

β -淀粉样蛋白 ($A\beta$) 在海马的沉积是阿尔茨海默病 (AD) 发病机制之一, 而 $A\beta$ 降解能力下降在 AD 发病过程中起着重要作用. 作为主要的 $A\beta$ 降解酶, 中性内肽酶 (NEP) 活性在轻度认知障碍 (MCI) 和 AD 患者均下降, 且与认知能力相关. 提高 NEP 活性, 促进 $A\beta$ 降解, 有望从根本上改变 AD 的发生和发展.

——杨红旗

中性内肽酶在阿尔茨海默病发病机制中的作用 *

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摘要 β -淀粉样蛋白(β amyloid, $A\beta$)在海马区的沉积是阿尔茨海默病(Alzheimer's disease, AD)发病的典型表现, 清除或降低 $A\beta$ 含量是治疗 AD 的目标之一. 较之 $A\beta$ 生成的增多, 体内降解 $A\beta$ 能力的下降在 AD 发病过程中显得更为重要. 尽管 $A\beta$ 在体内可以通过运输到血液和脑脊液途径来清除, 但大部分 $A\beta$ 被中性内肽酶(neprilysin, NEP)为代表的一类蛋白酶降解为小分子后从体内清除. 老年人、轻度认知障碍期(MCI)和 AD 患者的 NEP 活性显著下降, 且 NEP 活性下降与脑内 $A\beta$ 升高及 AD 患者认知功能损伤相关. NEP 有可能成为 AD 治疗的潜在药物靶点, 针对轻度认知障碍前期(pre-MCI)和 MCI, 提高 NEP 的活性, 促进 $A\beta$ 的降解, 有可能延缓 AD 的发生和发展.

关键词 阿尔茨海默病, $A\beta$ 降解酶, 中性内肽酶, β -淀粉样蛋白

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阿尔茨海默病(Alzheimer's disease, AD)的发病因素和机制十分复杂, 如内外环境因素^[1-2]、基因突变^[3]、蛋白质异常修饰^[4]及沉积^[5]、神经营养及可塑性改变^[6-7]、氧化应激^[8-9]、离子通道^[10]、金属离子代谢紊乱^[11]、能量代谢紊乱^[12]等. 但由于 β -淀粉样蛋白(β -amyloid, $A\beta$)在海马区的沉积是 AD 特征性的病理改变之一, 减少 $A\beta$ 的生成/沉积或者促进其清除已成为 AD 治疗的重要策略之一. 本文强调机体降解 $A\beta$ 能力对于 AD 发病和防治的重要性^[13-14].

吩(thiorphan)可以抑制放射性标记 $A\beta_{42}$ 的降解; 如果加入 NEP 抗体, 脑组织提取物中 NEP 降解 $A\beta_{42}$ 的能力也被抵消^[16], 推测 NEP 具有降解 $A\beta$ 的功能. NEP 基因敲除小鼠(NEP^{-/-}和 NEP^{+/-})与野生型小鼠相比, 对外源性 $A\beta_{42}$ 降解显著降低, 对内源性 $A\beta_{40}$ 和 $A\beta_{42}$ 降解亦降低^[17], 且在 NEP^{-/-}小鼠更加明显, 呈现基因量效关系. Wistar 大鼠脑室内注射 thiorphan, 可使其认知功能下降^[18]; NEP 过表达能够提高动物的认知功能, 且这种改善与 $A\beta$ 含量下降有关^[19]. NEP 功能缺失可以增加脑内淀粉

1 $A\beta$ 降解酶与 $A\beta$ 的动态平衡

Iwata 等^[15]将放射性标记的外源性 $A\beta_{42}$ 注射到大鼠海马区, 同时给予各种蛋白酶抑制剂, 发现中性内肽酶(neprilysin, NEP)特异性抑制剂四氢噻

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样斑块的沉积^[17];在淀粉样斑块大量沉积的转基因小鼠, NEP 基因治疗可以降低斑块沉积 60% 以上^[20].

如图 1 所示, $A\beta$ 的分泌、降解、沉积和运输(进入血液和脑脊液)处于动态平衡, 任何一个环节受到干扰使平衡失调, 均可以使 $A\beta$ 水平升高. 少

部分 $A\beta$ 通过血管途径(运输到血液和脑脊液)被清除, 大部分被蛋白酶, 如 $A\beta$ 降解酶($A\beta$ degrading enzymes, ADEs), 降解为小分子而清除. 如果提高 NEP 的活性促进 $A\beta$ 的降解(增加图 1 中 K2), 有可能抑制 AD 的发生、发展进程.

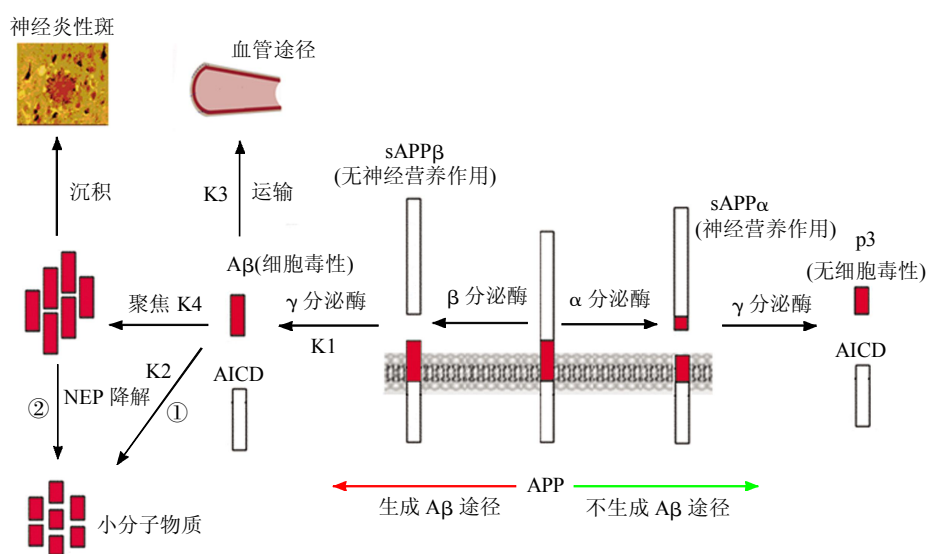


Fig. 1 APP processing pathways and $A\beta$ kinetic equilibrium system

图 1 APP 的代谢和 $A\beta$ 的动态平衡系统

(①见参考文献[17]; ②见参考文献[21]).

2 NEP 的生物学特性

NEP 的活性中心位于胞外段的含锌结构域, 它在神经元胞体合成后, 沿轴浆运输到突触前末梢, 这种运输方式与淀粉样蛋白前体(APP)的转运平行/类似, 因此可以降解在细胞外尤其是突触附近沉积的 $A\beta$, 包括降解 $A\beta$ 单体和寡聚体, 从而防止 $A\beta$ 寡聚体引起的神经元功能丧失^[21].

在转基因 AD 小鼠易受 $A\beta$ 累及的海马和皮层区, 随年龄增长出现显著的 NEP 表达下降, 而在不易受 $A\beta$ 累及的小脑则无此现象^[21]. AD 患者脑内氧化形式的 NEP 比例增高, 氧化后 NEP 活性显著降低^[23]; 随着年龄增长, AD 和对照组病人的 NEP 表达均下降, NEP 下降程度与脑内 $A\beta$ 升高相关^[24]. AD 患者的 NEP 活性下降不但与脑内 $A\beta$ 升高具有相关性, 还与 AD 患者的认知功能相关^[25]. NEP 敲除小鼠中, NEP 在海马区的活性显著下降, 升高的 $A\beta$ 寡聚体直接损害了海马神经元的突触可

塑性和动物的认知功能, 而这一切发生在淀粉样斑块形成之前^[26]. 因此, NEP 在 AD 的发病机制中起着关键性作用: 各种因素(包括年龄和各种病理过程的参与下)引起 NEP 活性下降, 其对 $A\beta$ 的降解能力降低, 使 $A\beta$ 在脑内的沉积增多, 经过一个较长的潜伏期, 导致受累者的认知功能下降或痴呆的发生.

3 中性内肽酶与 AD 早期发病机制

当 AD 患者出现明显的痴呆症状时, 尽管临床诊断相对容易明确, 但此时病情已无法逆转, 缺乏有效治疗手段. 在痴呆前阶段, 病情进展经过一个轻度认知功能障碍期(mild cognitive impairment, MCI). MCI 患者有主观和客观的记忆障碍, 而其他认知和社会功能则没有明显的缺陷. 研究显示, 约半数的 MCI 患者进展为 AD^[27], 因此 MCI 是适于进行早期干预的阶段. 最新版的 AD 诊断标准^[28-29]将 AD 视为一个包括 MCI 在内的连续的疾病过程, 即把 AD 分为无症状临床前期、MCI 和痴呆

期三个阶段. 如能在 AD 的早期即 MCI 期或者 pre-MCI 期给予适当的干预, 则有可能阻止甚至逆转疾病的进展. 该标准还将生物标记纳入到诊断标准中, 以便在研究中应用. 寻找 MCI 的生物标记是目前研究的热点, 有意义的指标为 $A\beta$ 纵向跟踪测定^[30-32]、 β 分泌酶测定^[33]及影像学^[34-35]的改变. 在早期 AD 即 MCI 患者颞叶和额叶, 观察到 NEP 基因表达下降^[36], 提示 NEP 在 AD 早期的发病机制中发挥了一定的作用; 同时, 在 MCI 患者的 CSF 中也检测到 NEP 活性下降^[37], NEP 有可能作为 AD 的一个生物标记物.

4 中性内肽酶活性的调节

NEP 基因治疗是最直接的治疗手段, 但由于安全性等原因, 目前还不能应用到人体, 而利用小分子物质提高 NEP 的活性则有可能成为 AD 治疗的新途径.

a. 生长抑素. 生长抑素(somatostatin, SST)能够剂量依赖性地增加 NEP 的活性, 使 $A\beta_{42}$ 水平显著下降^[38]; 在 SST 基因敲除小鼠, NEP 活性下降, $A\beta_{42}$ 水平升高^[38]; 在啮齿类、猩猩和人类观察到了 SST 的表达随年龄增长而下降, SST 活性在 AD 病人亦下降^[39]. NEP 基因表达和酶活性之间有着复杂的调节机制, 利用小分子物质如 SST 受体激动剂^[40]提高 NEP 的活性则有可能成为 AD 治疗的新途径.

b. 雌激素. 在去势大鼠的海马、小脑和壳核, NEP 的活性显著下降, 补充雌二醇则 NEP 活性回升^[41]. 雌激素随年龄增长而下降, 补充雌激素降低 AD 发病危险性, 除了调节 APP 的代谢外, 上调 NEP 的活性也是其机制之一.

c. APP 胞内段 (APP intracellular domain, AICD). 在 NB7 细胞, AICD 与 NEP 基因启动子的结合促进 NEP 基因表达和酶活性的提高^[42]; 瞬时表达早老素基因和 AICD 能使 NEP 活性恢复; γ -分泌酶抑制剂或者早老素缺失均使 NEP 基因表达和活性下降^[43], γ -分泌酶抑制剂对 NEP 是通过 AICD 发挥作用的^[42].

d. 酪氨酸激酶途径. 酪氨酸激酶抑制剂 Gleevec 能够在人神经母细胞瘤 H4 细胞提高 AICD, 从而增加 NEP 的基因转录、蛋白质表达和酶活性; 如果抑制 APP 和其同源类似物, Gleevec 对 NEP 的作用消失, 提示 Gleevec 对 NEP 的影响是通过 AICD 发挥作用的^[44].

e. 组蛋白去乙酰化途径. 组蛋白去乙酰化酶抑制剂丙戊酸(valproic acid, VA)能在 SH-SY5Y 细胞提高 NEP 活性, 腹腔注射丙戊酸能提高海马区 NEP 基因表达^[45]. AD 小鼠腹腔注射 VA 能够纠正其记忆缺陷, 并减少 $A\beta$ 沉积^[46]. 在 SH-SY5Y 细胞, NEP 基因启动子的组蛋白去乙酰化作用抑制 NEP 基因转录^[42], VA 抑制组蛋白去乙酰化作用是其发挥作用的分子基础, 这是表观遗传学机制参与 AD 发病过程的表现之一.

f. 其他. 铅的暴露^[47]和缺氧^[48]均能够促进 APP 表达和 $A\beta$ 的沉积, 降低 NEP 的基因表达, 并促进神经变性, 提示环境因素也对 NEP 的活性调节具有一定作用.

5 NEP 对 AD 治疗的展望

在衰老及其他危险因素存在下, NEP 发生不同程度的表达异常和 / 或活性下降, 伴随 $A\beta$ 降解减少或沉积增加; 纠正这些危险因素时 NEP 活性得到恢复, $A\beta$ 水平下降. NEP 在 AD 发病机制中所起的作用^[13-14], 为 AD 的治疗提供了潜在研究靶点. NEP 在 MCI 患者体内活性下降^[35-36], 提示该蛋白酶可能参与了早期 AD 的发病过程. 但 NEP 基因表达的调控机制尚未完全明了, 而利用小分子物质提高 NEP 的活性有可能成为 AD 治疗的途径. 由于 AD 发病机制的复杂性, 仅依靠 NEP 解决不了 AD 的治疗问题. 因此, 应该针对 MCI 乃至 pre-MCI, 结合 NEP、分泌酶调节剂、 $A\beta$ 聚集抑制剂以及免疫治疗等综合措施可能才是缓解 AD 发病的途径^[49].

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Role of Neprilysin in The Pathogenesis of Alzheimer's Disease*

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Abstract Deposition of β amyloid (A β) in hippocampus is a crucial progression in the pathophysiology of Alzheimer's disease (AD). Decreasing its formation and/or increasing its clearance have become a focus of AD therapy. As compared with increased A β production, decreased A β degradation plays a more important role in AD pathogenesis. Although A β can be cleared through transportation to the blood and cerebral spinal fluid pathway, the so-called "vascular system", most A β peptide was degraded to small molecules by a kind of protease called A β degrading enzyme represented by neprilysin (NEP). In the elderly, mild cognitive impairment and AD patients, the NEP activity is decreased, and the decreased NEP activity is correlated with A β content in brain and cognitive function impairment. If NEP activity was increased to degrade A β , it may inhibit AD progression and even have disease-modifying potential in AD and NEP thus may behave as a potential drug target for AD therapy.

Key words Alzheimer's disease (AD), A β degrading enzymes (ADEs), neprilysin (NEP), β amyloid (A β)

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