饮食干预肠道微生物调控认知和神经退行性疾病的作用机制

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摘要 神经退行性病变是认知功能退化和神经系统疾病的病理基础，受诸多机体内、外环境因素的影响。寄居于肠道中的微生物可影响机体健康和多种疾病的发生与发展，包括神经和精神疾病。肠道失调与阿尔茨海默病、帕金森病、亨廷顿病以及多发性硬化症等认知与运动功能障碍性疾病密切相关。研究发现，饮食干预可通过调节肠道微生物，改善肠-脑之间的联系，调控认知和情感等脑高级功能，缓解认知下降，抑制神经退行性病变，然而其内在机制尚不明确，可能与饮食干预调节肠道微生物群的构成及功能，进而改善肠道代谢、肠道内分泌等机制有关。本文通过分析饮食干预调节肠道微生物及相关的生理生化改变与脑认知和神经功能的关系，探讨饮食干预在肠道微生物与肠-脑联络与神经退行性疾病中的作用及机制。

关键词 饮食干预；肠道微生物；认知功能；神经退行性疾病；生酮饮食；地中海饮食
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研究发现，肠道微生物可通过参与机体的物质代谢与营养供应[1]，介导消化系统相关疾病[2]，调节人的心理、行为、认知和神经系统疾病[3]等影响机体的生理和病理过程。近年研究证实，肠道微生物群失调与阿尔茨海默病（Alzheimer's disease，AD）[4-5]、帕金森病（Parkinson's disease，PD）[6-7]、亨廷顿病（Huntington's disease，HD）[8]和多发性硬化症（multiple sclerosis，MS）[9]等神经退行性疾病关系密切。饮食干预可能是对肠道功能，尤其是寄居其中的微生物群影响最直接的因素。饮食干预可通过调节肠道微生物的构成和功能优化[10]，介导肠道神经系统与中枢神经系统的传导[11]，进而促进神经功能和改善认知[12]，缓解或治愈神经退行性疾病，然而其机制尚不明晰。本研究通过分析肠道微生物与肠-脑联络、饮食干预对神经退行性疾病和肠道微生物的调节作用，探讨肠道微生物在饮食干预认知功能和神经退行性疾病中的作用。

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1 肠道微生物与肠-脑联络

神经科学研究[13]发现，肠道微生物群失衡（或称为肠道失调）是导致机体致病的重要诱因。研究[14]认为，肠道微生物的多样化可促进健康，且与改善脑的学习记忆能力和机体行为的灵活性相关，而微生物多样性下降则与认知能力的损害高度相关。肠道微生物群的多样性及其组成受多种因素影响。肠道微生物群是胃肠道消化、营养物质和代谢物提取、合成和吸收等基本过程的调节者。肠道微生物群可通过竞争营养素、产生细菌素、保持肠上皮完整性等促进肠道对病原微生物的免疫反应[15]。肠道微生物的多样性和组成决定了其衍生代谢物、神经递质和短链脂肪酸（short-chain fatty acids，SCFAs），如丁酸、丙酸和乙酸等主要肠道代谢终产物的水平[16]。不同 SCFAs 之间的平衡对肠道健康至关重要，例如，丁酸盐的浓度与黏蛋白的产生有关，可发挥抗炎作用，并增加紧密连接蛋白水平，最终促进肠道屏障的完整性，降低肠道黏膜的通透性[16-17]。肠道微生物群的多样性及组成的失衡是肠道完整性缺失和功能受损的重要诱因，可导致肠道通透性增加和肠道炎症反应，致使肠道环境异常，进而可通过神经传导（迷走神经）、神经内分泌轴，如丘脑-垂体-肾上腺（hypothalamus-pituitary-adrenal，HPA）轴和免疫系统导致与大脑之间的信息沟通障碍和神经系统功能异常

[18],其中受影响最显著的是脑认知功能的退化[19]。

肠道功能失调参与了机体的致病过程，影响包括神经系统疾病[20-21]在内的各种疾病的发生和进展。无菌小鼠的研究[22]发现,缺乏肠道微生物的实验小鼠其认知能力存在显著缺陷,表明肠-脑间的联络与认知功能关系密切。肠道微生物具有复杂性、多样性和可塑性等特点,在调节不同个体健康和疾病的状态中差异显著[15]。因此,肠道微生物群可被视为一个多变性的动态微生态系统，会不断受到机体内外环境,如摄食营养、温度变化、情绪反应和特殊环境暴露等影响[23]。同时,肠道微生态的变化也会反作用于人的饮食偏好、情绪反应和行为表现等(如图 1)。

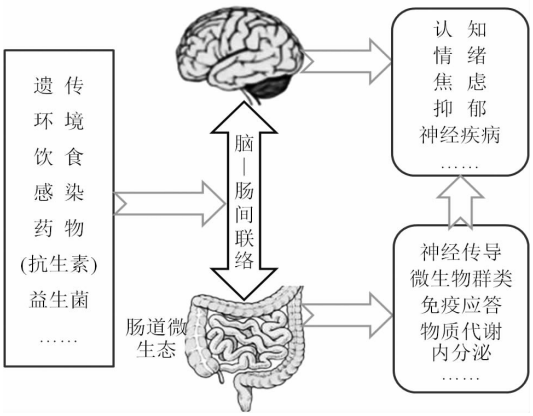

图 1 影响肠脑联络的因素及其对神经功能的影响示意图

Fig.1 Factors affecting gut brain connections and its impact on neural function

2 饮食干预对神经退行性疾病的调节作用

饮食干预是改善神经退行性疾病的重要手段，饮食干预与神经退行性疾病危险因素之间关系密切[24-25]。流行病学研究表明,过量的饱和脂肪酸摄入可通过加剧氧化应激和脂质过氧化而加强 AD[26-27]和 PD[28-29]的神经变性,高热量摄入与 HD 的早期发病呈正相关[30]。而饱和脂肪摄入增加可引起炎症反应，从而使外周免疫细胞进入中枢神经系统[31],这可能是不良饮食摄入导致神经疾病症状恶化的诱因。饮食摄入的营养素及其代谢产物可调节神经炎症,对神经功能产生有益影响。同时，饮食干预可改善神经退行性疾病病症中常见的功能失调和代谢紊乱。生酮饮食和地中海饮食以其独特的营养与保健功能，深受食用者和研究者青睐。

2.1 生酮饮食(KD)对神经退行性疾病的调控作用

生酮饮食(ketogenic diet，KD)的特点是脂肪含量高、蛋白质含量充足和低碳水化合物,摄取 KD 的目的是限制糖的酵解和增加脂肪酸氧化生成酮体，从而促使酮体取代葡萄糖成为大脑的主要能源物质。研究[32-33]发现,KD 对改善 AD、PD 和 HD 等神经退行性疾病效果显著。AD[34-35]和 HD[36]的动物实验以及 AD 患者的临床试验 [37] 均证实,KD 在改善神经退行性疾病中具有一定的成效。线粒体结构损伤和功能障碍是 AD、PD 和 HD 等神经退行性疾病的关键病理原因,KD 可通过抑制线粒体损伤来减轻神经系统疾病症状。KD 可通过刺激线粒体的生物发生、稳定神经突触功能及刺激脑源性神经营养因子 (brain-derived neurotrophic factor，BDNF) 的产生来抵御神经元的氧化应激损伤、促进神经元能量代谢的正常化,改善神经元功能[38]。KD 的神经保护机制可能部分通过其代谢所产生的酮体发挥作用。临床研究[37]证明,KD 可通过调控 AD 患者脑内的酮体 β-羟基丁酸酯的释放,进而降低 AD 的患病风险。PD 动物实验[39]发现，输注 β-羟基丁酸酯可缓解 MPTP 造模 PD 小鼠多巴胺(Dopamine，DA)能神经元缺失和运动功能障碍。由于 β-羟基丁酸酯可抑制神经递质 γ-氨基丁酸(γ-aminobutyric acid，GABA)的降解，从而增加脑内 GABA 的利用率[40]。此外,KD 还可促进儿童二十二碳六烯酸(Docosahexaenoic acid，DHA) 和其它脂肪酸如二十碳五烯酸(Eicosapentaenoic Acid，EPA)和亚油酸(linoleic acid，LA)水平的提高[41]。上述研究表明 KD 在改善机体能量代谢,调节肠道微生态,促进神经功能和缓解神经系统疾病中具有积极作用(如图 2)。

2.2 地中海饮食(MD)对神经退行性疾病的调控作用

地中海饮食(Mediterranean diet，MD)亦被证实可改善健康和降低多种疾病的发生风险。MD 特指地中海沿岸国家传统上所形成的饮食习惯，其特点是饮食中大量摄入水果、蔬菜、豆类、复合

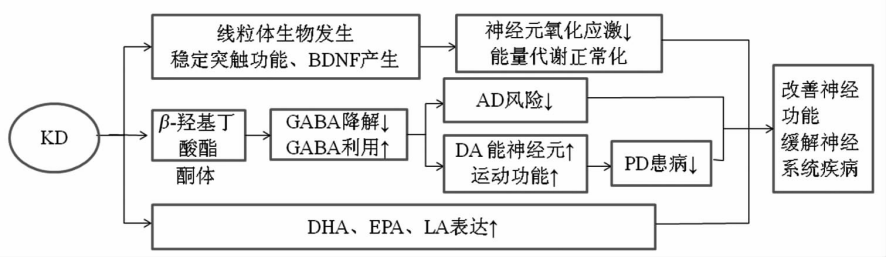

图 2　KD 对神经退行性疾病的调控示意图

Fig.2　Regulation of KD on neurodegenerative diseases

碳水化合物，适量食用鱼和橄榄油作为脂肪的主要来源，并配以适量的红酒饮用。大量研究认为 MD 可作为改善和治疗神经退行性疾病的有效方式。荟萃分析显示，MD 摄入量高的人群其认知量表评分显著增高[42]。临床研究发现，长期的 MD 摄入可降低 AD[43]和 PD[44]风险，但研究[45]却发现 MD 对 HD 未见明显的改善作用，其原因可能与 HD 受遗传影响较显著有关[46]。MD 富含单不饱和脂肪酸和多不饱和脂肪酸，长期摄入可降低 AD 和 PD 的发病风险[47]。MD 大量摄入鱼类食物，富含 DHA，是脑组织需求量较大的 ω-3 脂肪酸，可改善学习和记忆等脑高级认知功能[48]。

早期研究[49]已证实 DHA 可促进神经生长和学习以及神经免疫调节，补充 DHA 有助于改善神经退行性疾病[50-52]。临床检测显示，AD[53]和 PD[54]患者的 DHA 水平显著降低。饮食中摄入 DHA 和其它多不饱和脂肪酸可降低 AD 和 PD 等发病风险[55-57]。DHA 对 AD 和 PD 病理的干预机制可能与其激活 Akt/p-Akt 和 Bcl-2 信号途径，降低 AD 脑中的神经炎症和 β 淀粉样蛋白（amyloid β-protein，Aβ）沉积[58]，减轻 PD 脑中 DA 能神经元的死亡有关[59]。此外，MD 富含多酚、维生素 C、E、B_{12}、叶酸和类胡萝卜素等膳食抗氧化剂，饱和脂肪酸含量有限，可能有助于降低 PD 的风险[60]，可抵抗细胞膜受氧化应激损伤和脂质过氧化的有害影响，可预防神经疾病，促进脑健康（如图 3）。但目前在试验研究和临床研究之间尚存在部分分歧，若要弥合二者的差异，试验研究需深入探讨饮食干预的神经保护作用及其机制，而临床研究亦应进一步探索饮食干预对 AD 和 PD 及其它神经退行性疾病的治疗潜力。

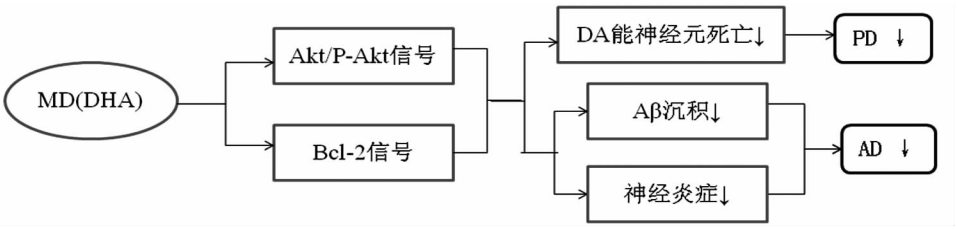

图 3　地中海饮食对神经退行性疾病的调控示意图

Fig.3　Regulation of Mediterranean diet on neurodegenerative diseases

3　饮食干预对肠道微生物的调节作用

肠道微生物具有高度可塑性，可对饮食摄入的变化做出迅速反应。饮食对肠道具有直接的刺激作用，可发挥塑造肠道微生物的重要作用，饮食干预可通过调节肠道微生物介导神经保护作用。饮食是塑造肠道微生物群落的关键因素，饮食构成的变化可通过调节肠道营养素的供应直接影响肠道微生物群落的组成和功能。研究[61]发现，“西方饮食”因大量摄入饱和脂肪酸和单糖的缘故，导致耐胆汁微生物类杆菌丰度增加，硬壁菌丰度降低。与动物性饮食相比，植物性饮食的摄入可提高膳食纤维发酵微生物群的丰度，诱导肠道内和循环血中的 SCFA 等代谢产物的增多[62]，促进肠道微生物群的复杂化。

研究[63]显示,KD 可降低脱硫弧菌和绿脓杆菌的丰度,增加嗜黏杆菌和乳酸杆菌的丰度,进而促进 SCFA 产生。但研究[32,64]发现,KD 降低了总体肠道微生物的多样性。另有证据[33]表明,KD 的影响是双相的,即在 KD 干预开始时期微生物多样性降低,随后恢复正常,进而超过原来的丰度。综上可见,KD 对肠道微生物群影响的研究还存在不一致的结果,还需进一步的研究积累,以明确其在调节肠道微生物与肠道健康中的作用。另外,研究[65]证实,坚持摄入 MD 可通过上调类杆菌、普雷沃菌的丰度和下调硬壁菌和乳酸杆菌的丰度,改善认知和脑健康。与西方饮食[66]相比,坚持 MD 的受试者粪便中丙酸和丁酸的含量增高,肠道微生物的多样性增加。

对富含脂肪酸鱼类的研究[67]发现,ω-3 脂肪酸的摄取增加可促进循环血中的 DHA 水平升高,其原因可能与膳食纤维的摄入促进了肠道代谢产生 SCFAs 的毛螺菌和瘤胃球菌的丰度增高相关。高蛋白膳食[68]和抗性淀粉膳食[69]均可通过调节肠道微生态,提高肠道微生物多样性,改善高脂膳食诱导的肠道微生物群失调和肠道代谢。其它营养素如多酚、维生素和部分微量营养素的摄入也可发挥塑造肠道微生物的功能[70]。此外,研究[71]发现,饮用黄酒可逆转高脂饮食导致的肠道微生物群的多样性失衡,其原因可能与黄酒在发酵过程中所产生的大量有益微生物有关。可见,不同类型膳食的摄入对调节肠道微生物具有一定的差异性,但与高脂膳食的负向调节作用相比,ω-3 脂肪酸膳食、高蛋白膳食以及多酚、维生素等膳食对肠道微生态的调节具有积极的意义(如图 4)。

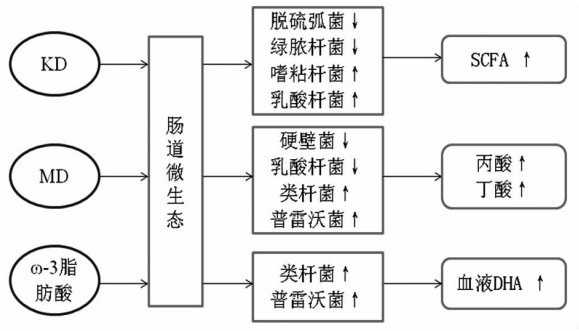

图 4 饮食干预对肠道微生物的调节示意图

Fig.4 Regulation of dietary intervention on gut microbiota

4 饮食干预肠道微生物对认知功能与神经退行性疾病的影响

肠道微生物在调节机体代谢和内分泌中发挥着关键作用。肠道微生物不仅是饮食摄入的反映,而且是肠道代谢的重要表征。研究发现饮食干预可通过介导肠道微生物的变化调节实验小鼠的认知功能和行为表现(如表 1)。

高脂膳食和高糖膳食诱导的肠道微生态改变是认知功能障碍和焦虑样行为产生的重要因素。在诸多饮食干预的研究中,高脂和高糖膳食在各种代谢性病理原因的探寻中发挥着关键作用,与 AD 和 PD 等神经退行性疾病的风险增加关系密切。研究发现,高脂膳食可通过调控肠道微生物引起认知障碍和肠神经炎症激活[74]。高脂膳食可导致实验小鼠焦虑样行为增加、认知功能下降,硬壁菌和拟杆菌丰度增加,软壁菌丰度下降[75],表明高脂膳食可诱导肠道微生物的改变增加焦虑样行为和损害认知,其机制可能是高脂膳食通过介导肠道微生物和肠道神经系统进而通过 HPA 轴介导的神经应激反应有关[76]。HPA 轴是肠道和大脑之间的重要信息沟通途径,HPA 轴功能障碍可能导致肠道通透性、肠道运动能力和肠道黏液生成的改变[77],补充多酚或通过其它相关饮食干预可改善肠道功能、逆转 HPA 轴的功能障碍[78]。长期高脂膳食可导致肠道微生物失调,进而通过肠-脑间的神经联络、免疫反应、生理生化和内分泌等途径对认知功能产生影响[79](如图 5)。另有研究[73]发现,高糖膳食对实验小鼠记忆功能的损害强于高脂膳食,其对肠道微生物的改变作用也大于高脂膳食。此外,高膳食纤维饮食可促进肠道微生物代谢产物的增加[80],如可诱导肠道代谢产生丰富的 SCFAs,已被证明有益于促进认知功能的提高。

再者,饮食中 DHA 的摄入被证明可降低 AD 和 PD 的患病风险。研究发现,DHA 可通过调节肠道微生物群,直接介导相关的基因表达和肠-脑间的神经传导[81]。动物实验[72]证明,补充富含 DHA 的 ω-3 多不饱和脂肪酸可调节小鼠肠道异杆菌和瘤胃球菌丰度,进而改善实验小鼠的认知功能和焦虑样行为,该研究还发现,补充 DHA 对不同性别

表 1　饮食干预对肠道微生物群和认知功能的影响

Table 1　Effects of dietary intervention on gut microbiota and cognitive function

作者(发表年份)	实验动物	饮食干预	干预时间/周	认知测试模式	认知测试结果	肠道检测结果
Davis 等[72](2017)	C57BL/6 雄性和雌性小鼠	DHA	4	OFT EPM SPT	雄性小鼠： 焦虑样行为↓ 空间记忆↑	雄性小鼠：乳球菌↓、念球菌↓ 链球菌↑、螺杆菌↑ 雌性小鼠：肠道微生物群未见显著变化
Magnusson 等[73](2015)	C57BL/6 雄性小鼠	HFD HSD	6	SDL OFT NOR MWM	空间记忆↓ (HSD)	梭杆菌↑、类杆菌↓ (HFD 和 HSD) 丹毒丝菌↑(HFD) 乳杆菌↑(HSD)
Bruce 等[74](2015)	C57BL/6 雄性小鼠	HFD	10	OFT EPM MBT TFC	空间记忆↓ 焦虑样行为↑	毛螺菌↑ 瘤球菌↑ 艾克曼菌↓ 肠道炎症激活↑
Kang 等[75](2014)	C57BL/6 雄性小鼠	HFD	16	TFC	恐惧情境记忆↓ 线索记忆↓	硬壁菌↑ 拟杆菌↓ 软壁菌↓

注：DHA：DHA 补充膳食；HFD：高脂膳食(High fat diet)；HSD：高糖膳食(High sucrose diet)；OFT：旷场实验(Open field test)；EPM：高架迷宫实验(Elevated plus maze)；SPT：糖水偏好实验(Sucrose preference test)；NOR：新奇事物识别实验(Novel object recognition)；SDL：跳台潜伏期测试(Step down latency)；MWM：Morris 水迷宫实验(Morris water maze)；MBT：大理石埋藏实验(Marble-burying test)；TFC：痕迹性恐惧记忆实验(Trace fear conditioning)。

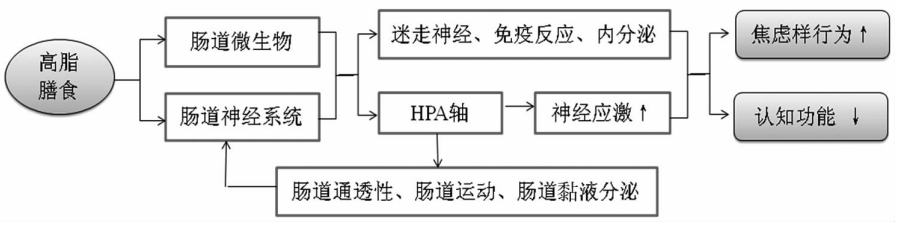

图 5　高脂膳食介导肠道微生态损害神经功能示意图

Fig.5　High fat diet mediates gut microecology and damage to neurological function

小鼠的肠道微生物和认知与行为的调节作用具有差异性，对雄性小鼠的干预效果明显优于雌性小鼠。关于性别因素影响饮食干预肠道微生物的差异性在近期的一项报道中也有涉及，研究[23]发现，高脂膳食修饰了雌性和雄性小鼠肠道微生态结构，但对雌性和雄性小鼠肠道微生物构成的调节作用不同，其原因可能与不同性别机体的能量代谢水平和激素水平的差异有关。膳食补充 EPA 和 DHA 可改变肠道微生物构成，减轻环境应激引起的皮质酮反应[82]。此外，利用微生物移植技术将食用鱼类脂肪酸小鼠的肠道微生物群移植到食用猪脂肪酸的小鼠肠道中可减轻饱和脂肪酸摄入引起的肥胖症状和炎症性反应[83]，表明鱼类脂肪酸补充可调节肠道微生物发挥抗炎作用，进一步证明肠道微生物在饮食干预增进健康中的积极作用(如图 6)。

KD 可通过调控肠道微生物发挥神经保护作用。动物实验发现，KD 干预可促进小鼠肠道内有益微生物的丰度和大脑血流量的增加，其内在原因可能是肠道内的有益微生物通过激活内皮型一氧化氮合酶（endothelial nitric oxide synthase，NOS）抑制雷帕霉素（mechanistic target of ra-

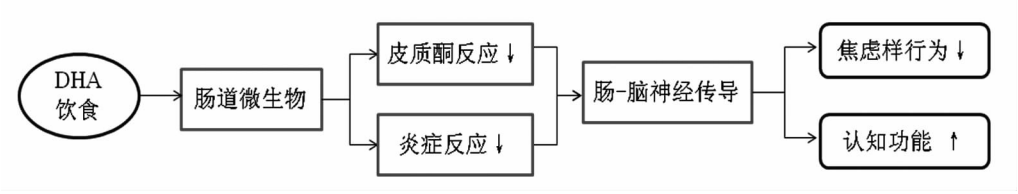

图 6 DHA 饮食介导肠道微生物改善神经功能示意图

Fig.6 DHA diet mediates gut microbiota to improve neurological function

pamycin，mTOR)相关信号的机制靶点,从而改善神经血管生成和脑的供血增多[63]。其机制还可能与 KD 干预调节肠道微生物诱导(D)-3-羟基丁酸酮体的产生增加，进而通过 G 蛋白偶联受体(G Protein-Coupled Receptors，GPCRs）信号通路和相关基因的表观遗传调控机制介导肠道和脑之间的信息传递有关。此外,研究[64]发现,KD 干预对无菌小鼠和抗生素介入小鼠失去抗癫痫作用，但将实验小鼠置于 SPF 微生物环境后其肠道微生物群恢复正常,KD 的抗癫痫效应又重新获得，其原因可能是肠道微生物通过调节血液中 γ-谷氨酰化的选择性代谢和其它生酮氨基酸的代谢来发挥其作用,进而诱导脑内的 GABA 水平升高(如图 7)。

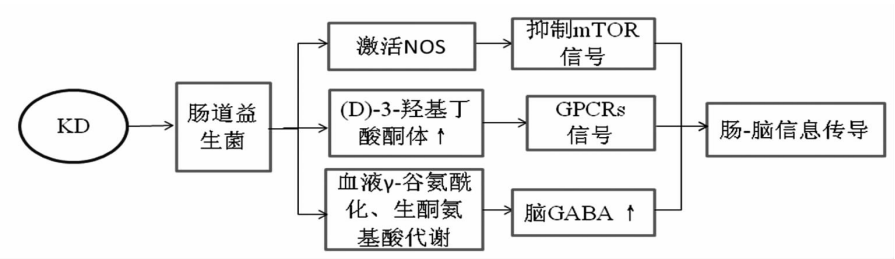

图 7 KD 介导肠道微生物改善神经功能示意图

Fig.7 KD mediates gut microbiota to improve neurological function

综上可见，不良的膳食摄入是导致肠道微生态环境变化,进而促使神经功能退化、认知下降和焦虑样行为的关键诱因，而合理的饮食干预是健康增进和疾病调理的有效方式，可在一定程度上改善神经退行性疾病的病理症候。饮食干预可介导肠道微生物改善认知功能和脑健康，故饮食干预与脑健康和神经退行性疾病之间可以肠道微生物为媒介发挥作用，进而抑制相关神经退行性疾病的发病和进展。

5 结语与展望

肠道微生物的多样性与完整性是机体健康的重要保障，与机体正常的生理功能和病理变化息息相关。肠道微生物与认知和情感等脑高级功能存在重要关联，肠道失调是多种神经退行性疾病的诱因。肠道微生物群所构成的肠道动态生态系统会不断受到机体内外环境因素的影响而发生改变。肠道微生物可能是神经退行性疾病的应激源和干预靶点，肠道微生物群失调可诱导认知功能损害和神经退行性疾病。饮食干预,如生酮饮食、地中海饮食和 ω-3 脂肪酸等的补充可通过调节肠道微生物介导肠-脑联络,改善认知功能、缓解神经退行性疾病；而长期的高脂或高糖膳食则可导致认知功能受损和神经退行性病变。然而,肠道微生物与认知功能和神经退行性疾病病理之间的因果关系尚未得到全面证实,还需要更多、更深的研究来明确不同饮食模式介导肠道微生物与认知和神经退行性疾病之间的关系，以为脑健康促进和神经退行性疾病的干预提供参考依据。

参 考 文 献

[1] NICHOLSON J K，HOLMES E，KINROSS J，et al. Host-gut microbiota metabolic interactions[J].

Science, 2012, 336(6086): 1262-1267.

[2] LOUIS P, HOLD G L, FLINT H J. The gut microbiota, bacterial metabolites and colorectal cancer[J]. Nat Rev Microbiol, 2014, 12(10): 661-672.

[3] CRYAN J F, DINAN T G. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour[J]. Nat Rev Neurosci, 2012, 13(10): 701-712.

[4] HU X, WANG T, JIN F. Alzheimer's disease and gut microbiota[J]. Sci China Life Sci, 2016, 59(10): 1006-1023.

[5] WU S C, CAO Z S, CHANG K M, et al. Intestinal microbial dysbiosis aggravates the progression of Alzheimer's disease in Drosophila[J]. Nat Commun, 2017, 8(1): 24.

[6] VAN KESSEL S P, EL A S. Bacterial metabolites mirror altered gut microbiota composition in patients with Parkinson's disease[J]. J Parkinsons Dis, 2019, 9(s2): S359-S370.

[7] FIELDS C T, SAMPSON T R, BRUCE-KELLER A J, et al. Defining dysbiosis in disorders of movement and motivation[J]. J Neurosci, 2018, 38(44): 9414-9422.

[8] GERALDINE, KONG, KIM-ANH, et al. Microbiome profiling reveals gut dysbiosis in a transgenic mouse model of Huntington's disease[J]. Neurobiology of Disease, 2020, 135: 1-9.

[9] WRIGHT M L, CHRISTINA F, HOUSER M C, et al. Potential role of the gut microbiome in ALS: A systematic review[J]. Biol. Res. Nursing, 2018(20): 513-521.

[10] OJEDA P, BOBE A, DOLAN K, et al. Nutritional modulation of gut microbiota - the impact on metabolic disease pathophysiology[J]. J Nutr Biochem, 2016, 28: 191-200.

[11] GOEHLER L E, PARK S M, OPITZ N, et al. Campylobacter jejuni infection increases anxiety-like behavior in the holeboard: possible anatomical substrates for viscerosensory modulation of exploratory behavior[J]. Brain Behav Immun, 2008, 22(3): 354-366.

[12] SAVIGNAC H M, TRAMULLAS M, KIELY B, et al. Bifidobacteria modulate cognitive processes in an anxious mouse strain[J]. Behavioural Brain Research, 2015, 287: 59-72.

[13] SKOLNICK S, GREIG N. Microbes and monoamines: Potential neuropsychiatric consequences of dysbiosis[J]. Trends in Neurosciences, 2019, 42(3): 151-163.

[14] DAVIDSON G L, COOKE A C, JOHNSON C N, et al. The gut microbiome as a driver of individual variation in cognition and functional behaviour[J]. Philos Trans R Soc Lond B Biol Sci, 2018, 373(1756): 1-12.

[15] RINNINELLA E, RAOUL P, CINTONI M, et al. What is the healthy gut microbiota composition? A Changing ecosystem across age, environment, diet, and diseases[J]. Microorganisms, 2019, 7(1): 1-22.

[16] CAMPBELL S C, WISNIEWSKI P J, NOJI M, et al. The effect of diet and exercise on intestinal integrity and microbial diversity in mice[J]. PLoS One, 2016, 11(3): e150502.

[17] MATSUMOTO M, INOUE R, TSUKAHARA T, et al. Voluntary running exercise alters microbiota composition and increases n-butyrate concentration in the rat cecum[J]. Biosci Biotechnol Biochem, 2008, 72(2): 572-576.

[18] WESTFALL S, LOMIS N, KAHOULI I, et al. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis[J]. Cell Mol Life Sci, 2017, 74(20): 3769-3787.

[19] GAREAU M G. Cognitive function and the microbiome[J]. International Review of Neurobiology, 2016, 131: 227-246.

[20] CATANZARO R, ANZALONE M, CALABRESE F, et al. The gut microbiota and its correlations with the central nervous system disorders[J]. Panminerva Med, 2015, 57(3): 127-143.

[21] PATTERSON E, RYAN P M, CRYAN J F, et al. Gut microbiota, obesity and diabetes[J]. Postgrad Med J, 2016, 92(1087): 286-300.

[22] GAREAU M G, WINE E, RODRIGUES D M, et al. Bacterial infection causes stress-induced memory dysfunction in mice[J]. Gut, 2011, 60(3): 307-317.

[23] 彭利利, 丁宁, 赵正刚, 等. 高脂饮食对不同性别小鼠肠道菌群的影响[J]. 食品工业科技, 2020, 41(1): 86-90.
PENG L L, DING N, ZHAO Z G, et al. Effects of high-fat diet on gut microbiota in male and female mice[J]. Science and Technology of Food Industry, 2020, 41(1): 86-90.

[24] ERRO R, BRIGO F, TAMBURIN S, et al. Nutritional habits, risk, and progression of Parkinson disease[J]. J Neurol, 2018, 265(1): 12-23.

[25] SOLFRIZZI V, PANZA F, FRISARDI V, et al. Diet and Alzheimer's disease risk factors or prevention: the current evidence[J]. Expert Rev Neurother, 2011, 11(5): 677-708.

[26] PETROV D, PEDROS I, ARTIACH G, et al. High-fat diet-induced deregulation of hippocampal insulin signaling and mitochondrial homeostasis deficiences contribute to Alzheimer disease pathology in rodents[J]. Biochim Biophys Acta, 2015, 1852(9): 1687-1699.

[27] STUDZINSKI C M, LI F, BRUCE-KELLER A J, et al. Effects of short-term western diet on cerebral oxidative stress and diabetes related factors in APP x PS1 knock-in mice[J]. J Neurochem, 2009, 108(4): 860-866.

[28] BOUSQUET M, ST-AMOUR I, VANDAL M, et al. High-fat diet exacerbates MPTP-induced dopaminergic degeneration in mice[J]. Neurobiol Dis, 2012, 45(1): 529-538.

[29] MORRIS J K, BOMHOFF G L, STANFORD J A, et al. Neurodegeneration in an animal model of Parkinson's disease is exacerbated by a high-fat diet[J]. Am J Physiol Regul Integr Comp Physiol, 2010, 299(4): R1082-R1090.

[30] STUDZINSKI C M, LI F, BRUCE-KELLER A J, et al. Effects of short-term western diet on cerebral oxidative stress and diabetes related factors in APP x PS1 knock-in mice[J]. J Neurochem, 2009, 108(4): 860-866.

[31] BUCKMAN L B, HASTY A H, FLAHERTY D K, et al. Obesity induced by a high-fat diet is associated with increased immune cell entry into the central nervous system[J]. Brain Behav Immun, 2014, 35: 33-42.

[32] NEWELL C, BOMHOF M R, REIMER R A, et al. Ketogenic diet modifies the gut microbiota in a murine model of autism spectrum disorder[J]. Mol Autism, 2016, 7(1): 37.

[33] SWIDSINSKI A, DORFFEL Y, LOENING-BAUCKE V, et al. Reduced mass and diversity of the colonic microbiome in patients with multiple sclerosis and their improvement with ketogenic diet[J]. Front Microbiol, 2017, 8: 1-9.

[34] BECKETT T L, STUDZINSKI C M, KELLER J N, et al. A ketogenic diet improves motor performance but does not affect β-amyloid levels in a mouse model of Alzheimer's Disease[J]. Brain Research, 2013, 1505: 61-67.

[35] BROWNLOW M L, BENNER L, AGOSTINO D D, et al. Ketogenic diet improves motor performance but not cognition in two mouse models of Alzheimer's pathology[J]. PLoS ONE, 2013, 8(9): e75713.

[36] RUSKIN D N, ROSS J L, JR. KAWAMURA M, et al. A ketogenic diet delays weight loss and does not impair working memory or motor function in the R6/2 1J mouse model of Huntington\"s disease[J]. Physiology & Behavior, 2011, 103(5): 501-507.

[37] HENDERSON S T, VOGEL J L, BARR L J, et al. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial[J]. Nutrition & Metabolism, 2009, 6(1): 31.

[38] YONI, GENZER, MAAYAN, et al. Effect of dietary fat and the circadian clock on the expression of brain-derived neurotrophic factor (BDNF)[J]. Molecular & Cellular Endocrinology, 2016, 430: 49-55.

[39] TIEU K, PERIER C, CASPERSEN C, et al. D-β-Hydroxybutyrate rescues mitochondrial respiration and mitigates features of Parkinson disease [J]. Journal of Clinical Investigation, 2003, 112(6): 892-901.

[40] SUZUKI Y, TAKAHASHI H, FUKUDA M, et al. β-hydroxybutyrate alters GABA-transaminase activity in cultured astrocytes[J]. Brain Research, 2009, 1268: 17-23.

[41] DAHLIN M, HJELTE L, NILSSON S, et al. Plasma phospholipid fatty acids are influenced by a ketogenic diet enriched with n-3 fatty acids in children with epilepsy[J]. Epilepsy Research. 2007, 73(2): 199-207.

[42] PSALTOPOULOU T, SERGENTANIS T N, PANAGIOTAKOS D B, et al. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis[J]. Annals of Neurology, 2013, 74(4): 580.

[43] MOSCONI L, MURRAY J, TSUI W H, et al. Mediterranean diet and magnetic resonance imaging-assessed brain atrophy in cognitively normal individuals at risk for Alzheimer's disease[J]. Journal of Prevention of Alzheimers Disease, 2014, 1(1): 23.

[44] ALCALAY R N, GU Y, MEJIA-SANTANA H, et al. The association between Mediterranean diet adherence and Parkinson's disease[J]. Movement Disorders Official Journal of the Movement Disorder Society, 2012, 27(6): 771-774.

[45] MARDER, KAREN. Relationship of mediterranean diet and caloric intake to phenoconversion in huntington disease[J]. Jama Neurology, 2013, 70(11): 1382-1388.

[46] MO C, HANNAN A J, RENOIR T. Environmental factors as modulators of neurodegeneration: insights from gene-environment interactions in Huntington's disease[J]. Neurosci Biobehav Rev, 2015, 52: 178-192.

[47] KAMEL F, GOLDMAN S M, UMBACH D M, et al. Dietary fat intake, pesticide use, and Parkinson's disease[J]. Parkinsonism Relat Disord, 2014, 20(1): 82-87.

[48] GHAREKHANI A, KHATAMI M R, DASHTI-KHAVIDAKI S, et al. The effect of omega-3 fatty acids on depressive symptoms and inflammatory markers in maintenance hemodialysis patients: a randomized, placebo-controlled clinical trial[J]. European Journal of Clinical Pharmacology, 2014, 70(6): 655-665.

[49] SALEM N J, LITMAN B, KIM H Y, et al. Mechanisms of action of docosahexaenoic acid in the nervous system[J]. Lipids, 2001, 36(9): 945-959.

[50] HACIOGLU G, SEVAL-CELIK Y, TANRIOVER G, et al. Docosahexaenoic acid provides protective mechanism in bilaterally MPTP-lesioned rat model of Parkinson's disease [J]. Folia Histochem Cytobiol, 2012, 50(2): 228-238.

[51] OZSOY O, SEVAL-CELIK Y, HACIOGLU G, et al. The influence and the mechanism of docosahexaenoic acid on a mouse model of Parkinson's disease[J]. Neurochem Int, 2011, 59(5): 664-670.

[52] FURMAN R, AXELSEN P H. The effects of omega-3 fatty acid deficiency during development on oxidative fatty acid degradation during maturity in a mouse model of Alzheimer's disease [J]. Neurobiol Aging, 2019, 79: 66-74.

[53] TULLY A M, ROCHE H M, DOYLE R, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study [J]. Br J Nutr, 2003, 89(4): 483-489.

[54] FABELO N, MARTIN V, SANTPERE G, et al. Severe alterations in lipid composition of frontal cortex lipid rafts from Parkinson's disease and incidental Parkinson's disease [J]. Mol Med, 2011, 17(9/10): 1107-1118.

[55] YE Q, YUAN X L, YUAN C X, et al. Zishenpingchan granules for the treatment of Parkinson's disease: a randomized, double-blind, placebo-controlled clinical trial[J]. Neural Regen Res, 2018, 13(7): 1269-1275.

[56] BARBERGER-GATEAU P, LETENNEUR L, DESCHAMPS V, et al. Fish, meat, and risk of dementia: cohort study [J]. BMJ, 2002, 325(7370): 932-933.

[57] YASSINE H N, BRASKIE M N, MACK W J, et al. Association of docosahexaenoic acid supplementation with alzheimer disease stage in apolipoprotein E epsilon4 carriers: A review[J]. JAMA Neurol, 2017, 74(3): 339-347.

[58] CALON F, LIM G P, YANG F, et al. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model[J]. Neuron, 2004, 43(5): 633-645.

[59] HACIOGLU G, SEVAL-CELIK Y, TANRIOVER G, et al. Docosahexaenoic acid provides protective mechanism in bilaterally MPTP-lesioned rat model of Parkinson's disease [J]. Folia Histochem Cytobiol, 2012, 50(2): 228-238.

[60] GAO X, CASSIDY A, SCHWARZSCHILD M A, et al. Habitual intake of dietary flavonoids and risk of Parkinson disease[J]. Neurology, 2012, 78(15): 1138-1145.

[61] TURNBAUGH P J, RIDAURA V K, FAITH J J, et al. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice[J]. Science Translational Medicine, 2009, 1(6): 6r-14r.

[62] WU G D, CHEN J, HOFFMANN C, et al. Linking long-term dietary patterns with gut microbial enterotypes[J]. Science, 2011, 334(6052): 105-108.

[63] MA D, WANG A C, PARIKH I, et al. Ketogenic diet enhances neurovascular function with altered gut microbiome in young healthy mice[J]. Sci Rep, 2018, 8(1): 6670.

[64] OLSON C A, VUONG H E, YANO J M, et al. The gut microbiota mediates the anti-seizure effects

of the ketogenic diet[J]. Cell, 2018, 173(7): 1728-1741.

[65] FILIPPIS F D, PELLEGRINI N, VANNINI L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome[J]. Gut, 2016, 65(11): 1812-1821.

[66] GUTIÉRREZ-DÍAZ I, FERNÁNDEZ-NAVARRO T, SÁNCHEZ B, et al. Mediterranean diet and faecal microbiota: a transversal study[J]. Food & Function, 2016, 7(5): 2347-2356.

[67] BIDDLE A, STEWART L, BLANCHARD J, et al. Untangling the genetic basis of fibrolytic specialization by lachnospiraceae and ruminococcaceae in diverse gut communities[J]. Diversity, 2013, 5(3): 627-640.

[68] 林涅, 袁坤, 陈桂兰, 等. 高蛋白饮食通过调控肠道菌群影响肥胖相关研究进展[J]. 医学综述, 2019, 25(10): 1960-1964.
LIN N, YUAN K, CHEN G L, et al. Research progress in high protein diet regulating gut microbes to influence obesity[J]. Medical Recapitulate, 2019, 25(10): 1960-1964.

[69] 王志凡, 杨秀琳, 陈旺盛, 等. 抗性淀粉对饮食诱导肥胖大鼠排便状况及肠道菌群的影响[J]. 动物营养学报, 2016, 28(5): 1626-1632.
WANG Z F, YANG X L, CHEN W S, et al. Effects of resistant starch on defecation and intestinal microflora of diet induced obesity rats[J]. Chinese Journal of Animal Nutrition, 2016, 28(5): 1626-1632.

[70] DIANA S, ALMEIDA L M, DINIS T C P. Dietary polyphenols: A novel strategy to modulate microbiota-gut-brain axis[J]. Trends in Food Science & Technology, 2018, 78: 224-233.

[71] 王丽媛, 秦文, 霍军生, 等. 黄酒对高脂饮食小鼠的肥胖指标及肠道菌群的影响[J]. 中国酿造, 2019, 38(12): 53-57.
WANG L Y, QIN W, HUO J S, et al. Effects of Huangjiu on obesity-related indexes and gut microbiota in high-fat diet mice[J]. China Brewing, 2019, 38(12): 53-57.

[72] DAVIS D J, HECHT P M, JASAREVIC E, et al. Sex-specific effects of docosahexaenoic acid (DHA) on the microbiome and behavior of socially-isolated mice[J]. Brain Behav Immun, 2017, 59: 38-48.

[73] MAGNUSSON K R, HAUCK L, JEFFREY B M, et al. Relationships between diet-related changes in the gut microbiome and cognitive flexibility[J]. Neuroscience, 2015, 300: 128-140.

[74] BRUCE-KELLER A J, SALBAUM J M, LUO M, et al. Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity[J]. Biological Psychiatry, 2015, 77(7): 607-615.

[75] KANG S S, JERALDO P R, KURTI A, et al. Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition[J]. Mol Neurodegener, 2014, 9(36): 1-12.

[76] SIVANATHAN S, THAVARTNAM K, ARIF S, et al. Chronic high fat feeding increases anxiety-like behaviour and reduces transcript abundance of glucocorticoid signalling genes in the hippocampus of female rats[J]. Behavioural Brain Research, 2015, 286: 265-270.

[77] FUNG T C, OLSON C A, HSIAO E Y. Interactions between the microbiota, immune and nervous systems in health and disease[J]. Nature Neuroscience, 2017, 20(2): 145-155.

[78] LI G, WANG G, SHI J, et al. Trans-resveratrol ameliorates anxiety-like behaviors and fear memory deficits in a rat model of post-traumatic stress disorder[J]. Neuropharmacology, 2018, 133: 181-188.

[79] 朱思睿. 高脂膳食诱导肠道菌群失调与认知功能损害关系研究进展[J]. 中国公共卫生, 2018, 34(3): 453-457.
ZHU S R. Progress in researches on relationship between high fat diet-induced gut dysbiosis and cognition impairment[J]. Chin J Public Health, 2018, 34(3): 453-457.

[80] HANSTOCK T L, MALLET P E, CLAYTON E H. Increased plasma D-lactic acid associated with impaired memory in rats[J]. Physiology & Behavior, 2010, 101(5): 653-659.

[81] MÜLLER C P, REICHEL M, MÜHLE C, et al. Brain membrane lipids in major depression and anxiety disorders[J]. Biochim Biophys Acta, 2015, 1851(8): 1052-1065.

[82] PUSCEDDU M M, EL AIDY S, CRISPIE F, et al. N-3 polyunsaturated fatty acids (PUFAs) reverse the Impact of early-life stress on the gut microbiota[J]. PLoS ONE, 2015, 10(10): e139721.

[83] CAESAR R, TREMAROLI V, KOVATCHEVA-DATCHARY P, et al. Crosstalk between gut micro-

biota and dietary lipids aggravates WAT inflammation through TLR Signaling[J]. Cell Metab, 2015, 22(4): 658-668.

Mechanism of Dietary Intervention Gut Microbiota in Regulating Cognition and Neurodegenerative Diseases

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Abstract Neurodegenerative diseases are the pathological basis of cognitive function degradation and nervous system diseases, which are affected by many internal and external environmental factors. Microbes living in the gut can affect health and the occurrence and progress of many diseases, including nervous and mental diseases. Intestinal disorders are closely related to cognitive and motor dysfunction diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease and multiple sclerosis and so on. It was found that dietary intervention can improve the relationship between gut and brain, regulate the advanced brain functions such as cognition and emotion, alleviate cognitive decline and inhibit neurodegenerative diseases. But the internal mechanism is not clear, which may be related to dietary intervention regulating the composition and function of gut microbiota, thereby improving intestinal metabolism, intestinal endocrine and other mechanisms. This paper analyzes the relationship between dietary intervention and the regulation of gut microbiota and related physiological and biochemical changes, brain cognition and neural function, and discusses the role and possible mechanism of dietary intervention in gut microbiota, gut brain connections and neurodegenerative diseases.

Keywords dietary intervention; gut microbiota; cognitive function; neurodegenerative diseases; ketogenic diet; Mediterranean diet