

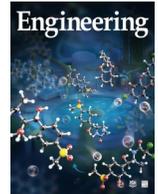


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膳食脂质在预防脑衰老中的干预作用

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摘要

随着人类寿命的延长,与衰老相关的脑部疾病的负担,尤其是老年痴呆,正日益增加。脑衰老会增加认知障碍的风险,表现为逐渐丧失的神经元功能,这主要是源于脂质稳态紊乱而导致的突触可塑性受损。因此,补充膳食脂质有望预防脑衰老。本文从结构和机制两个角度总结了膳食脂质在脑功能中的重要作用。流行病学和动物研究提供了多不饱和脂肪酸(PUFA)在大脑健康中作用的证据。干预结果表明,磷脂(包括磷脂酰胆碱、磷脂酰丝氨酸和缩醛磷脂)能有效缓解衰老过程中的认知障碍,其中缩醛磷脂的效率高过磷脂酰丝氨酸。缩醛磷脂由于其特殊的乙醚键和在神经元突触后膜的丰富性,而在临床试验中成为公认的营养素。未来的研究应检测缩醛磷脂在缓解脑衰老疾病方面的剂量依赖性作用,并应发展其临床应用的提取和储存方法。

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1. 引言

中国60岁及以上老年人口约为2.64亿,占总人口的18.7%,随着经济发展和医疗保健水平的提高,中国老年人口比例持续上升[1]。老年人(60岁以上)疾病占全球医疗开支的23% [2],其中神经系统疾病是导致老年人残疾和死亡的主要原因[3]。2018年,中国60岁及以上人群中痴呆症的患病率为5.30% [4],约占全球痴呆患者总数

的25% [5]。此外,60%~70%的痴呆病例是由阿尔茨海默症(AD)引起的[6]。在中国,与阿尔茨海默症相关的费用支出占国内生产总值(GDP)的1.47%,而全球范围内阿尔茨海默症相关的费用支出占全球所有国家GDP的1.09%,这表明中国在阿尔茨海默症方面的社会经济开支高于全球平均水平[7]。与衰老相关的神经退行性疾病是老龄化社会呈现出的主要社会和经济问题。

为了解决这些问题,中国科学院提出了“中国脑计

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划”，旨在探究脑部疾病的认知变化、诊断和干预的神经机制。此外，国际生命科学研究欧洲分会启动了“脑衰老营养支持”项目，收集营养素对大脑健康影响的证据，希望制定精准的脑衰老营养干预计划。尽管有大量数据表明特定营养干预对认知功能和大脑健康有益，但人们对治疗机制不完全理解，所以这些营养和生物活性化合物的药理潜在效果有待进一步评估。

脑衰老的特征是神经元功能逐渐下降，最终导致轻度认知障碍（MCI）、阿尔茨海默症和其他形式的痴呆症[8]。因此，防止神经元功能下降可延缓脑衰老，以及随之而来的、与年龄相关的神经退行性疾病。脂质（尤其是磷脂）是神经元膜结构的主要成分，对于大脑神经元的结构和功能必不可少。微量营养素（如维生素和矿物质）也对维持大脑功能很重要。这些营养素水平不足会导致大脑功能障碍[9-10]。本文讨论了膳食脂质在预防脑衰老中的作用，以及干预方法和潜在机制。

2. 脑衰老机制

2.1. 突触可塑性与脑衰老

大脑的功能单元是神经元，它们相互发送电化学信号，以执行大脑的复杂和基本功能。为了保证功能的正常运转，神经元必须能够通过突触相互通信。化学突触由突触间隙、突触前膜和突触后膜组成[11]。在突触传递过程中，囊泡与突触前膜融合后，神经递质被释放到突触间隙中。然后，神经递质与突触后膜的树突棘微区中的受体相结合，将神经信号传递到突触后神经元[11]。

认知障碍是阿尔茨海默症和脑衰老的一个特征，很大程度上是突触可塑性的细胞和分子机制失衡造成的[12]

（图1）。突触可塑性是指在已存在的突触中突触传递强度和效率的活力依赖性变化，它长期以来在人类的学习和记忆中发挥关键作用[12-13]。在老龄动物中，不同脑区如脑纹状体、小脑和下丘脑的突触数量及功能都会发生变化。这些变化会分别影响运动协调、活动协调和内分泌等功能[14-16]。然而，突触数量和功能的最显著的变化发生在海马体和前额皮层，这些位置与学习和记忆功能受损有关[17-18]。此外，与年轻动物相比，老龄动物对长时程增强诱导具有更高的阈值，而对长时程抑制诱导的阈值较低[18-19]。

突触可塑性与突触结构变化有关，如现有树突的结构特征的变化、棘突密度和分布的变化以及新突触接触点的稳定等。在衰老过程中，海马体（CA）3区和齿状回的棘突密度降低，但CA1区域则未受影响[20]。棘突是兴奋性突触的主要部位，其数量的减少可能反映了突触密度的下降[21]。老龄动物的海马体CA1区域的神经元的突触后致密区有所降低，而这是许多参与信号传导和可塑性的关键蛋白的所在位置[20,22]。随着年龄增长，海马体CA1区域的树突树长度和复杂性会增加，而在前额皮层区域则会减少[20]。

建立记忆的可塑性变化需要一系列至关重要的神经活动，包括神经递质、激酶系统和腺苷三磷酸酶（ATPase）的活化、 Ca^{2+} 流入、基因表达和翻译的诱导，以及蛋白质调节[11,13]。这些活动的效率受突触膜上功能蛋白的影响[23]。例如，谷氨酸能系统通过突触膜上的N-甲基-D-天冬氨酸（NMDA）受体控制 Ca^{2+} 流入神经元。NMDA受体的密度随年龄增长而降低，代谢型谷氨酸受体亚型3和亚型5的密度也是如此[24-25]。细胞内 Ca^{2+} 变化的幅度和持续时间通过调节突触传递以及介导突触后膜上的树突生

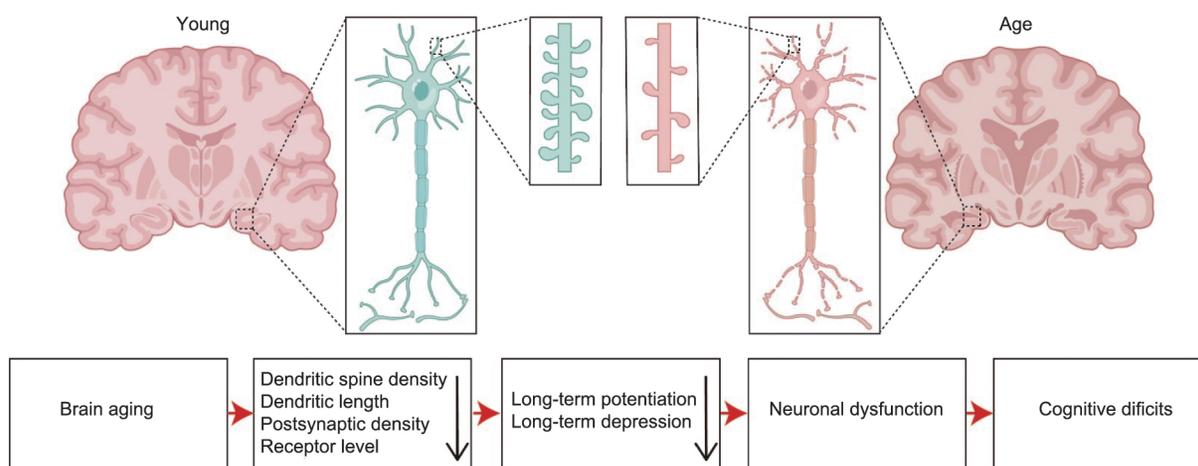


图1. 衰老导致认知缺陷的示意图。衰老导致突触结构发生变化，包括树突棘密度降低、树突长度缩短、突触后密度减小和受体水平下降，这些影响长时程增强和长时程抑制，最终导致神经元功能障碍和认知缺陷。

长和收缩来影响突触可塑性[26–27]。

2.2. 脂质稳态对于突触可塑性的重要性

突触富含多种脂质种类，包括磷脂酰胆碱（PC）、磷脂酰乙醇胺（PE）、磷脂酰丝氨酸（PS）、鞘脂，以及其他微量成分，如胆固醇和磷酸肌醇[28–29]。这种独特的脂质组成对于突触的结构和功能至关重要。例如，脂质组成的变化决定了膜的黏度和流动性，从而控制膜分子的流动性和侧向扩散[28]。脂质双分子层的组成会对膜脂质和相关蛋白的空间结构产生影响[30]。此外，脂质还可能会影响关键突触蛋白质复合物的定位或激活[31]。总的来说，鉴于脂质在突触膜结构和功能中的重要性，以及突触膜与突触可塑性之间的联系，可以推断脂质稳态对突触可塑性和正常脑功能至关重要。

大脑富含脂质[32]，其在人类20岁以前不断增加，在50岁左右开始逐渐减少[33]。脂质失调被认为是多种认知障碍的潜在原因[34–35]。据报道，眶额叶皮层灰质中的二十二碳六烯酸（DHA）和花生四烯酸（ARA）含量在衰老过程中显著降低[36]。磷脂是膜的主要成分，衰老过程中脂质成分紊乱会影响膜的流动性，导致神经递质的转运、释放和接受受损[37]。甘油三酯、磷脂酰胆碱、磷脂酰乙醇胺、磷脂酰丝氨酸、鞘磷脂和固醇等成分在阿尔茨海默症或脑衰老中发生改变，这些变化可能导致膜流动性和完整性受损[38–42]。脂质组成的微小变化都可能影响大脑功能，包括结构发育、神经冲动传递、神经发生、突触发生以及髓磷脂的形成等[32,43]。由于脂质主要通过饮食摄入，因此膳食脂质补充是预防与脑衰老相关疾病的一种有前景的干预手段。

3. 多不饱和脂肪酸(PUFA)与大脑功能

脑衰老往往伴随着营养不良。补充n-3 PUFA、磷脂酰丝氨酸、复合维生素B和黄酮类化合物（无论是单独干预或综合干预）均能够减缓大脑萎缩和认知功能的下降，并且降低与年龄相关的神经退行性疾病的风险[44]。较低的维生素B1和B12水平与更高的大脑组织损失风险密切相关[9–10]，维生素C能减少阿尔茨海默症患者和小鼠模型中淀粉样 β 蛋白（A β ）的形成和聚集[45–46]。有趣的是，黄酮类化合物能缓解阿尔茨海默症引起的神经元死亡[47]。在这些补充剂中，PUFA是改善大脑功能的主要脂质组分。

3.1. PUFA对大脑功能至关重要

DHA和二十碳五烯酸（EPA）是大脑中最丰富的n-3

PUFA，而ARA则是最丰富的n-6 PUFA[48]。有趣的是，特定脑区中PUFA的丰度与单不饱和脂肪酸的存在呈负相关[48]。事实上，只有一小部分脂肪酸作为信号分子，或作为翻译后修饰的底物。大多数脂肪酸（尤其是n-3 PUFA）以酰基链的形式被纳入膜脂质中，影响膜蛋白的组成、结构和功能[49–50]。这是脂肪酸在大脑中最重要的功能。神经元膜脂肪酸的组成可调节膜的物理特性和生物学活性，这对高效地进行突触传递很重要[51–52]。此外，线粒体内膜脂肪酸的不饱和程度可能通过控制电子传递链通量的速率影响ATP合成和反应性氧化物（ROS）的产生[51]。

EPA和DHA的高不饱和度赋予它们影响膜流动性的能力，而这对于突触可塑性至关重要[53]。n-3 PUFA还能通过募集膜结合酶（钠钾离子依赖性ATPase）和调节蛋白激酶C的活性来调节信号转导[54–55]。此外，经证明，DHA具有抗氧化特性，这有助于保护大脑免受退行性损害[56]。除了PUFA的含量之外，n-6 PUFA与n-3 PUFA的比值也很重要，因为它影响体内由其衍生的前列腺素的平衡[57–58]。

3.2. PUFA的补充对认知功能的影响

PUFA对大脑功能的有益作用已经得到广泛研究（表1[59–70]）。血浆中的n-3 PUFA含量水平与认知功能存在强相关性，并且补充n-3 PUFA（2.3 g·d⁻¹）可延缓阿尔茨海默症患者的认知能力下降[59]。血浆中EPA或DHA的浓度越高，海马体和杏仁体的萎缩程度越轻，进而患阿尔茨海默症的概率越低[71–72]。此外，在健康个体中，也观察到了PUFA的补充对认知和记忆的益处[60–63]。

DHA作为广泛研究的n-3 PUFA之一，其丰度与大脑功能密切相关[73–74]，补充DHA（2 g·d⁻¹）可改善轻度认知障碍患者的认知功能[64]。作为膜的组分，DHA可以调节膜的流动性，进而影响新神经纤维和突触的形成及分化、突触连接的完善、神经递质释放和记忆巩固过程[73, 75–76]。DHA补充可以增强自发谷氨酸能突触活性，并促进初级神经元中NMDA受体的表达[77]。最近，还发现DHA可以通过激活谷胱甘肽过氧化物酶4来保护神经元膜脂质免受过氧化损伤[78]。这些发现表明，n-3 PUFA（尤其是DHA）可能有助于缓解认知障碍和衰老相关的脑部疾病。

然而，膳食DHA的补充并不总是有效的，尤其是在老年人群中。例如，在一项多领域阿尔茨海默症预防试验中，补充n-3 PUFA（DHA 800 mg·d⁻¹ + EPA 225 mg·d⁻¹）无法改善轻度认知障碍和轻度阿尔茨海默症患者的

表1 补充PUFA对认知下降的缓解情况

| Model | Compound | Dose and duration | Effects | Ref. |
|--|----------|--|--|------|
| Aged 65–83; AD (174 subjects) | n-3 PUFA | 2.3 g·d ⁻¹ ; 6 months | Improved cognitive impairment; dose-response relationship between preservation of cognitive functioning and plasma levels of n-3 PUFAs | [59] |
| Aged 50–75; healthy (65 subjects) | n-3 PUFA | 2.2 g·d ⁻¹ ; 26 weeks | Improved executive function, exerted beneficial effects on brain microstructure integrity and diastolic blood pressure | [60] |
| Aged 40–85; loneliness-related memory problems (138 subjects) | n-3 PUFA | 1.25 or 2.5 g·d ⁻¹ ; 4 months | Attenuated loneliness-related verbal episodic memory declines | [61] |
| Aged 50–75; healthy (44 subjects) | n-3 PUFA | 2.2 g·d ⁻¹ ; 26 weeks | Improved recall of object locations | [62] |
| Aged ≥ 55; healthy (485 subjects) | DHA | 900 mg·d ⁻¹ ; 24 weeks | Improved immediate and delayed verbal recognition memory scores, but not working memory or executive function tests | [63] |
| Aged ≥ 65; MCI (219 subjects) | DHA | 2 g·d ⁻¹ ; 12 months | Improved cognitive function (full-scale intelligence quotient, information, and digit span) and slowed the progression of hippocampal atrophy | [64] |
| Aged ≥ 70; cognitive decline (1525 subjects) | n-3 PUFA | DHA 800 mg·d ⁻¹ + EPA 225 mg·d ⁻¹ ; 3 years | No significant effects on cognitive performance | [65] |
| Aged 66–76; cognitive impairment (57 subjects), AD (19 subjects) | n-3 PUFA | DHA 625 mg·d ⁻¹ + EPA 600 mg·d ⁻¹ ; 4 months | No significant effects on cognitive performance | [66] |
| Aged ≥ 75; without cognitive impairment or MCI (99 subjects) | n-3 PUFA | 1050 mg·d ⁻¹ ; 1 year | No significant effects on cognitive performance; patients in intervention group with normal nutritional status showed an improvement in MMSE versus a worsening in the group with malnutrition | [67] |
| Aged ≥ 65; normal or MCI or moderate cognition impairment (199 subjects) | n-3 PUFA | DHA 180 mg·d ⁻¹ + EPA 120 mg·d ⁻¹ ; 6 months | No significant effects on cognitive performance | [68] |
| Aged 60–80; coronary patients (2911 subjects) | n-3 PUFA | DHA-EPA 384 mg·d ⁻¹ , ALA 1.9 g·d ⁻¹ ; 40 months | No significant effects on cognitive performance | [69] |
| Aged ≥ 65; healthy (302 subjects) | n-3 PUFA | 1800 or 400 mg·d ⁻¹ ; 26 weeks | No significant effects on cognitive performance | [70] |

ALA: α -linolenic acid; MMSE: mini-mental state examination.

认知能力[65]。在健康老年人群和认知障碍人群，也有关于n-3 PUFA的负作用的报道[66–70]。这些无效干预可能归因于DHA在穿过血脑屏障时吸收不良和效率低下[79]。

3.3. PUFA在大脑中的活性形式

在磷脂中的sn-1和sn-2链富含大量的PUFA，磷脂中n-3/n-6 PUFA比例失衡，与抑郁症和视网膜病有关[80–81]。DHA是大脑中最丰富的PUFA，尤其是在突触膜中，其中32%~40%的磷脂含有DHA [82]。研究发现，DHA对大脑功能的益处源于增加的DHA磷脂。此外，无论是从增加大脑DHA水平的角度还是改善记忆功能的角度，以磷脂形式补充DHA比以游离脂肪酸或甘油三酯形式补充更有效[83–86]。对于此效率差异，可能的机制解释如下：膳食中的脂肪酸或甘油三酯形式的DHA经胰脂肪酶消化，形成未酯化的游离酸，主要以甘油三酯形式包含在乳糜微粒中。然而，膳食中磷脂形式的DHA经磷脂酶A2消化形成溶血磷脂，这些溶血磷脂被包含在乳糜微粒或高密度脂蛋白中。此外，血脑屏障优先摄取溶血磷脂形式的DHA，

有效地将其富集于大脑[83]。因此，与PUFA相比，补充磷脂能更有效地改善大脑功能[87–88]。

4. 磷脂在脑衰老中的作用

4.1. 大脑中的磷脂组成

磷脂占神经元总膜脂质的60%以上[43,89]。磷脂具有相似的结构，其中两个脂肪酸连接到甘油骨架的sn-1和sn-2位置，而在sn-3位置具有不同的磷酸头部基团(图2)。根据sn-3位置的头部基团，磷脂主要分为磷脂酰胆碱、磷脂酰乙醇胺、磷脂酰丝氨酸、磷脂酰肌醇、磷脂酸和心磷脂[88]，如图2(a)所示。PE是哺乳动物脑部最丰富的磷脂[87]。此外，突触微区的磷脂组成也不尽相同：囊泡膜富含PS，而突触后膜的周围密集区和脂筏则分别富含PE和PC [38,90]，如图3(a)所示。动态磷脂重塑允许膜形态迅速改变，从而实现突触传递，这意味着维持关键的磷脂组成对于保持突触结构的完整性是必需的[38,91]。

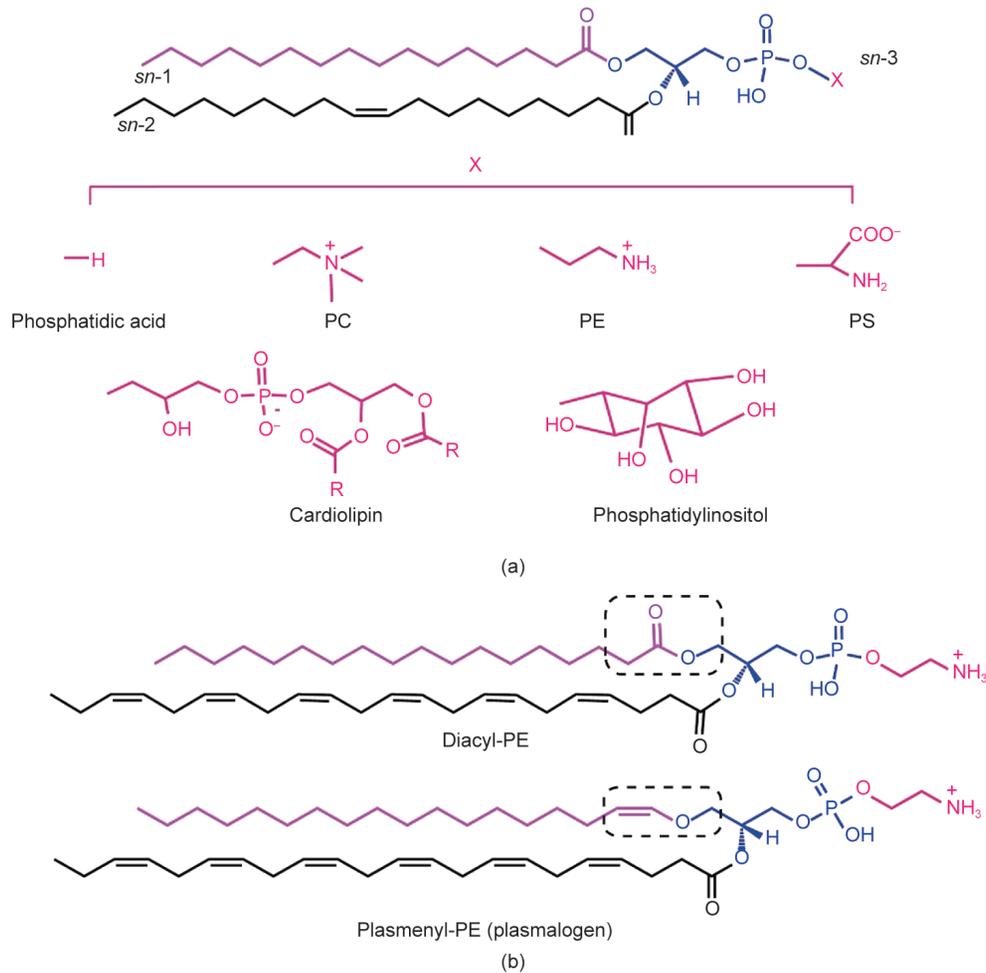


图2. (a) 不同头部基团的磷脂结构; (b) PE的两种主要结构。R: 脂肪酸; X: 头部基团。

4.2. 大脑功能障碍时磷脂的变化

研究发现, 阿尔茨海默症患者血浆中的磷脂酰胆碱含量发生了显著的变化[92]。磷脂酰胆碱浓度, 特别是不饱和磷脂酰胆碱, 包括PC 36:5、PC 38:6和PC 40:6, 在阿尔茨海默症患者和老年人群中较低, 这可能与海马体萎缩有关[41,92–93]。此外, 血酯基磷脂酰胆碱(plasmanyl-PC)(16:0/2:0)的聚集与tau蛋白的高度磷酸化和神经元损失有关[38]。

磷脂酰丝氨酸对神经元膜、髓磷脂, 尤其是突触的正常功能运作至关重要。DHA-PS占灰质中磷脂酰丝氨酸的80%以上[94], DHA-PS的减少与大脑功能障碍相关[39, 95]。在小鼠加速衰老实验中发现, DHA-PS水平有所降低, 这些小鼠寿命缩短、具有认知障碍, 且海马A β -肽含量增加[95]。在阿尔茨海默症患者中也发现类似的结果[39]。

磷脂酰乙醇胺主要以缩醛磷脂(plasmeyl-PE)和二酰基磷脂酰乙醇胺(diacyl-PE)两种形式存在[图2(b)]。缩醛磷脂的特性是在sn-1位置存在乙烯醚键连接,

其磷酸头部基团的95%或95%以上为乙醇胺, 还含有少量的胆碱[96–97]。缩醛磷脂的含量会随着年龄的增长逐渐增加, 直至40岁左右达到峰值, 之后到70岁开始大幅下降[98]。此外, 大脑中缩醛磷脂(18:0/22:6)的含量水平, 而非diacyl-PE(18:0/22:6), 与认知能力的下降相关[99]。在早期的AD[100]、帕金森病[101]、精神分裂症[102]和肢近端型点状软骨发育不良[103]患者中, 都发现了缩醛磷脂缺乏问题。此外, 人类和动物的研究还表明, 缩醛磷脂缺乏是阿尔茨海默症和痴呆症的病因之一[104]。另外, 在氧化应激响应中, 缩醛磷脂含量降低而diacyl-PE则保持不变, 这说明缩醛磷脂可能通过自身被氧化从而保护生物体免受氧化应激的影响[105]。

5. 磷脂对脑衰老的干预作用

磷脂有益于大脑功能(包括认知功能)[87]。持续4个月的富含磷脂的饮食, 可以改善血管密度和突触可塑性, 从而防止处于衰老期的小鼠的记忆力下降问题[106]。

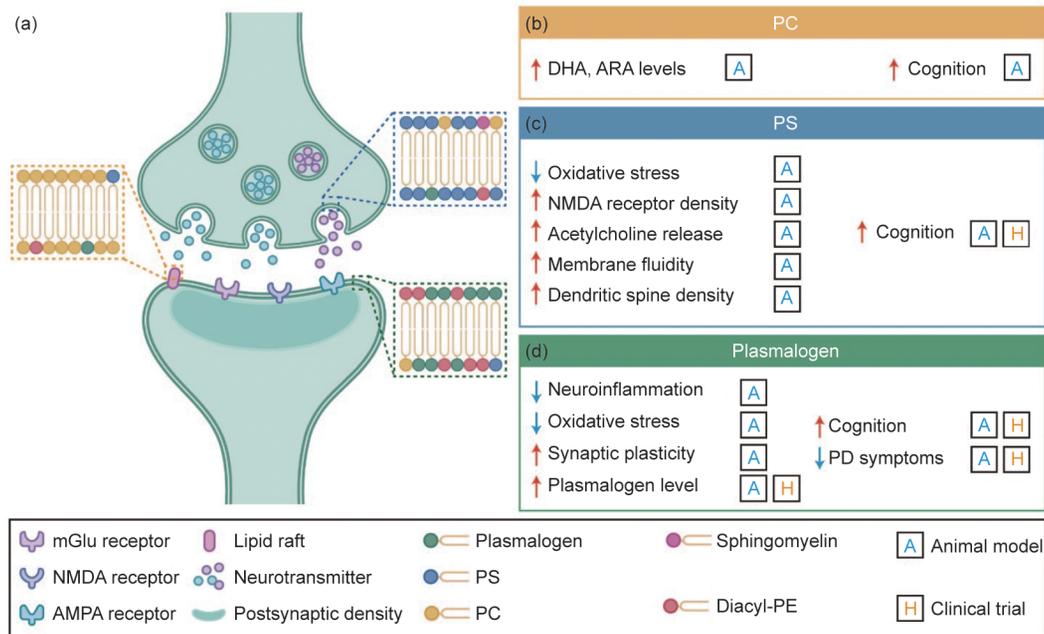


图3. (a) 不同突触微观结构中的特定磷脂：在脂筏（黄色）、囊泡膜（蓝色）和周围密集区（绿色）中，均包含丰富的磷脂酰胆碱（PC）、磷脂酰丝氨酸（PS）和缩醛磷脂；(b)~(d) 它们对大脑功能均有所影响。

从牛奶中提取的磷脂已被证实能够改善高度完美主义男性的认知表现[107]。不同磷脂的种类对脑衰老的干预效果也不尽相同。表2 [101,107–116]和图3 (b)~(d)中的一些研究，对磷脂酰胆碱、磷脂酰丝氨酸和缩醛磷脂对与老年相关的脑部疾病的影响进行了评估。

5.1. 磷脂酰胆碱

膳食磷脂酰胆碱是乙酰胆碱的前体，它可通过激活海马体和前额皮层的胆碱能神经元来改善认知障碍[117–118]。补充磷脂酰胆碱可增加小鼠体内血浆中的DHA和ARA含量水平，增强小鼠的学习能力[118]与空间记忆力[119]。尽管磷脂酰胆碱有望改善记忆力衰退，但关于磷脂酰胆碱可以增强阿尔茨海默症患者或老年认知障碍患者记忆力的证据还有待进一步研究。

5.2. 磷脂酰丝氨酸

突触前膜包含丰富的磷脂酰丝氨酸，磷脂酰丝氨酸会参与神经递质的释放，而该过程又依赖于突触前膜的去极化作用和 Ca^{2+} 的流入。提高磷脂酰丝氨酸的含量可以增加神经元膜的流动性，进而增加ATPase的活性，以促进神经元之间的通信[120–121]。给老龄小鼠补充磷脂酰丝氨酸，可增加NMDA受体的密度，从而达到长时程增强作用[121]。补充磷脂酰丝氨酸还可通过延缓锥体树突棘密度的下降减缓树突连接丢失的速率[122]。此外，磷脂酰丝氨酸还能保护神经元膜免受氧化损伤[123]，并通过增

加乙酰胆碱在大脑中的释放来激活胆碱能神经元，从而有效治疗AD [108]。美国食品药品监督管理局（FDA）已对膳食磷脂酰丝氨酸降低老年痴呆症患病风险的有效性进行了评估[124]。补充磷脂酰丝氨酸（ $100\sim 300\text{ mg}\cdot\text{d}^{-1}$ ）能有效减缓或逆转脑衰老过程中的结构和生物化学变化，提高即时和延迟的言语记忆力，还可以预防有记忆障碍的老年人群或痴呆症患者的认知能力下降问题[108–112]。这种有效性在含DHA的磷脂酰丝氨酸中尤为明显[113–114]。磷脂酰丝氨酸还能有效增强运动能力，然而，它对于因衰老而导致的运动障碍的影响仍待研究[125]。

大多数用于营养干预的磷脂酰丝氨酸均提取自大豆，由丝氨酸和提取自大豆的磷脂酰胆碱在磷脂酶D的催化下而制得[126]。在大脑中，磷脂酰丝氨酸是通过由磷脂酰丝氨酸合酶2所催化的磷脂酰乙醇胺中的乙醇胺与丝氨酸的置换反应而合成，或者是通过由磷脂酰丝氨酸合酶1所催化的磷脂酰胆碱中的胆碱与丝氨酸的置换反应而合成的[94]。此外，大脑中的磷脂酰丝氨酸会优先使用DHA磷脂[94]。根据FDA报道，在提取大豆的磷脂酰丝氨酸中，脂肪酸总含量的62%为亚油酸（C18:2），另外还有油酸（C18:1, 15%）、棕榈酸（C16:0, 14%）、 α -亚麻酸（C18:3, 5%）以及硬脂酸（C18:0, 4%），但无DHA [127]。这一报道意味着提取自大豆的磷脂酰丝氨酸（口服）或许仅可为大脑中磷脂酰丝氨酸的合成提供丝氨酸和磷脂骨架，这可能解释了机体对较高剂量（ $100\sim 300\text{ mg}\cdot\text{d}^{-1}$ ）大豆磷脂酰丝氨酸的补充需求。

表2 在人体中补充磷脂对认知下降的缓解情况

| Model | Compounds | Dose and duration | Effects | Refs. |
|---|--------------|---|--|-------------|
| High-perfectionist (54 subjects) | Phospholipid | Bovine milk-derived phospholipid 2.7 g/d; 6 weeks | Improved post-stress reaction time performance on an attention-switching task | [107] |
| Aged 50–69; MCI (78 subjects) | PS | Soybean-derived PS 100 or 300 mg/d; 24 weeks | Improved delayed verbal recall | [108] |
| Aged 50–90; memory complaints (30 subjects) | PS | Soybean-derived PS 300 mg/d; 12 weeks | Increased cognitive parameters (memory recognition, memory recall, executive functions, and mental flexibility) | [109] |
| Aged 65–78; age-related cognitive decline (18 subjects) | PS | Bovine cortex-derived PS 300 mg/d; 12 weeks | Improved immediate memory, recall, and learning rate | [110] |
| Aged 65–93; moderate to severe cognitive decline (494 subjects) | PS | Bovine cortex-derived PS 300 mg/d; 6 months | Increased behavioral and cognitive parameters (as evaluated by PGRS and BSRT) | [111] |
| Aged 65–91; dementia patients (35 subjects) | PS | Bovine cortex-derived PS 300 mg/d; 6 weeks | Improved memory behavior (as evaluated by Peri Scale) | [112] |
| Aged 64–81; memory complaints (131 subjects) | PS | DHA-PS 100 mg/d; 15 weeks | Improved verbal immediate recall; participants with good cognition at baseline also showed improvements in immediate and delayed verbal recall, learning ability, and time to reproduce complex graphics in post-hoc analysis; improved sustained attention and memory recognition (as evaluated by computerized tool and the CGI-C) | [113]–[114] |
| Aged 65–85; mild AD and MCI (328 subjects) | Plasmalogen | Scallop purified plasmalogen 1 mg/d; 24 weeks | No significant differences in primary and secondary outcomes; improved cognitive parameters in females under 77 years old with mild AD in subgroup analysis (as evaluated by WMS-R, secondary outcome) | [115] |
| Aged 40–60; mild forgetfulness (49 subjects) | Plasmalogen | Ascidian purified plasmalogen 1 mg/d; 12 weeks | Increased score in composite memory (sum of verbal and visual memory scores) | [116] |
| Aged 60–75; PD (10 subjects) | Plasmalogen | Scallop purified plasmalogen 1 mg/d; 24 weeks | Improved clinical symptoms (as evaluated by PDQ-39) | [101] |

BSRT: Buschke Selective Reminding Test; CGI-C: Clinical Global Impression of Change rating scale; PDQ-39: Parkinson's Disease Questionnaire; PGRS: Plutchik Geriatric Rating Scale; WMS-R: Wechsler Memory Scale—Revised.

5.3. 磷脂酰乙醇胺

对磷脂酰乙醇胺的干预主要集中在缩醛磷脂上。缩醛磷脂富集于突触后膜的周围密集区，参与多种大脑功能，包括囊泡融合、膜筏组成、内质网应激、跨膜蛋白功能和胆固醇转运，这些对于突触可塑性都非常重要[128–130]。它还可以作为活性氧/氮类的清除剂，参与脂质过氧化过程[129–130]。此外，研究表明缩醛磷脂通过抑制Toll样受体4的内吞作用，在抗神经炎症中发挥关键作用[131]。缩醛磷脂还可作为底物通过阳离子交换反应合成PS [132]。通过动物实验发现，与diacyl-PE相比，口服缩醛磷脂能更好地在皮质缩醛磷脂（18:0/22:6）富集，并改善具有认知缺陷的大鼠的学习能力[133]。体外实验也得到了类似的结果[134]。在人体研究中，给77岁以下轻度阿尔茨海默症女性口服缩醛磷脂（1 mg·d⁻¹）可改善她们的认知能力[115]，并且对轻度健忘志愿者的言语和视觉记忆力也呈现剂量依赖性到的改善效果[116]。缩醛磷脂对脑部的

益处还体现在帕金森病患者当中，可将血浆和红细胞中的缩醛磷脂含量恢复至接近正常的水平，同时改善部分临床症状，如日常活动能力、社交能力、认知能力和身体不适[101]。此外，缩醛磷脂的前体分子——1-*O*-十八烷基-*sn*-甘油（OG）和*sn*-2位置含有DHA的烷基-二酰基缩醛磷脂前体（PPI-1011），也已被证明能够通过增加缩醛磷脂水平分别改善肢近端型点状软骨发育不良和帕金森病的症状[135–136]。

用于营养干预的缩醛磷脂通常提取自扇贝，其富含n-3 PUFA。由于缩醛磷脂在*sn*-1位置特有的乙烯醚键和突触后膜周围密集区的丰度，临床试验中改善脑衰老功能所需的缩醛磷脂有效剂量（1 mg·d⁻¹）远低于PS（100 mg·d⁻¹）。然而，动物实验在有效剂量角度表现出不一致，这可能是由于给药方式的差异所致[137–138]。在动物研究中，通常通过灌胃给予缩醛磷脂，将缩醛磷脂直接暴露于胃中。然而，缩醛磷脂的乙烯醚键在酸性条件下不稳定，大部分

缩醛磷脂会在胃中分解成醛类物质[139]。这可能是动物实验中需要更高剂量的原因。口服胰岛素肠溶胶囊可以预防胃酸环境对胰岛素结构和效果的影响[140]。因此，微胶囊包装和靶向递送可能会提高缩醛磷脂的利用率。

6. 结论

神经系统疾病是全球面临的巨大挑战之一，因此，开发能够改善衰老过程中大脑功能的营养干预措施变得越来越重要。脑内脂质具有复杂的结构和功能多样性，在细胞内和细胞间的信号传导中起着至关重要的作用。临床和机制分析表明，相比于PUFA，磷脂酰丝氨酸和缩醛磷脂干预能通过维持脂质稳态更好的改善认知功能受损和大脑衰老。在用于营养干预的磷脂酰丝氨酸中，DHA和其他n-3 PUFA的含量较低，而缩醛磷脂通常含有高含量水平的n-3 PUFA。由于其结构中特有的乙烯醚键以及在突触后膜中的丰度，缩醛磷脂在老龄化过程中改善脑功能方面可能比磷脂酰丝氨酸更有效。缩醛磷脂前体分子的临床有效性也证明了其重要性。然而，尽管其功能值得关注，但由于其对酸的不耐受性和易氧化的乙烯醚键，临床试验和动物研究中的有效剂量不一致。此外，由于其他机制尚不明确，缩醛磷脂仍未得到广泛应用。综上所述，膳食磷脂可能是减缓脑衰老最有前景的物质，但仍需要大量研究来探索消化和代谢途径，以及生物有效性。缩醛磷脂可能是最有前景的脑部保护性磷脂之一，需要进一步研究其潜在机制和实际应用。

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Compliance with ethics guidelines

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