion in the tail of the pancreas (short arrow) was intrapancreatic accessory spleen. C: Arterial phase of contrast-enhanced CT showed the insulinoma and the intrapancreatic accessory spleen showed similar intense arterial enhancement. (Reproduced from ref. [61])

射性摄取程度较治疗前显著降低, 与该患者在治疗后低血糖发生频率明显降低、胰岛素和C肽应答反应一致(图3)。

除散发胰岛素瘤外, GLP-1受体显像也有助于制定多发性内分泌肿瘤1型(multiple endocrine neoplasia type-1, MEN-1)患者的手术计划。MEN-1患者的胰腺神经内分泌肿瘤可为有功能或无功能性, 常为多发, 且同时发生在胰腺头、体、尾部, 以往为了达到肿瘤切除干净的目的, 常需行大范围的胰腺手术甚至全胰切除^[70], 术后胰腺的内外分泌功能受损、并发症多^[71]。近年的研究发现, 直径<2 cm的无功能性胰腺神经内分泌肿瘤的转移率低, 并且积极的手术切除<2 cm的无功能性胰腺神经内分泌肿瘤并未使患者得到生存获益^[72,73]。因此, 2016年欧洲神经内分泌肿瘤协会指南推

图3 无水酒精注射治疗的胰岛素瘤病例。患者男性, 32岁, 反复意识障碍13年, 临床高度怀疑胰岛素瘤。10年前外院行远端胰体尾切除术, 病理未见胰岛素瘤病灶, 术后低血糖症状未缓解。A, B: ^{68}Ga -exendin-4 PET/CT见胰头部摄取异常增高灶, 考虑胰岛素瘤, 后患者行超声内镜引导下无水酒精注射治疗该病灶, 术中同时行穿刺活检, 病理证实为胰岛素瘤。术后4天的血糖监测提示血糖水平正常, 胰岛素和C肽水平较术前明显下降。C, D: 术后第8天复查 ^{68}Ga -exendin-4 PET/CT见胰头部肿瘤放射性摄取较术前明显降低。(摘自文献[68])

Figure 3 Ethanol ablation of an insulinoma. A 32-year-old man had repeated confusion for 13 years, and insulinoma was clinically considered. He underwent distal pancreatectomy in an outside hospital 10 years ago, but the pathohistological examination did not find a tumor, and his symptoms persisted. A, B: ^{68}Ga -exendin-4 PET/CT showed a lesion with intense radioactivity in the pancreatic head, suggesting insulinoma. The subsequent endoscopic ultrasound guided biopsy of the lesion confirmed the insulinoma, and ethanol ablation of the tumor was performed. C, D: A repeated ^{68}Ga -exendin-4 PET/CT performed 8 days after the intervention showed obviously reduced radioactivity in the tumor of the pancreatic head. (Reproduced from ref. [68])

荐[74], MEN-1胰岛素瘤均需手术切除以控制低血糖, 而对于MEN-1无功能性胰腺神经内分泌肿瘤, 如肿瘤直径 $\geq 2\text{ cm}$ 才建议手术切除, 如直径 $< 2\text{ cm}$ 则建议随诊观察。2019年, Antwi等人[75]报道了 ^{68}Ga -DOTA-exendin-4 PET/CT探测MEN-1有临床意义的胰腺病灶(胰岛素瘤或直径 $\geq 2\text{ cm}$ 的无功能性胰腺神经内分泌肿瘤)的敏感性为84.6%(95%CI 54.6~98.1), 特异性为100%(95%CI 85.8~100), 准确性为94.6%(95%CI 81.8~99.3), 其诊断效能优于磁共振, 有助于制定胰腺手术计划、避免不必要的胰腺切除。

胰岛素瘤大多为良性, 恶性胰岛素瘤(伴有转移)约占所有胰岛素瘤的10%。与良性胰岛素瘤不同的是, 恶性胰岛素瘤可能缺乏GLP-1受体表达。在2011年Wild等人[76]报道的一项恶性胰岛素瘤的研究中, 仅36%的恶性胰岛素瘤表达GLP-1受体, 而2型生长抑素受体在恶性胰岛素瘤中的表达率达73%。虽然GLP-1受体阳性的恶性胰岛素瘤占少数, 但有文献也报道过 ^{68}Ga -exendin-4摄取阳性的伴多发转移的恶性胰岛素瘤(图4), 且摄取强度与良性胰岛素瘤并无差别[61,77,78]。近年来, 有研究报道成功合成了 ^{177}Lu 标记的exendin-4, 并在动物模型中研究了其药代动力学特性[79,80], 这些研究进展有助于将来进一步研究GLP-1受体阳性的恶性胰岛素瘤的多肽受体核素治疗(peptide receptor radionuclide therapy, PRRT)。

5 GLP-1受体显像需注意的问题

GLP-1受体显像有几个需要注意的问题。首先, GLP-1受体在少数组织有生理性表达, 其中位于十二指肠的Brunner's腺体的表达程度较高[19,81], 可能会导致错误判读GLP-1受体显像, 如将十二指肠Brunner's腺体的生理性摄取判读为胰岛素瘤病灶, 或误将胰头部的胰岛素瘤报告为十二指肠Brunner's腺体的生理性摄取[38,39,59,81,82] (图5和6)。2020年发表的一项研究显示, 该原因导致的GLP-1受体PET/CT的结果误判率为0.6%, 而SPECT/CT由于图像分辨率和信噪比不如PET/CT, 结果误判率为9.0%[82], 因此在阅片时需对胰头区异常摄取加以关注和鉴别。

其次, exendin-4示踪剂经肾脏排泄, 所以GLP-1受体显像中肾脏有非常明显的放射性浓聚, 可能影响观察邻近的病变, 如文献报道部分胰尾部胰岛素瘤的检出可能受肾影放射性浓聚的影响[59,83]。虽然近期一项研究表明双时相的 ^{68}Ga -exendin-4 PET/CT采集并未提高肿瘤的靶本比[84], 考虑到示踪剂在肿瘤中的有效半衰期比其在肾脏中的滞留时间长[38], 延迟采集的GLP-1受体显像仍有助于检出胰尾部的胰岛素瘤[38,59,61,78] (图6)。

放射性核素标记的多肽示踪剂在肾脏排泄的过程中会被近端肾小管重吸收, 在肾小管细胞内, 多肽示踪剂降解为氨基酸片段, 氨基酸片段的代谢产物之后会重新进入血液循环, 但被放射性金属核素螯合的氨基

图 4 胰腺钩突部胰岛素瘤患者 ^{68}Ga -exendin-4 PET/CT (A: PET最大密度投影图; B: 横断层融合图), 可见钩突部胰岛素瘤放射性摄取异常增高(A, B, 长箭头), 胰腺颈体尾部见轻度生理性摄取(A, 短箭头)。恶性胰岛素瘤肝转移患者 ^{68}Ga -exendin-4 PET/CT (C: PET最大密度投影图; D: 横断层融合图), 可见肝内大量转移灶, 放射性摄取异常增高(D, 短箭头), 胰腺体尾部胰岛素瘤原发灶摄取明显增高(D, 长箭头)。 (摘自参考文献[78])

Figure 4 ^{68}Ga -exendin-4 PET/CT of a patient with an insulinoma in the uncinate process (A: maximum intensity projection of PET; B: PET/CT axial fusion image) showed focal intense uptake in the uncinate process (A, B, long arrow) and physiological mild uptake in the distal pancreas (A, short arrow). ^{68}Ga -exendin-4 PET/CT of a patient with malignant insulinoma (C: maximum intensity projection of PET; D: PET/CT axial fusion image) showed multiple liver metastases with intense radioactivity (D, short arrow) and the primary tumor in the body and tail of the pancreas (D, long arrow). (Reproduced from ref. [78]).

酸片段会持续滞留在肾小管细胞的溶酶体内^[85-88], 造成放射性在肾脏持续聚集。为了降低GLP-1受体显像中肾脏的放射性浓聚, 北京协和医院Luo等人^[89,90]采用琥珀酰明胶注射液(一种临床常用的血浆胶体容量替代液)预滴注的方法阻断exendin-4示踪剂在肾脏中的重吸收, 将肾脏的放射性浓聚降低了将近60%。这种方法简便、安全、易行, 不仅有利于降低肾脏所接受的辐射剂量, 也有利于检出邻近肾脏的胰尾部病灶^[83,91]。除这种方法以外, 有一些研究还通过修饰exendin-4示踪剂结构的方法来减少其在肾小管中的重吸收, 加速肾脏排泄。例如, ^{18}F 标记的exendin-4示踪剂如 ^{18}F -TTCOCys40-exendin-4, ^{18}F -[Nle¹⁴, Lys⁴⁰]exendin-4就有更好的药代动力学特性, 肾脏中的放射性滞留量更少^[51,92], 还有研究在exendin-4示踪剂结构中加入白蛋白结合基团, 修饰金属螯合剂结构, 通过刷状缘膜酶介导的化合物降解或采用受体拮抗剂的结构等方法可显著降低exendin-4示踪剂在肾脏中的浓聚^[93-97]。这类经结构修饰后的exendin-4示踪剂在临床应用的效果

图 5 胰岛素瘤患者 ^{68}Ga -exendin-4 PET/CT (A: ^{68}Ga -exendin-4 PET最大密度投影图; B, C: 横断层融合图像)。胰腺钩突部胰岛素瘤 ^{68}Ga -exendin-4摄取异常增高(A, B, 长箭头), 十二指肠Brunner's腺体可见局灶性摄取轻度增高区(A, C, 短箭头), 胰腺颈、体、尾部可见弥漫均匀生理性摄取(A, C, 虚线长箭头)。 (摘自文献[78])

Figure 5 ^{68}Ga -exendin-4 PET/CT of a patient with insulinoma (A: maximum intensity projection of ^{68}Ga -exendin-4 PET; B, C: PET/CT axial fusion image). The insulinoma in the uncinate process of the pancreas showed intense uptake of ^{68}Ga -exendin-4 (A, B, long arrow), while the Brunner's gland in the proximal duodenum also had some focal radioactivity (A, C, short arrow). There was mild and physiological uptake in the distal pancreas (A, C, dashed long arrow). (Reproduced from ref. [78])

图 6 胰尾部胰岛素瘤患者 ^{68}Ga -exendin-4 PET/CT。A~C: 示踪剂注射后1小时PET/CT图像, 十二指肠Brunner's腺体可见局灶性摄取增高灶(细箭头), 胰尾部胰岛素瘤被肾影掩盖未能显示; D~E: 2小时PET/CT延迟采集图像可见胰尾部胰岛素瘤(粗箭头)。 (摘自参考文献[59])

Figure 6 ^{68}Ga -exendin-4 PET/CT of a patient with insulinoma in the tail of the pancreas. A~C: PET/CT imaged 1 hour showed the uptake in the Brunner's gland in the proximal duodenum (thin arrow), while the insulinoma in the distal pancreatic tail was masked by the highly radioactive kidney. D~E: PET/CT imaged 2 hours clearly showed the insulinoma in the distal pancreatic tail (thick arrow). (Reproduced from ref. [59])

还有待进一步研究。

由于exendin-4本身是用于治疗2型糖尿病的药物, 具有生物活性, 所以在GLP-1受体显像中使用exendin-4示踪剂可能降低血糖^[38], 增加胰岛素瘤患者低血糖发生的风险。因此在行GLP-1受体显像时, 建议监测患者血糖, 并且通过静脉输液的方式维持血糖稳定^[39,65,78]。另外, 研究报道静脉注射exendin-4示踪剂偶

尔会发生恶心、呕吐的副反应^[38,61,65,78]。

6 GLP-1受体显像的研究前景

除胰岛素瘤以外, GLP-1受体显像还可用于研究其他胰腺β细胞相关疾病。胰岛β细胞增生症是由于局灶或弥漫性的胰岛β细胞含量增高导致的胰岛素分泌过多, 临床上表现与胰岛素瘤相似。准确区分局灶型或弥漫型胰岛β细胞增生是治疗及预后的关键: 局灶型可行胰腺局部切除, 手术创伤小、预后好; 弥漫型可能需行全胰切除术, 手术创伤大并需终身胰岛素治疗。新生儿及婴儿期起病的先天性胰岛β细胞增生症为基因突变所致, 国际共识认为¹⁸F-DOPA PET是诊断局灶型或弥漫型先天性胰岛β细胞增生症最有效的方法^[98~100]。然而¹⁸F-DOPA PET对成人胰岛β细胞增生症的诊断价值非常有限, 因为成人的胰腺外分泌组织大量摄取¹⁸F-DOPA, 无法区分病变与正常的胰岛^[101]。GLP-1受体显像有可能在胰岛β细胞增生症的研究中发挥作用。2015年, Christ等人^[102]报道了一例经手术切除的局灶型胰岛β细胞增生症, 术前⁶⁸Ga-exendin-4 PET/CT显示胰腺体尾部的放射性浓聚明显高于其余胰腺组织, 与病理上体尾部的胰岛细胞增生、GLP-1受体密度增高一致。北京协和医院Luo等人^[61]也报道了在其研究的高胰岛素血症性低血糖的队列中, 有4例临床诊断胰岛β细胞增生症的患者, PET/CT图像显示胰腺有节段性或弥漫性的⁶⁸Ga-exendin-4摄取增高。GLP-1受体显像在该病中的意义还有待进一步研究。

胰岛移植是治疗胰岛素依赖性糖尿病的方法之一。2010年, Pattou等人^[103]曾报道过用¹¹¹In-DTPA-exendin-4显像的方法评价移植的胰岛活性的病例。这例患者因胰岛素瘤切除了超过80%的胰腺组织, 随后进行了正常胰岛的移植。在胰岛移植术后, GLP-1受体显像可见移植部位有¹¹¹In-DTPA-exendin-4摄取, 与移植胰岛的功能评估结果一致。除这例病例报告以外, 还有一些动物模型的临床前研究也探索了将GLP-1受体显像用于评价移植胰岛的活性^[51,53,104,105]。这些研究为将来开展GLP-1受体显像评估胰岛移植手术的效果提供了基础。

GLP-1受体显像理论上可用来研究糖尿病中胰腺β细胞含量的变化。2014年, Brom等人^[106]对比了5例1

型糖尿病患者和健康志愿者的GLP-1受体显像, 发现1型糖尿病患者的exendin示踪剂摄取明显降低; 然而Nalin等人^[107]在链脲霉素诱导的糖尿病猪模型中并未观察到类似的结果。鉴于胰岛只占正常胰腺组织的1%~2%, 用GLP-1受体显像定量或半定量胰腺β细胞含量尚有技术上的挑战。例如, 肾脏对exendin-4示踪剂的浓聚会导致溢出信号影响周围组织放射性摄取参数的测量准确性^[108,109], 影响胰腺β细胞含量的半定量测定。因此, 从技术上改善肾脏的放射性浓聚、通过光子信号校正、线性化流形学习等方式提高定量参数测量准确性, 可能有助于将来进一步探索GLP-1受体显像在糖尿病中的研究价值。

Christ等人^[38]曾报道过术前¹¹¹In-DOTA-exendin-4 SPECT/CT显像、术中γ探测仪引导进行胰岛素瘤切除术, 而之后的exendin-4光学分子探针的研究则致力于探索术中近红外荧光成像引导胰岛素瘤手术。Reiner等人^[110,111]研发了第一代和第二代靶向GLP-1受体的近红外荧光分子探针, 证明了荧光信号强度与胰腺β细胞含量相关联; Brand等人^[112]研发了用Cy5作为荧光介质的第三代示踪剂, 合成了能用⁶⁴Cu标记的PET-近红外荧光双模态分子探针⁶⁴Cu-E4-F1, 这种双模态分子探针在动物模型中显示了很好的探测敏感性, 能够显示<2 mm的胰岛素瘤病灶。2020年, Boss等人^[113]则成功合成了人体安全性更高的光学分子探针exendin-4-IR-Dye 800CW, 并在动物模型中得以验证, 为GLP-1受体靶向的光学成像引导胰岛素瘤手术的临床转化研究打下了基础。

7 总结

胰岛素瘤的诊断和手术治疗离不开影像学准确的定位诊断。鉴于GLP-1受体显像对胰岛素瘤有非常理想的诊断效能和优势, 北京协和医院总结了相关研究经验, 建立了GLP-1受体显像的技术规范^[78], 致力于在临床应用、推广GLP-1受体显像技术, 帮助提高胰岛素瘤临床诊治水平。除胰岛素瘤定位诊断外, GLP-1受体显像技术还有望在胰岛β细胞增生症、胰岛移植活性评估等方面的研究中发挥作用, 此外研究exendin-4光学分子探针有助于开发胰岛素瘤术中导航技术应用。

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Advances of glucagon-like peptide-1 receptor imaging for localization of insulinoma

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The diagnosis and surgical treatment of insulinoma is dependent on accurate localization with imaging modalities. Glucagon-like peptide-1 (GLP-1) receptor imaging that targets pancreatic β cells, was recently established for localization of insulinoma in patients with hyperinsulinemic hypoglycemia. It has proven to be a sensitive and specific method for preoperative localization of insulinoma. This review introduces the development, clinical research, and perspective of GLP-1 receptor imaging mainly in insulinoma.

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