

To what extent can we stave off Alzheimer's?

早期综合干预有助延缓阿尔茨海默症的发生

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摘要 阿尔茨海默症(Alzheimer's disease, AD)的典型病变包括认知异常、脑内amyloid β (A β)沉积形成的老年斑(senile plaque)、异常磷酸化Tau蛋白形成的神经纤维缠结(neurofibrillary tangles, NFTs)、胶质细胞激活以及脑萎缩。在近100多年的研究过程中, 国内外同行把研究重点集中在AD的临床阶段, 追求单一靶点的药物。然而, 这些努力尚未在临床治疗上实现重大突破。当前, AD临床前阶段(preclinical phases)的早期病理变化和干预措施研究受到了相当的重视。为了延缓老年痴呆的发生, 在强调多靶点药物研发的同时, 其他干预方法, 包括改善生活习惯、调节饮食、参与社会活动、进行适当的体育锻炼等, 也在AD的防治中得以研究与应用。

关键词 阿尔茨海默症, 认知功能损害, 老年斑, 神经纤维缠结, 多靶点干预

2005年7月1日, 美国Science杂志在纪念创刊125周年之际提出了125个重大科学问题, 其中第91个问题是: “我们能够在多大程度上延缓阿尔茨海默症(Alzheimer's disease, AD)的发生?”^[1]。如果能够在老年期延迟5~10年发病, 将可能改善数百万老人的健康。研究者们正在探索激素、抗氧化剂、精神和体能方面的干预, 是否对延缓该疾病的发生具有帮助?

阿尔茨海默症属于老年获得(非遗传)性疾病, 虽然该病的发生与许多因素相关, 但衰老被认为是造成AD最直接的危险因素。根据《国家人权行动计划2012~2015》, 我国人口的平均寿命逐渐提高, 由1960年的人均预期寿命43.5岁, 到2010年, 人均预期寿命已增长至73.5岁, 2015年达到74.5岁。陈竺在“2012生态文明贵阳会议”上预计, 到2020年, 中国人的平均期望寿命有望达到77岁。伴随我国社会的老龄化进程, AD的发病率逐年增加。根据国际“痴呆指南(Dementia Guide)”公布的结果(表S1), 年龄80~84岁、老年痴呆的患病率可达11.6%; 年龄超过90岁,

40%以上的老年人会发生痴呆。延缓AD的发生, 就相当于在延年益寿的同时, 还要延缓脑老化和脑功能的退行。这是人类有史以来梦寐以求的事, 也是难以解决的世界难题!

1 窗口前移是目前研究与防治阿尔茨海默症的基本战略方针

近20年来, AD的药物研究在临床试验阶段几乎全线溃败^[2], 使得国内外同行不得不重新考虑AD的研究和防治战略。“全线崩溃”的原因可能是AD的干预和治疗主要集中在临床期, 即AD病程的晚期。在此阶段, 患者脑内神经元丢失已经十分严重, 即便进行治疗, 效果也难以显现^[3]。2012年5月15日, 美国政府宣布“国家阿尔茨海默症计划”。其核心内容之一就是AD的研究与防治窗口提前到痴呆前阶段, 将早期诊断、早期干预作为AD研究的战略重点, 为解决AD这一人类重大脑疾病寻求突破口。

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我国同行在2012年年初也提出了“AD的基础和临床研究窗口前移”的战略思想,同年8月在*Prog Biochem Biophys*正式出版了相关专辑^[4]。也就是说,防治老年痴呆需要在疾病发生发展的临床前期,才可能获得延缓AD的进程(图1)。Sperling等人^[5]提出了AD的二级预防的概念,试图获得有效干预以及延缓AD的效果。

研究及防治AD的窗口前移,包括对轻度认知损害前期(pre-mild cognitive impairment, pre-MCI)、轻度认知损害(mild cognitive impairment, MCI)的病理基础和临床开展研究。同时,重视寻找引发老年认知损害的危险因素,包括衰老因素在内的糖尿病、高血脂、高血压、免疫功能失调^[6]等。Sevigny等人^[7]制备出健康老人体内存在的Aducanumab抗体,用于为期1年的Ib期临床试验,发现该抗体对临床前轻度认知损害(MCI)患者具有一定的治疗效果。因此,阐明这些疾病与AD之间的关系,防治糖尿病、高血压、高血脂、免疫功能失调及其并发症的发生发展,将有望直接或间接延缓老年痴呆的发生。

2 阿尔茨海默症属于代谢性疾病

糖尿病^[8,9]、高血脂血症^[10]等是AD的危险因素。AD患者脑内存在能量代谢失调^[11],包括核酸代谢失调^[12]以及表观遗传的异常^[13]。尽管AD的病理机制十分复杂,但不少的学者认为,AD属于脑能量代谢失调性疾病^[14,15]。既然AD属于代谢性疾病,让我们从代谢性疾病的角度来审视AD。糖、脂或核酸代谢的

失调,往往与不良生活方式及环境因素相关。由于AD人群(人口患病的比例)迅速递增的趋势,明显不符合哈迪-温伯格平衡(Hardy-Weinberg Equilibrium),因此Hu等人^[16]认为,导致AD的环境因素远比遗传因素重要。人类代谢失调疾病的发生具有一个基本特性,即年龄越小所患的疾病越与遗传因素相关;年龄越高发生的疾病,越与内外环境因素相关(图2)^[17]。

日本九州大学Ohara等人^[18]在1017例糖尿病病人(年龄>60岁)随访约15年,发现糖尿病患者随增龄出现记忆障碍和痴呆的风险,比非糖尿病患者高2倍以上。AD患者,普遍具有脑内能量代谢失调^[11]。法国科学家Lester-Coll等人^[19]发现,AD患者脑内存在胰岛素抵抗,能量代谢失调,他们将AD称之为第三型糖尿病(type 3 diabetes mellitus)。Pan等人^[20]通过维生素B₁衍生物苯磷硫胺改善AD模型小鼠的能量代谢失调,可以起到改善小鼠空间记忆障碍的效果,同时可以减少脑内老年斑和神经纤维缠结数量。

脂代谢失调也是部分AD病人共同具有的病症,apolipoprotein E4 (ApoE4)就是其中的一个典型例子。该因子基因的携带或脂代谢失调,被认为是散发性AD的危险因素之一^[21]。尽管采用ApoE4作为生物标志物,筛选出的不全是AD病人,其中也包括一定比例的心血管疾病患者,但毕竟可作为初筛的标记分子之一。脂筏与AD之间的关系,也越来越受到同行的重视^[22];白质变性、神经节苷脂的缺乏等亦与AD发生发展相关^[23]。从血管衰老的角度来看,AD与微循环功能失调关系密切,而血管性痴呆则由于大、小动脉血管的病变所致。

Tong等人^[24]发现,随着年龄增加,体内甲醛的含量也增加;Qiang等人^[25]观察到,小鼠在衰老过程中,内源甲醛代谢失调的原因是:产生甲醛的敏感性

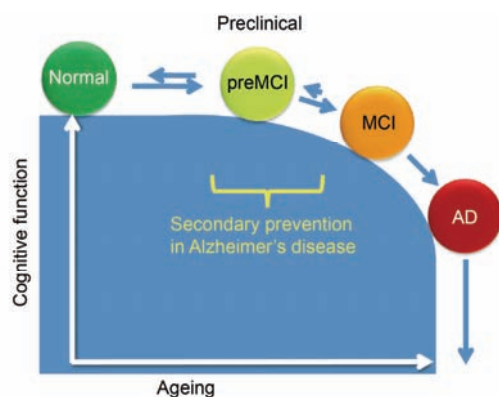


图1 (网络版彩色)阿尔茨海默症的研究和预防窗口前移到临床前期。preMCI, 轻度认知损害前期; MCI, 轻度认知损害; AD, 痴呆期^[4,5]。

Figure 1 (Color online) The windows for research and prevention of Alzheimer's disease should be brought forward to preclinical phases

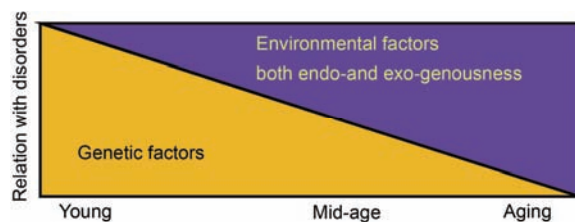


图2 (网络版彩色)代谢性疾病的发生与基因和环境之间的关系。越是幼年时期发生的疾病,越与遗传因素相关;越是老年时期发生的疾病,越与内外环境因素相关^[17]。

Figure 2 (Color online) The relation of dysmetabolic disorders with genetic and environmental factors

胺氧化酶(semicarbazide-sensitive amine oxidase, SSAO)酶活性增加,而降解甲醛的乙醇脱氢酶3(alcohol dehydrogenase III, ADH3)活力下降.临床检验显示,AD病人体内的甲醛浓度显著高于正常对照,体内甲醛浓度与认知损伤程度呈正相关^[26].甲醛参与DNA、RNA、组蛋白等甲基化^[27].因此,甲醛代谢失调,可以通过影响表观遗传学,以及蛋白质的异常修饰和分子聚集,从而造成包括学习记忆在内的认知损伤^[28,29].

3 模拟散发性阿尔茨海默症的动物模型

阿尔茨海默症的散发性病例占了绝大多数^[30].内外环境因素与基因的相互作用是散发性AD发生发展的基本原因.目前,国内外同行采用组学的方法,从不同的角度来认识AD^[31],发现越来越多的蛋白和基因与老年认知损害相关^[32].然而,不可回避的一个规律是:如果一种疾病与越多的基因相关,则与某一种基因相关性就越低.如果采用多个基因的组合,从老年人群中筛选AD,虽然可以获得较高的准确性,但同时具有几个基因突变的病例,在临床上则少之又少.因此,从某一种或几种基因的突变建立动物模型,研究AD的分子机制或药物靶点,也许可以解决个别患者的问题.

现存的转基因动物模型基本上由单基因或几个基因的组合,通过转基因操作而建立的,如根据APP (amyloid precursor protein)突变引起家族性AD,建立的APP转基因模型动物;基于PS1 (presenilin 1)和PS2 (presenilin 2)突变引起家族性AD的PS转基因模型动物;根据ApoE4等位基因与AD有剂量依赖关系,建立的ApoE4转基因模型动物;根据过度磷酸化Tau蛋白导致NFTs形成的Tau蛋白转基因模型,以及这些基因的双重、三重乃至五重转基因动物模型等.这些转基因鼠的建立,有助于了解AD发病机制和推动药物研制的发展.但从目前药物在临床试验中的结果来看,尚未获得十分理想的结果.针对单靶点或少数几个靶点的药物,难以解决散发性AD的治疗问题.因此,需要建立散发性AD的动物模型,提供给AD的研究基础并推动药物研发.

值得一提的是,一种基于核糖代谢失调的散发性老年痴呆鼠模型. Wei等人^[33]发现,核糖修饰的蛋白质单体具有比其寡聚体和多聚体更强的细胞毒性. Wu等人采用核糖喂食C57野生型小鼠6个月,使其出现类似人类AD的典型病理表现,如海马区出现A β 沉

积,似老年斑的形成;皮层和海马Tau蛋白的异常磷酸化^[34],似神经纤维缠结的形成^[35];胶质细胞的激活,炎症因子的释放^[36];小鼠在行为实验中出现明显的认知异常,如学习记忆的损伤,同时伴有焦虑的表现,但无运动障碍.

另一种值得一提的是,基于内源甲醛代谢失调的模拟AD的猴模型^[37]. Yang等人^[37]喂食一定浓度的甲醇,猕猴在3个月后出现工作记忆障碍,1~2年后,脑内出现老年斑,以及Tau蛋白的异常磷酸化,且有类似神经纤维缠结的形成.脑室注射甲醛也可以获得类似的结果.猴模型的建立,进一步证实甲醛代谢失调在AD发生发展中的作用,同时,这些模型也可能用于AD发病机制、干预措施、药效的研究.

4 多靶点药物的研制成为防治阿尔茨海默症的热点

越来越多的证据显示,阿尔茨海默症的致病因素的作用是长期的、多方面的.因此,多靶点药物的探索与研发,成为国内外同行的共识,从不同角度探索潜在的药物靶点,如AD相关蛋白^[38]、相关神经递质及其受体等作为靶点^[39].

采用多靶点药物治疗AD,与传统中医药的方剂不谋而合^[40]. Hou等人^[41]采用中医药“聪明汤”进行实验,在清除AD转基因小鼠脑内A β 和缓解认知损伤方面获得了明显的效果. Li等人^[42]研究了中药提取物何首乌二苯乙烯苷、山茱萸环烯醚萜苷、淫羊藿黄酮、淫羊藿苷等多种拟AD动物模型和细胞模型的影响及其作用机制.这些中药的特点是作用在AD复杂发病机制的多靶点和多途径,尤其是具有神经保护和神经营养或再生作用,且对线粒体和突触具有明显的保护作用,可望用于AD的早期干预或轻度认知障碍的治疗,从而延缓痴呆的发生与进程. Zhang等人^[43]发现补肾化浊的中药复方制剂可以改善MCI的认知功能. Wang等人^[44]对缺血性中风研发的“通络救脑”方剂,在保护脑神经元及胶质细胞功效,干预AD方面也被研究同行所重视^[45]. 通过传统中医理论,研究者们对不同类型、不同个体、不同发展阶段的老年认知损伤已经有了深刻认识,如将AD分为五型,即肾虚髓亏型、气虚血瘀型、痰浊阻窍型、郁火扰心型、湿困脾阳型.通过辨证论治,针对不同的个体,开出药方经过煎煮,筛选和分析在煎煮过程中产生的新型有效化合物,寻找更多治疗AD的新药.

慢性脱水被认为是老年认知损害的共同症状,而AD患者更是如此。Buffa等人^[46]研究结果表明,体重下降是AD的主要临床特征。轻度到中度认知损害患者体重减轻的发生率分别为30%和40%,并且随痴呆病情的发展和加重,体重减轻的发生更加普遍和明显^[47]。Albert等人^[48]观察被试者(上午9~10点)的喝水量及喝水次数,以喝水次数的多少为指标判定被试者的“渴觉”。他们发现AD患者组的老人不仅摄水量少,而且渴觉降低。相关性分析表明,AD患者的喝水量与其MMSE (mini-mental state examination, 简易智力状况检查量表)分数成正相关。Eskelinen等人^[49]对芬兰1409名65~79岁老年人群进行了21年的追踪调查,发现中年时期每天喝3~5杯咖啡的人,可以降低他们在老年时期AD的患病的危险。

Li等人^[50]采用4%NaCl饲喂小鼠3个月建立慢性脱水模型,发现慢性脱水可以导致小鼠脑内甲醛的升高以及5-羟色胺的降低,并伴有穿梭箱学习范式的迟缓。进一步的研究发现,10月龄小鼠的饮水量及饮水频率均显著低于3月龄,且10月龄小鼠脑内甲醛浓度及血清精氨酸加压素(Arginine vasopressin, AVP)浓度显著高于3月龄。慢性脱水损害认知功能,继而又使患者忘记饮水而加重脱水^[48]。值得注意的是,内源甲醛的升高作为一种刺激源,特别是在腹腔注射甲醛的条件下,刺激下丘脑-垂体-肾上腺轴(hypothalamus-pituitary-adrenal cortex axis, HPA),提高血管紧张素II(angiotensin II, ANG II)和AVP水平,从而影响小鼠饮水量及饮水频率。所以,甲醛和AVP代谢障碍可能形成了一种恶性循环,加速饮水量的降低,从而导致慢性脱水。Li等人招募了20名被试者,观察了不同饮水方式(习惯饮水组、饮水剥夺组、定量饮水组)对内源甲醛浓度的影响。在定量饮水组中,其午餐前的尿甲醛浓度显著低于饮水剥夺组^[51]。这些结果表明,按照《中国居民膳食营养素参考摄入量》所建议的饮水量,特别是在早晨醒来后饮水(成年男性350 mL,成年女性300 mL),可以显著降低甲醛在人体内的浓度。因此,养成良好的饮水习惯,可防止甲醛在体内的过度积累,以消除内源甲醛的异常蓄积^[52]。

5 生活方式的干预将成为延缓阿尔茨海默症综合防治的战略之一

代谢性疾病的发生发展往往与不良生活方式相关,包括生活状态、饮食、心理状态、工作压力、经

济状况、教育水平等,都可能影响AD的病程^[53~55]。既然影响老年人认知的因素复杂多样,那么早期、综合、系统的干预就可能起到延缓AD的效果。

世界各国同行采用不同干预方法,来延缓老年痴呆发生,并且获得了一些有意义的结果。综合性的多筹干预(multidomain intervention),即同时对多种因素进行调理是AD干预的最新趋势^[56],也是AD一级预防和二级预防的重要手段。干预的对象包括健康老年人和AD高风险人群,干预的手段包括体育锻炼、认知训练、营养指导、饮食控制、心血管疾病危险因素的控制等,已经获得了一些积极的成果^[57]。

参加社会活动,包括听音乐、唱歌、瑜伽、健步走等,在改善和保持老年认知功能方面也取得了一定的进展^[58~60]。Ngandu等人^[56]筛查了2654位老人(60~77岁)并对其中1260位进行历时两年的生活方式干预,包括饮食的种类、能量的摄入、锻炼的方式、起居等。结果显示,生活方式(复合因素)的干预,可以改善或保持老年人认知功能。Richard等人^[61]筛选了3700位老年人(70~78岁),对其中1004位的体重、血糖、血压等,包括生活方式(锻炼量、吸烟量等)进行6年时间的随机干预。结果显示,多因素的生活方式干预可以降低痴呆发生的风险。Mortimer等人^[60]发现,太极拳对老年认知的保护具有显著作用,这是行为干预起到良好效果的典型例子之一。Banmidis等人^[57]认为,认知和身体训练可以有效延缓老年认知损害。Liu等人^[55]从生活方式中寻找老年痴呆的防治及干预措施,他们认为实行积极、休闲的生活方式以及健康的合理饮食,避免危险因素,可有效地降低老年痴呆发病风险。Zhou等人^[63]发明了一种能够改善AD病人昼夜节律紊乱的光疗法(美国FDA批准的AD非药物治疗之一)。Li等人^[64]通过语言等执行功能的干预,能够对MCI患者的语言认知在主观或客观上起到一定的促进效果。Jia等人^[65,66]在AD的早期诊断、早期干预方面做了大量的工作,并且在AD的干预方面取得了预期的效果。干细胞治疗也是一种有希望的疗法。由于老年人体内环境与年轻人具有较大的差别,如何改善老化的内环境,使得干细胞能够存活、分化、准确加入到复杂而又精确的神经网络中去行使正常功能,成为干细胞治疗需要突破的瓶颈。

6 展望

延缓老年痴呆的发生,不但在科学上是一块难

啃的骨头,同时也是非常复杂的系统工程.需要在社会、医院、家庭等各个层面密切配合,共同开展工作,营造一个适合我国老年人群幸福生活的环境,使得老年人群具有健康的生活方式^[62].老年人能够活到老,学到老;既要延年益寿,又要缓解脑功能的退

行.然而,彻底阐明AD的发病机制,研制出国内外公认的早期、准确、操作方便的生物标志物及其诊断方法,发明长期有效、低毒、副作用小的药物,使阿尔茨海默症的发生延缓5~10年,要做到这一点,还有相当长的路要走.

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补充材料

表 S1 年龄与痴呆患病率之间的关系

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中国科学院生物物理研究所研究员. 提出和论证了“内源甲醛代谢失调是老年认知损害的危险因素”的学说, 并提倡合理饮水清除体内包括甲醛在内的毒性代谢产物, 从而保护中枢神经系统; 提出和论证了“2 型糖尿病的核糖代谢失调”学说, 强调核糖代谢失调与糖尿病并发症, 包括与老年性痴呆之间的关系.

Early multidomain intervention to stave off Alzheimer's disease

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Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills, and eventually the ability to carry out the simplest tasks. In most people with Alzheimer's symptoms first appear in their mid-60s. The typical lesions of Alzheimer's disease (AD) feature in cognitive impairment, amyloid β (A β) deposits (senile plaque), hyperphosphorylation of Tau in neurofibrillary tangles (NTFs), glial cells activation and cerebral atrophy. The plaques and tangles in the brain are considered to be the main features of Alzheimer's disease. Loss of connections between neurons in the brain deteriorates neuronal message transmission between different parts of the brain, and from the brain to muscles and organs in the body. Over one hundred years, a great deal of research has been focused on the dementia of clinical phase, and on single-target drugs to intervene the progression of AD. However, a real breakthrough in the treatment still needs to be made to stave off AD. Currently, to clarify early pathological changes of pre-clinical stage is imperative to understand AD. Although aging, family history and susceptibility genes have been considered to be the most important factors, the rapid increase of AD patients does not conform to Hardy-Weinberg equilibrium. Therefore, environmental factors are more important than genetic factors in AD. The onset of human metabolic disorders becomes more related and vulnerable to endogenous and exogenous environmental pathogenic factors than genetics. Different environmental factors had been found to disrupt the binding affinity of Tau to microtubules or DNA, and to diminish the stability of its cellular skeleton by inducing Tau phosphorylation and amyloid β deposition. For example, five year-old monkeys (*Macaca mulatta*) which were administrated with low concentrations of methanol for 2 years and suffered from senile plaque, A β deposits, neurofibrillary like-tangles in parietal lobe and hippocampus. However, the direct relation between these environmental factors and neurodegenerative diseases is still waiting to be clarified. In order to stave off the onset and progression of AD, different interventions are emphasized and applied in AD treatments, such as developing multiple targeting drugs, ameliorating lifestyle, regulating diet, providing music care, attending physical exercises, and participating in social activities. Chronic dehydration is regarded as a common symptom of patients with age-related cognitive impairment, particularly those with Alzheimer disease. Chronic dehydration in mice results in dysregulation of brain formaldehyde, which decreases the level of 5-HT and slows learning in shuttle box. Establishing good water intake habits not only effectively eliminates excess formaldehyde and other metabolic products but also yields valuable approaches to reducing the risk of AD prior to the onset of the disease. The multidomain intervention will be one of comprehensive therapies for AD patients, especially for those in preclinical phase.

Alzheimer's disease, cognitive impairment, senile plaque, neurofibrillary tangles, therapeutic intervention with multiple targets

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