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阿尔茨海默病与糖尿病共病关系的机制探究

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摘　要

阿尔茨海默病(Alzheimer's Disease, AD)是一种神经退行性疾病，主要表现为认知障碍，且是一种不可逆转的疾病。尽管近年来对AD发病机制的研究已经取得了许多成就，但还是没有发现能根治AD的方法。糖尿病(Diabetes Mellitus, DM)是一种异质性疾病，其特征是高血糖和胰岛素分泌不足，二者均会加剧神经炎症。通过研究AD的病理生理学特征、AD的遗传基础及病发后免疫系统的变化与DM的病理生理学特征及其遗传风险因素，表明了DM与AD具有相同的共病关系。本文以探讨AD与DM共病关系机制进行综述，旨在通过针对DM的发病机制来对AD进行有效的预测和预防。

关键词

阿尔茨海默病，糖尿病，神经炎症，胰岛素

Exploration of the Mechanism of the Comorbidity Relationship between Alzheimer's Disease and Diabetes Mellitus

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Abstract

Alzheimer's Disease (AD) is a kind of neurodegenerative disease, mainly manifested by cognitive

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impairment, and is an irreversible disease. Although many achievements have been made in the study of the pathogenesis of AD in recent years, no cure for AD has been found. Diabetes Mellitus (DM) is a heterogeneous group of diseases characterized by high blood sugar and insufficient insulin secretion, both of which exacerbate neuroinflammation. The study of the pathophysiology of AD, the genetic basis of AD, the changes of immune system after the onset of AD, the pathophysiology of DM and its genetic risk factors showed that DM and AD had the same comorbidity relationship. This article reviews the mechanism of the comorbidity relationship between AD and DM, aiming at the effective prediction and prevention of AD by targeting the pathogenesis of DM.

Keywords

Alzheimer's Disease, Diabetes Mellitus, Neuroinflammation, Insulin

1. 引言

阿尔茨海默病(Alzheimer's Disease, AD)是一种神经退行性疾病，对个人和社会都有巨大的影响，其已被确定为研究重点[1]。据估计，全世界有近 5000 万人受到包括 AD 在内的神经退行性疾病的影响，并间接影响了数以千万计的亲人多年来认知能力下降的生活，到 2050 年，该疾病的患病率预计将增加一倍以上[2] [3]。虽然有许可的治疗方法可以缓解 AD 的症状，但还需要提高对发病机制的理解，以便研究出改善疾病的治疗方法[4]。2 型糖尿病(Diabetes Mellitus Type 2, T2DM)的患病率和发病率在全球范围内迅速增加，占所有糖尿病(Diabetes Mellitus, DM)病例的 90%以上[5]。识别 DM 高危人群非常重要，因为早期干预可能会延迟甚至预防 DM。T2DM 是一种复杂的疾病，由多个基因座与生活方式和环境因素相互作用引起[6]。研究表明，慢性 T2DM 与神经退行性变密切相关，尤其是 AD [7]。本文将总结 DM 特征，分析 DM 引起的多种因素在 AD 发病机制中的作用。

2. AD 的病理学特征

2.1. AD 的病理特征

2.1.1. *β*-淀粉样蛋白沉积

β-淀粉样蛋白(Amyloid *β*-protein, A*β*)是由一个大型的 I 型跨膜蛋白淀粉样蛋白前体蛋白(Amyloid Precursor Protein, APP)所产生的[8]。APP 有缺陷的分裂，通过末－分泌酶(BSAS1)和末－分泌酶产生不溶性的 *β* 纤维，从而 *β* 化，扩散到突触断裂，干扰突触信号[9] [10]。A*β* 最终可聚集成不溶性原纤维，并在人脑中形成淀粉样沉积物，这是许多神经退行性疾病的标志[11]。而 A*β* 组成的细胞外神经炎斑块是 AD 的神经病理学特征之一[12]。A*β* 在大脑中为记忆和认知服务的区域进行性脑沉积是 AD 的一个不变和决定性特征[13]。研究结果表明，A*β* 的寡聚形式可能会介导 AD 的进一步病理，在 AD 脑裂解物中已鉴定出多种细胞毒性寡聚 A*β* 物质，其可以在大脑中发挥多种致病作用[14]。随着年龄的衰老，会出现与其年龄相关的并发症，这些可能会影响 A*β* 聚集和积累的速率，加速 A*β* 触发下游病理的速率，或直接加剧下游病理，从而调节失智症的发作[15]。经过几年的聚集，A*β* 将会以某种方式触发 AD 型 tau 病理学的加速，促使神经退行性病变增加[16] [17]。此外，已经证明晚期糖基化终产物(Advanced Glycation End products,

AGEs)和 Aβ 一起增加了神经毒性[18]。因此，AD 的预防策略应该侧重于治疗促进 Aβ 积累的疾病。

2.1.2. 神经纤维缠结

神经原纤维缠结(Neuro Fibrillary Tangle, NFT)是 AD 的神经病理学特征之一，其具有动态的成熟期，伴随着渐进性神经功能障碍和认知缺陷[19]。tau 是一种本质上无序的蛋白质，是主要的微管相关蛋白之一[20]。当神经元中磷酸化和去磷酸化的稳态受到干扰时，tau 将被过度磷酸化并失去结合微管的能力，导致神经元和突触结构受损[21]。NFT 的形成是由于过度磷酸化的 tau 蛋白(tau protein, p-tau)发生错误折叠，导致 p-tau 与微管的亲和力降低，增加了 p-tau 的聚集和纤维化，聚集成成对螺旋细丝[22]。这些结构改变将导致更有组织的聚集，并最终在神经元内形成 NFT，组成 AD 神经纤维缠结的主要成分[12]。当携带缠结的神经元死亡时，这些神经元就会变成神经元外缠结[23]。这些缠结与细胞蛋白质发生异常相互作用，阻止蛋白质执行正常功能。这些蛋白质是神经细胞之间失去连接的前体，最终导致神经细胞死亡和脑组织损失[24]。因此，p-tau 的过度磷酸化会形成 NFT，并沉积在细胞中，不再发挥维持细胞结构的功能[25]。积累 Aβ 和过度磷酸化的 tau 被认为是共存的[26]。

2.1.3. 神经炎症

AD 的病理生理机制不局限于神经组织，同时与大脑免疫反应有关[27]。神经炎症导致并加速了长期的神经退行性疾病，包括 AD 在内的慢性疾病在早期发展中发挥着核心作用[28]。神经炎症是中枢神经系统(Central Nervous System, CNS)对损伤所产生的神经胶质细胞，特别是星形胶质细胞和小胶质细胞的积累引起的炎症[29]。小胶质细胞是 CNS 实质细胞中巨噬细胞的主要种类，在神经炎症中起重要作用[30]。在 AD 的早期阶段，激活的小胶质细胞通过吞噬作用清除 Aβ [31]。在长期接触后，小胶质细胞能使清除 Aβ 的效率降低，并开始对大脑产生负面影响，使 Aβ 积累，从而形成细胞外斑块，持续刺激小胶质细胞的激活[32] [33]。小胶质细胞的过度活化使其处于反应状态，其特征是显著的表型和形态改变，并伴随促炎细胞因子的高表达，从而形成长期的炎症[34]。研究结果表明，药物抑制剂 NLRP3 抑制剂能够抑制 NLRP3 炎症体激活，阻止认知功能的下降，减少记忆障碍和睡眠障碍，对病理反应性小胶质细胞具有保护作用[35] [36]。因此，NLRP3 炎症体通过调节 NLRP3 驱动的神经炎症反应被评价为 AD 的治疗靶点[37]。

2.2. AD 的遗传基础和危险因素

AD 被认为是一种与若干风险因素相关的多因素疾病，例如年龄增加、遗传因素、头部损伤、血管疾病、感染和环境因素(重金属、微量金属等) [38]。通常，AD 被诊断为早发性家族性(Early-Onset Familial AD, EOFAD)或晚发性散发性[39]。EOFAD 是一种罕见的常染色体显性遗传性疾病(约占所有 AD 患者的 5%)，通常在 65 岁之前出现。而散发性 AD 是该疾病的主要非遗传形式(约占所有 AD 患者的 95%)，通常在 65 岁后出现[40]。APP、早老素 1 (Presenilin 1, PS1)和早老素 2 (Presenilin 2, PS2)这三种基因突变已被确定为 EOFAD 的致病因素[41]。这些与 EOFAD 相关的突变通过应用程序基因复制，改变 APP 的淀粉样蛋白生成过程，增强 Aβ 肽的产生[42]。EOFAD 的存在直接影响了 Aβ 的产生并影响了 AD 的风险，常认为它的积累是 AD 发病机制的核心[43]。而散发性 AD 有已知的风险，但没有晚发性 AD 的致病基因[44]。载脂蛋白(Apolipoprotein, Apo)基因的 Apoε4 等位基因，编码一种参与胆固醇代谢和脂质转运的蛋白质，已被确定为 AD 的主要遗传风险因素。拥有一个 e4 等位基因拷贝的个体患 AD 的几率高出三倍[45]。其它的机制包括对突触功能、神经毒性、tau 过度磷酸化和神经炎症的影响[46]。

2.3. AD 病发后免疫系统的变化

免疫系统现在被认为是 AD 的主要因素[47]。AD 患者大脑中的淀粉样蛋白 β 肽(Beta Amyloid Peptide, β-AP)是该疾病的主要原因[48]。免疫细胞对错误折叠的 Aβ 和 tau 的识别可以在 AD 中引发一系列复杂的

免疫反应，进而导致神经炎症和神经退行性变[49]。研究表明，基线炎症升高的老年人会导致 T 和 B 细胞缺陷，从而使身体对病毒感染的免疫反应降低[50]。在 AD 的最初阶段，了解免疫系统是如何工作，以及免疫系统与压力水平的关系似乎很重要。为了分析这一点，在轻度 AD 患者和健康志愿者中使用酶联免疫吸附测定(Enzyme Linked Immunosorbent Assay, ELISA)测量唾液中的免疫球蛋白 A (Immunoglobulin A, IgA)和皮质醇，并比较和关联这两种生物标志物的产生。在没有 AD 的参与者中，皮质醇较低时，IgA 较高，而患有 AD 的参与者则相反[51]。

3. DM 的病理生理学

3.1. DM 的类型和病理生理学特征

DM 是一组异质性疾病，具有某些共同特征，高血糖是其共同特征。1979 年，美国的国家糖尿病数据组(National Diabetes Data Group, NDDG)发布了第一个世界范围内公认的 DM 分类方案，并根据药物治疗将 DM 分为两大类：胰岛素依赖型糖尿病(Insulin-Dependent Diabetes Mellitus, IDDM)和非胰岛素依赖性糖尿病(Non-Insulin-Dependent Diabetes Mellitus, NIDDM) [52]。DM 又分为几类，包括 1 型糖尿病(Diabetes Mellitus Type 1, T1DM)、T2DM、青年期成熟期糖尿病(Maturity Onset Diabetes of the Young, MODY)、妊娠期糖尿病(Gestational Diabetes Mellitus, GDM)、新生儿糖尿病(Neonatal Diabetes Mellitus, NDM)，以及因内分泌疾病、类固醇使用等引起的继发性糖尿病[53]。不同类型 DM 的临床表现或多或少相似，并且由于致病因素的不同，每种类型都具有高度的异质性[54]。T1DM 被定义为由自身免疫性胰腺 β 细胞破坏引起的胰岛素缺乏导致的高血糖状态[55]。T2DM 是一种多基因疾病，位于不同染色体上的多个基因导致其易感性。由于许多环境因素与基因相互作用产生疾病，遗传因素的分析更加复杂[56]。大多数 NDM 或 MODY 患者患有常染色体显性遗传性糖尿病[57]。许多 MODY 患者，尤其是葡萄糖激酶型 MODY，可在妊娠期首次诊断[58]。

胰岛素抵抗和胰岛素分泌不足

胰岛素抵抗(Insulin Resistance, IR)是包括 T2DM 在内的许多代谢性疾病的关键致病成分，被定义为胰岛素靶向组织对胰岛素生理水平的反应性降低的状态[59]。越来越多的证据表明慢性低度炎症反应在 IR 发病机制中的作用。肥胖患者的脂肪组织的特征是脂肪分解增加，游离脂肪酸过量释放，也是促炎细胞因子的来源。这两个因素都可能抑制胰岛素的作用[60]。碳水化合物的消化改变和吸收改变、糖原储备耗尽、糖异生增强和肝糖过多、B 细胞功能障碍、外周组织对胰岛素的抵抗以及胰岛素信号通路受损是导致高血糖的根本原因[61]。胰岛素缺乏症将导致严重代谢失衡和死亡的缺陷[62]。研究发现，链脲佐菌素诱导的糖尿病小鼠的胰岛素缺乏降低了大脑、下丘脑和海马中线粒体 ATP 的产生和/或柠檬酸合成酶和细胞色素氧化酶的活性。这些脑区线粒体融合蛋白的减少和分裂蛋白的增加，可能导致线粒体功能的改变[63]。而且胰岛素缺乏是诱导 tau 激酶 PKA 活性并导致 tau 磷酸化的直接触发因素。胰岛素治疗的可逆性强调了胰岛素作为 AD 和其它 tau 病早期疾病改良干预的潜力[64]。

3.2. DM 的遗传和环境风险因素

许多遗传学研究已经证明 DM 及其并发症都有明确的遗传成分[65]。T1DM 是由于遗传和免疫破坏了大量的 B 细胞，导致胰岛素分泌不足，更容易发生微血管并发症。T2DM 以 IR 为主，导致动脉粥样硬化，更容易发展成为大血管并发症[66]。在表观遗传学因素包括脱氧核糖核酸(Deoxyribonucleic acid, DNA)甲基化和组蛋白翻译后修饰，这些因素与病理因素直接相关，如氧化应激(Oxidative Stress, OS)、炎症介质的产生和高血糖。这些因素使 DM 病理中基因表达和靶细胞发生改变，而 DNA 序列没有特定变化[67]。

DM 的平均发病年龄为 42.5 岁，可能是由高糖高热量饮食、低体力活动、遗传易感性和生活方式所致[68]。肥胖在 DM 中起着重要作用[69]。DM 可能导致多种疾病和长期并发症，最终导致死亡[70]。环境因素和营养不良同样是表观遗传状态的原因。长期的证据表明，环境刺激会改变基因表达，从而导致染色质的表观遗传学变化[67]。

4. AD 和 DM 可能的共病机制

4.1. 高血糖对神经系统的影响

T2DM 和 AD 具有年龄相关性，人口老龄化的增加使这两种疾病的发病率逐渐增加。T2DM 是 AD 的一个重要危险因素[71]。高血糖是 DM 的基本特征，tau 与导致小胶质细胞过度激活的几种机制有关[72]。研究表明，高血糖与认知能力下降有关，葡萄糖水平升高会导致大脑等脆弱组织的 OS。有缺陷的胰岛素信号通过促进 Aβ 的形成或通过增加对神经内 Aβ 产生的炎症反应来影响神经退行性变[73]。慢性高血糖减少了三重转基因 AD (3xTg-AD)新生神经元的复杂性和分化，并降低了神经元成熟的关键内在调节剂 β-连环蛋白的水平，增加了 OS 甚至神经退化[74] [75]。此外，高血糖导致活性氧(Reactive Oxygen Species, ROS)的过量产生，使传入神经末梢敏感，并可能导致运动升压反射过度[76]。

4.2. OS 和神经炎症反应

OS 是 AD 的主要病理机制之一[77]。OS 是细胞和组织的氧化和抗氧化系统之间的失衡，是氧化自由基和相关 ROS 过度产生的结果[78]。久坐、超重和营养不良会导致 ROS 的产生增加，从而导致慢性 OS 状态。在 T2DM 患者中，OS 改变了胰腺胰岛素分泌和激素对靶细胞的作用，导致了微血管和大血管并发症[79]。人体内的炎症过程是一种涉及多种细胞类型和介质的生理反应。脑外伤或中风后的急性炎症过程也可能导致病变形成延长，导致严重的神经元损伤。CNS 中延长的炎症过程可能会对神经元系统造成严重损害[80]。炎症是肥胖、T2DM 或神经退行性疾病等疾病的常见因素。慢性炎症被认为是与衰老相关的不同疾病的致病机制的一部分[81]。而且慢性过度的神经炎症是 AD 等神经退行性疾病的一个关键特征。炎症和神经退行性疾病风险的增加与 T2DM 和 IR 有关，这表明减轻 T2DM 病理的治疗可能也能成功治疗神经炎症和神经变性病理[82]。

4.3. 炎症介质和免疫细胞在共病过程中的作用

高血糖具有广泛的分子和细胞作用，影响 OS、促炎反应的上调和血管变化[83]。运动是治疗 T2DM 的有效一线疗法，通过部分减少激素介导的炎症来改善胰岛素的作用[84]。胶质细胞、肥大细胞和 T 细胞可以在大脑的神经炎症条件下相互激活，并增强神经炎症。此外，来自大脑的炎症介质也可以通过有缺陷的血脑屏障进入外周系统，将免疫细胞募集到大脑中，并加剧神经炎症[85]。大脑炎症是 AD 的一个关键病理标志。因此，AD 的临床和免疫病理学证据可能得到炎症介质的支持，包括细胞因子、趋化因子、补体系统、急性期蛋白和氧化介质[86]。此外，近年来，已经证明胰岛素可以减弱全身炎症反应，并调节某些免疫细胞的增殖、凋亡、分化和免疫功能，特别是与严重创伤、烧伤或败血症相关的单核细胞/巨噬细胞、中性粒细胞和 T 细胞[87]。免疫系统在 AD 的发展、进展和潜在治疗中发挥着重要作用，并参与决定晚期 AD 患者随后的后遗症和发病结果。更好地了解参与 AD 局部和全身免疫反应的免疫介质可能有助于介导 AD 的发展，并采用抗炎药和免疫策略治疗患者[88]。

4.4. 血管病变和血液供应不足的影响

DM 是一种慢性代谢性疾病，其特征是高血糖，随着时间的推移，会对心脏、血管、眼睛、肾脏和

周围神经造成严重损害[89]。DM 的多种潜在病理生理过程导致 DM 患者小血管和/或大血管动脉粥样硬化的高发病率[90]。血管异常被分类为血管肿瘤或血管畸形。血管瘤被确定为良性肿瘤，其经历了以内皮细胞增殖和高细胞性为特征的活跃生长阶段，随后在最初的十年中逐渐消退。血管畸形被描述为源自毛细血管、静脉、淋巴管、动脉或其组合的结构性先天性畸形[91]。大脑的缺血性损伤引发了一系列事件，使神经元死亡，诱导神经退行性变，从而可能导致 AD。脑血管疾病会导致 AD 神经病理学变化，包括脑萎缩和 Aβ 等异常蛋白质的积累[92]。证据表明，人类和动物大脑的短暂缺血再灌注与 AD 相关的神经毒性分子的神经元积累有关，如 APP 和修饰的 tau 蛋白的所有部分。缺血性脑损伤后，APP 和 tau 蛋白在蛋白质和基因水平上的病理变化可能导致 AD [93]。

4.5. 细胞能量代谢紊乱和 AD 的关联

DM 与胰岛素信号传导的改变有关，这可能导致葡萄糖摄取减少、能量消耗细胞代谢禁止以及抑制肝脏中葡萄糖向脂肪转化[94]。大脑的高能量需求使其对能量燃料供应和线粒体功能的变化敏感。葡萄糖供应和线粒体功能的缺陷是众所周知的大脑衰老的标志，在 AD 等神经退行性疾病中尤为突出[95]。身体的 DM 状态会通过影响葡萄糖向大脑的转运和降低葡萄糖的代谢来增加 AD 的发病率[96]。高血糖状态使脑细胞暴露，在葡萄糖的有害影响下，使蛋白质糖基化增加，并导致不同的非精神并发症[97]。在生物能量学和改良临床前 AD 认知复合物、生物能量学与海马体积之间观察到正相关，而在生物能量论与蛋白质高信号之间观察到负相关，而系统性线粒体功能障碍与认知能力下降有关[98]。总而言之，细胞能量代谢紊乱影响 AD 的发病机制，葡萄糖供应和线粒体功能的缺陷在 AD 发病机制中具有重要性[99]。

5. 结论与展望

5.1. 结论

综上所述，DM 与 AD 的发病机制有着十分密切的关系，在 DM 引发的高血糖下大脑供应能量不足，可导致大脑在缺乏能量的情况之下产生 AD 等神经退行性疾病，而 DM 中缺陷的胰岛素信号可以促进 Aβ 的形成或增加对神经内 Aβ 产生的炎症，炎症也是导致神经炎症的常见因素，二者有着密切的共同发病机制。此外，DM 还可以导致血管及其血管周围神经造成严重损害，引发大脑缺血，引发神经元死亡，导致 AD 神经病理学变化。

5.2. 展望

虽然目前还未发现可以根治 AD 的药物和方法，但随着对 DM 与 AD 的共同发病机制的深入探讨，能发现其中 DM 与 AD 有着十分密切的关系，DM 产生的各个方面因素都对 AD 的发病机制有着影响，有望通过针对 DM 的发病机制来对 AD 的发病进行有效的预测和预防，同时，对于防治 DM 与 AD 两种疾病也有重要的指导意义。

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