

GLP-1受体激动剂治疗阿尔茨海默病的研究进展

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摘要

胰高血糖素样肽1受体激动剂(Glucagon-like peptide-1 receptor agonists, GLP-1RAs)是一类安全有效的降糖药物, 具有外周和中枢的双重作用。随着对该类药物作用机制的深入研究, 现已有大量的研究表明GLP-1RAs除了具有良好的降糖效果外, 还具有心血管保护作用以及肾脏保护作用, 而GLP-1RAs是否具有神经保护作用, 则是一个新的探索领域。2型糖尿病(T2DM)作为痴呆的危险因素, 已被证实和痴呆之间具有共同的病理生理机制。在人脑中, GLP-1R被发现存在于海马、丘脑、纹状体、杏仁核、下丘脑、颞叶皮质等调控认知功能的中枢及边缘神经系统结构区域, 且GLP-1R的表达已被观察到在特定的细胞亚型中对记忆和学习功能有至关重要的影响, 大量的动物模型及一些临床研究已经展现了GLP-1RAs潜在的神经保护作用, 随着对GLP-1RAs神经保护机制及作用效果的研究, GLP-1RAs或可能成为防治认知障碍的新药物, 尽管其确切机制尚未完全确定。在本综述中, 我们旨在探讨GLP-1RAs治疗阿尔茨海默症的相关机制, 并介绍其目前在临床研究中的相关进展。

关键词

GLP-1受体激动剂, 阿尔茨海默症, 认知障碍, 发病机制

Research Progress of GLP-1 Receptor Agonists in the Treatment of Alzheimer's Disease

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of safe and effective hypoglycemic agents that exert dual effects on both the peripheral and central nervous systems. With advances in understanding their mechanisms of action, numerous studies have demonstrated that GLP-1RAs not only provide effective glycemic control but also offer cardiovascular and renal protective benefits. The potential neuroprotective effects of GLP-1RAs represent a novel area of investigation. Type 2 diabetes mellitus (T2DM), a known risk factor for dementia, shares common pathophysiological mechanisms with neurodegenerative diseases. In the human brain, GLP-1 receptors (GLP-1Rs) are expressed in central and peripheral nervous system regions involved in cognitive functions, including the hippocampus, thalamus, striatum, amygdala, hypothalamus, and temporal lobe cortex. The expression of GLP-1Rs in specific neuronal subtypes has been shown to play a critical role in memory and learning processes. Numerous animal studies and some clinical trials have demonstrated the potential neuroprotective effects of GLP-1RAs. As research into the neuroprotective mechanisms and effects of GLP-1RAs progresses, these agents may emerge as promising therapeutics for preventing cognitive impairment, although their precise mechanisms remain to be fully elucidated. This review aims to explore the mechanisms by which GLP-1RAs may treat Alzheimer's disease and to summarize current advances in clinical research.

Keywords

GLP-1 Receptor Agonists, Alzheimer's Disease, Cognitive Impairment, Pathogenesis

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1. 引言

胰高血糖素样肽 1 受体激动剂(Glucagon-like peptide-1 receptor agonists, GLP-1RAs)是一类安全有效的降糖药物,具有外周和中枢的双重作用,具体表现为刺激葡萄糖依赖性胰岛素分泌与生物合成,抑制胰高血糖素的分泌与胃排空,同时减少食物摄入[1],从而有效降低糖尿病患者 HbA_{1c} 和 FPG,其促胰岛素分泌作用具有血糖依赖性,因此有效避免了传统抗糖尿病药物容易发生低血糖不良反应的风险。胰高血糖素样肽 1 受体(GLP-1R)广泛分布于胰腺、肺、脑、心脏、肾和胃肠等组织细胞膜上,随着对该类药物作用机制的深入研究,现已有大量的研究表明 GLP-1RAs 除了具有良好的降糖效果外,还具有心血管保护作用以及肾脏保护作用,而 GLP-1RAs 是否具有神经保护作用,则是一个新的探索领域。研究发现,在人脑中, GLP-1R 广泛存在于海马、丘脑、纹状体、杏仁核、下丘脑、颞叶皮质等调控认知功能的中枢及边缘神经系统结构区域,且 GLP-1R 的表达已被观察到在特定的细胞亚型中对记忆和学习功能有至关重要的影响,大量的动物模型及一些临床研究已经展现了 GLP-1RAs 潜在的神经保护作用[2]。研究表明 GLP-1RAs 能逆转脑内 A β 的生成和沉积,并减轻由此产生的神经损伤,改善胆碱能功能[3]-[5],还能减少阿尔兹海默病(Alzheimer's disease, AD)大鼠脑内 Tau 蛋白的异常磷酸化,提高学习记忆能力[6]。

阿尔茨海默病(Alzheimer's disease, AD)是全球最常见的神经退行性疾病,是痴呆最常见的类型。2 型糖尿病(T2DM)作为痴呆的危险因素,可以通过 T2DM 和痴呆之间共同的病理生理机制来解释,这些机制包括高胰岛素血症和胰岛素抵抗、糖代谢受损、 β 淀粉样蛋白沉积、tau 蛋白过度磷酸化、脑炎症、线粒

体功能障碍或微血管改变[1]。近年来, 基于 AD 与 T2DM 所致痴呆具有共同特征的研究进展, GLP-1RAs 作为 T2DM 的有效药物, 参与多种可能对阿尔茨海默病有益的生物学途径, 包括改善血脑屏障完整性和维护血管健康, 促进小胶质细胞和星形胶质细胞的内稳态, 对适应性免疫细胞(包括自然杀伤细胞和活化调节性 T 细胞)的积极作用, 提高突触活力等[7]-[16]。目前世界范围内已有不少正在进行的关于 GLP-1RAs 改善认知功能的临床研究, 其中 evoke 和 evoke+试验是第一个大规模的全球试验, 旨在研究司美格鲁肽(semaglutide)对早期生物标志物证实的 AD 患者的疾病改善潜力, 包括探索 semaglutide 对神经炎症在内的多种病理生理过程的血浆和 CSF 生物标志物的影响, 该试验的主要阶段预计于 2025 年完成, 52 周的延期将持续到 2026 年 10 月。无独有偶, 福建医科大学附属协和医院团队也已公示一项“Semaglutide 通过改善胰岛素抵抗和能量代谢提高阿尔茨海默病患者认知能力”的 III 期临床试验。由于治疗 AD 的传统药物疗效欠佳, 且近年来新药研发困难重重, 故对当下新型药物潜在治疗作用的研究或可为阿尔兹海默病的防治提供新思路。

2. 阿尔兹海默病的主要发病机制

AD 的发病机制尚不清楚, 近年来存在诸多的研究热点, β 淀粉样蛋白的异常沉积、Tau 蛋白的异常磷酸化、神经炎症反应、胆碱能系统失调、氧化应激与线粒体功能障碍、胰岛素抵抗、谷氨酸兴奋性毒性、基因突变假说以及肠道菌群紊乱等机制在 AD 的发生发展中扮演了重要角色。这些机制相互交织, 形成复杂的病理网络, 共同推动疾病进展。

3. GLP-1RAs 治疗阿尔兹海默症的作用机制

GLP-1RAs 通过多靶点、多通路机制干预 AD 核心病理进程, 包括抑制神经炎症、减少 $A\beta$ 和 Tau 病理积累、激活神经保护性信号通路(如 AMPK)、改善脑能量代谢及胰岛素敏感性, 最终改善突触功能和认知能力[12][17]-[20]。其机制不仅限于单一通路, 而是通过多重作用形成协同效应, 为 AD 的治疗提供了潜在疾病修饰策略。

3.1. GLP-1RAs 改善胰岛素抵抗

胰岛素长期以来一直被认为与阿尔兹海默病相关, 有研究表明, 患有阿尔兹海默病的成年人在身体外周组织中的胰岛素功能失调会通过多种机制如葡萄糖神经毒性、血管损伤以及晚期糖基化终产物的积累对大脑功能产生负面影响[21]。胰岛素还参与蛋白质稳态调节, 影响 β 淀粉样蛋白的清除以及 tau 蛋白的磷酸化[22]。有证据表明, 全身胰岛素抵抗或高循环胰岛素水平会通过下调内皮胰岛素受体来影响血脑屏障的功能, 从而降低血脑屏障对胰岛素的通透性。这种通透性的变化可能导致脑内胰岛素水平降低以及胰岛素促进的神经和神经胶质活动减少[23]。大脑中葡萄糖代谢的失调是 AD 发病和进展的关键问题[24]-[28], 脑内葡萄糖代谢异常与大脑胰岛素和胰岛素样生长因子(IGF)抵抗有关, 这种抵抗破坏了调节神经元存活、能量产生、基因表达和可塑性的信号通路[17]。过去几年的研究表明, 即使在没有并发 T2DM 的情况下, AD 患者的大脑也会发生胰岛素抵抗[29]。GLP-1 受体激动剂可能通过增强胰岛素信号通路的敏感性, 改善脑胰岛素抵抗[30]。此外, GLP-1 受体激动剂还能促进葡萄糖依赖性胰岛素分泌, 间接增加脑内葡萄糖代谢, 改善脑组织的能量供应[18]。最新的 GLP-1RAs 通过偏向性激动(选择性激活下游信号通路)显示出更强的减重效果和改善胰岛素反应的能力, 这种机制可能通过增加 cAMP 产生、减少受体内化等方式, 增强 GLP-1R 的信号传导, 从而更有效地改善胰岛素敏感性[31]。

3.2. GLP-1RAs 的抗炎作用

神经炎症是中枢神经系统中由小胶质细胞和星形胶质细胞介导为主的先天性和复杂的免疫反应[32],

该过程的特点是在感染、创伤、缺血性损伤和毒素等多种可能的病理损伤下, 活化的小胶质细胞会表现出一系列相关的表型, 以小胶质细胞和星形胶质细胞为主的固有免疫细胞被激活产生促炎性细胞因子、趋化因子、小分子信使以及活性氧物质, 另一部分被激活的小胶质细胞亚型(通常被称为“替代激活”或“抗炎”型), 它们会分泌抗炎细胞因子, 并表现出其他修复功能[33], 当抗炎与促炎信号之间的平衡(如在阿尔茨海默病中所见)被打破, 大脑则出现慢性炎症[34]-[36]。脑内慢性炎症被认为不仅与神经退行性变有关, 还会加剧 β -淀粉样蛋白和 tau 蛋白的病变, 这表明炎症是阿尔茨海默病发病机制的根本触发因素[35][37]。GLP-1RAs 通过调节小胶质细胞极化、抑制炎症和氧化应激、改善线粒体功能、激活特定信号通路以及多靶点协同作用等多种机制减少神经炎症, 从而发挥神经保护作用[38]-[41]。在抑制神经炎症方面 GLP-1RAs 能抑制小胶质细胞中 NLRP3 炎症小体的激活, 减少神经炎症反应, RNA 测序显示 GLP-1RAs 可降低脑内小胶质细胞的 NLRP3 表达, 从而减轻 $A\beta$ 诱导的神经毒性[12][19]。在脊髓损伤(SCI)模型中, GLP-1R 激活通过 PI3K/ARAP3/RhoA 信号通路靶向小胶质细胞, 调节小胶质细胞极化, 将促炎的 M1 型小胶质细胞逆转为抗炎的 M2 型, 从而减轻神经炎症[39]。此外, GLP-1R 激活还能抑制小胶质细胞中反应性星形胶质细胞的产生, 减少反应性星形胶质细胞激活[39]。

3.3. GLP-1RAs 抗氧化应激与改善线粒体功能

氧化应激是活性氧(ROS)和活性氮(RNS)物质的产生与抗氧化防御之间严重失衡的状态, 导致生物大分子(如蛋白质、脂质、DNA/RNA)发生氧化或硝化损伤[42]。这些损伤不仅见于晚期 AD, 也在轻度认知障碍(aMCI)甚至无症状的临床前 AD (PCAD)阶段就已出现, 说明氧化应激是早期事件[43]。AD 患者的线粒体功能障碍导致电子传递链(ETC)异常, ATP 生成减少, 同时伴随活性氧(ROS)过度产生。 $A\beta$ 在线粒体内积累会进一步加剧 ROS 生成, 形成氧化应激的恶性循环, 从而损伤神经元[44][45]。GLP-1RAs 通过激活 PI3K/Akt 信号通路, 减轻 $A\beta$ 诱导的星形胶质细胞糖酵解下降, 从而提高氧化磷酸化(OXPHOS)水平并减少活性氧(ROS)产生, 提升星形胶质细胞的糖酵解能力改善了星形胶质细胞对神经元的支持作用并促进神经保护效应[46]。另有研究显示, 在 $A\beta$ 处理后的星形胶质细胞中, GLP-1RAs 能拮抗活性氧(ROS)的过度产生、线粒体膜电位(MMP)崩溃及细胞毒性, 同时, GLP-1RAs 通过 cAMP/PKA 通路增强了受损星形胶质细胞对神经元的支持能力[47]。

3.4. GLP-1RAs 减少 $A\beta$ 聚集和 tau 蛋白过度磷酸化

淀粉样蛋白假说(Amyloid Cascade Hypothesis)作为 AD 发病机制的主流理论已主导该研究领域数十年[48]。该假说认为, β -淀粉样蛋白($A\beta$)的病理积累是 AD 发病的核心驱动因素, 这一过程源于 β -和 γ -分泌酶(secretases)对淀粉样前体蛋白(APP)的连续蛋白水解作用[49], 而主要的病理积累过程是由 $A\beta$ 产生和 $A\beta$ 清除之间的不平衡所驱动的[48]。Tau 是一种微管相关蛋白, 在维持神经元微管稳定性及促进轴突生长方面具有重要作用[50]。Tau 蛋白主要包括 t-tau 蛋白和 p-tau 蛋白, 在 AD 中, 过量的 p-tau 蛋白异常聚集在神经细胞内积累成神经元纤维缠结(Neurofibrillary tangles, NFT), 导致神经元功能受损和通讯障碍, 最终引发神经元丢失和脑萎缩[51], 而神经元纤维缠结(NFTs)形成以及随后的神经元功能障碍和神经退行性变均被认为是 $A\beta$ 产生和 $A\beta$ 清除之间失衡的下游过程[48]。早期有研究探讨了利拉鲁肽对晚期阿尔茨海默病的小鼠是否具有神经修复作用。该研究对 14 月龄 APP/PS1 和同窝对照组小鼠腹腔注射利拉鲁肽(25 nmol/kg bw), 时间为两个月, 发现利拉鲁肽能够改善 APP/PS1 小鼠的空间记忆能力, $A\beta$ 斑块的总体负荷减少了 33%, 炎症减少了 30%, 而齿状回的神经元祖细胞计数增加了 50%, 与 APP/PS1 生理盐水组小鼠相比, APP/PS1 利拉鲁肽组小鼠的 LTP 显著增强, 并与海马和皮质中突触数量的增加相印证[5]。最近的研究显示血浆 GLP-1 在 AD 模型小鼠中的水平与 AD 患者的 $A\beta$ 负荷呈负相关, GLP-1RAs 通过增

强 GLP-1 信号传导, 激活 5' AMP 活化蛋白激酶(AMPK)信号通路, 特别是 CaMKK2-AMPK 轴, 这一过程可减少 β -分泌酶 1 (BACE1)对淀粉样前体蛋白(APP)的切割, 从而降低 $A\beta$ 的产生[20]。除此之外, GLP-1RAs 可通过调节胰岛素信号通路和抑制炎症反应, 直接或间接降低 Tau 蛋白的过度磷酸化, 减缓 NFT 的形成[52] [53]。在 Tau 蛋白病转基因小鼠(hTauP301L)模型中, 利拉鲁肽降低了病理特异性 Tau 蛋白磷酸化, 并改善了运动功能[53]。

3.5. GLP-1RAs 在不同人群中神经保护作用的差异机制

GLP-1RAs 作为治疗 T2DM 的有效药物, 在不同人群尤其是糖尿病患者与非糖尿病患者中的神经保护作用机制上可能存在差异。高血糖和胰岛素抵抗是糖尿病相关认知功能障碍的重要诱因, 在临床观察中, GLP-1RAs (如 semaglutide 和 tirzepatide)在 2 型糖尿病和肥胖患者中显示出预防痴呆的潜在作用[51], 这表明代谢状态可能影响 GLP-1RAs 的神经保护效果。糖尿病患者存在系统性慢性炎症, GLP-1RAs 通过抑制 T 细胞介导的炎症反应和减少促炎细胞因子(如 IL-6、TNF- α)的产生, 减轻神经炎症[54], 非糖尿病患者中, GLP-1RAs 的抗炎作用可能更多通过直接调节小胶质细胞活化和血脑屏障完整性实现[55]。

4. GLP-1RAs 在 AD 治疗中面临的挑战

GLP-1RAs 通过多靶点、多通路机制干预 AD 核心病理进程已在多个临床前研究被证实, 但其在 AD 治疗仍面临许多挑战。

4.1. BBB 穿透效率问题

GLP-1RAs 的神经保护作用需通过血脑屏障(BBB)作用于脑内靶点, 但天然 GLP-1 难以有效穿透 BBB, 因此, GLP-1RAs 在阿尔茨海默病(AD)治疗中的 BBB 穿透效率是一个关键问题。近期开发的 GLP-1/GIP 双受体激动剂(如利拉鲁肽)显示出更高的 BBB 穿透效率, 在 AD 动物模型中能更有效地改善神经退行性病变, 在动物模型中显示出优于单一 GLP-1RAs 的神经保护效果, 为 AD 治疗提供新方向[56] [57]。

4.2. 生物标志物与个体化治疗

目前缺乏可靠的生物标志物预测 GLP-1RAs 的疗效。血浆 GLP-1 水平与 $A\beta$ 负荷的负相关性局限于临床前研究, 还需更多临床数据支持。evoke 和 evoke + 试验探索了 semaglutide 对早期生物标志物证实的 AD 患者包括神经炎症在内的多种病理生理过程的血浆和 CSF 生物标志物的影响, 这一大规模临床试验有望补充这一空白。

4.3. GLP-1RAs 副作用及耐受性

在老年人群中, AD 患病率随年龄增长而显著增加, 30%的 65 岁个体存在老年斑(SPs), 而 80 岁时这一比例升至 50%~60% [58]。GLP-1RAs 的主要副作用集中在胃肠道反应, 如恶心、呕吐和腹泻, 这些症状在老年患者中可能更为明显[59]。长期使用 GLP-1RAs 可能导致体重显著下降, 在老年人群的使用中需考虑营养不良和少肌症的风险。因此, 老年患者使用 GLP-1RAs 需个体化评估, 同时重点关注胃肠道反应及营养状态。

5. 讨论

阿尔茨海默病病因尚不明确, 发病机制高度复杂, 目前针对患有 AD 或轻度认知障碍(MCI)的患者开展的众多旨在清除大脑中各种形式 $A\beta$ 的临床试验结果并不理想, 尽管观察到患者的淀粉样蛋白负荷有所降低, 但他们的认知功能似乎并未得到改善[60] [61], 因此, 多靶点、多机制治疗策略亟需被提出。GLP-

1RAs 通过多靶点、多通路机制干预 AD 核心病理进程已在多个临床前研究被证实, 同时, 虽观察到 GLP-1RAs 通过 AMPK 等通路发挥作用, 但其在 AD 中的详细神经保护机制仍需深入探索。同时值得我们注意的是, GLP-1RAs 可通过降低血糖和体重间接影响 AD 风险, 这些因素是否为主要中介因素尚不明确, 还需更多的研究排除混杂效应。目前, GLP-1RAs 治疗 AD 患者的临床证据仍不充分, 现有支持性证据主要来自动物模型和小规模临床试验, 大规模 III 期随机对照试验结果尚未公布, 其真实的疗效仍需进一步验证。我们相信在不远的将来, 随着科学家们不断探索, 以及更多验证 GLP-1RAs 治疗作用的临床试验得到开展, 能够进一步找到 GLP-1RAs 在 AD 患者中治疗的有效证据。

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