本文引用:郭兴,胡明慧,孙亚男,等. 脂质在帕金森病发生中的作用及机制研究进展[J]. 新乡医学院学报,2024,41(4):392-396. DOI:10.7683/xxyxyxb.2024.04.018.

【综述】

脂质在帕金森病发生中的作用及机制研究进展

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摘要: 帕金森病(PD)是一种蛋白质构象疾病。生理状态的α-突触核蛋白(ASN)为无序单体,病理状态的ASN为聚合状态。ASN沿神经轴的病理性传播与PD的临床表现密切相关。病理性ASN可引起氧化应激,而神经炎症和相邻细胞中的蛋白质改变可加剧ASN的神经毒性,导致神经变性和神经元死亡。ASN可吸引并结合带负电荷的脂质,是脂质代谢调节、多巴胺产生和炎症反应中的关键介质,参与PD的发生发展。脂肪酸、甘油酯、磷脂等脂质异常代谢与ASN聚集密切相关,因此,脂质异常代谢在PD发生发展中发挥重要作用。本文主要综述脂质在PD发生发展中的作用及机制研究进展,以期为PD防治措施研究提供参考。

关键词: 脂质;帕金森病;α-突触核蛋白
中图分类号: R742.5 **文献标志码:** A **文章编号:** 1004-7239(2024)04-0392-05

Research progress on the role and mechanism of lipids in the occurrence of Parkinson's disease

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Abstract: Parkinson's disease (PD) is a protein conformational disease. Alpha-synuclein (ASN) in the physiological state is a disordered monomer, and ASN in the pathological state is in an aggregated state. The pathological spread of ASN along the neuraxis is closely related to the clinical manifestations of PD. Pathogenic forms of ASN evoke oxidative stress, while neuroinflammation and protein alterations in neighboring cells intensify ASN toxicity, and result in neurodegeneration and neuronal death. Studies have also shown ASN is a key player in lipid metabolism regulation, dopamine production, and inflammatory responses by the binding and attraction to negatively charged lipids, and participates in the occurrence and development of PD. Abnormal lipid metabolism such as fatty acids, glycerides, and phospholipids is closely related to ASN aggregation. Therefore, abnormal lipid metabolism plays an important role in the occurrence and development of PD. This article mainly reviews the research progress on the role and mechanism of lipids in the occurrence and development of PD, to provide references for research on PD prevention and treatment measures.

Key words: lipids; Parkinson's disease; alpha-synuclein

脂质在许多生物过程中发挥作用,对大脑的发育及功能维持尤为重要。近年来,研究表明,脂质与第二大中枢神经系统退行性疾病——帕金森病(Parkinson's disease,PD)的发生发展有关[1-3]。尽管具体机制尚不清楚,但脂质与α-突触核蛋白(alpha-synuclein,ASN)结合形成α-螺旋脂质-蛋白质复合物,从而形成不溶性聚集体的研究已得到广泛关注[4-5]。本文将对脂肪酸(free fatty acids,FFAs)、甘油脂类、磷脂酸、鞘脂及甾醇等脂质分子在PD发生、发展中的作用及机制相关研究进展进行综述,以期为PD的预防、治疗措施的研究提供参考。

1 脂质分子在PD发生中的作用

1.1 FFAs与PD的发生

研究显示,与健康对照者相比,PD患者血浆中

DOI:10.7683/xxyxyxb.2024.04.018
收稿日期:2023-02-15
基金项目:河南省科技攻关项目(编号:222102310708);河南省高等学校重点科研项目(编号:23A310010);河南省自然科学基金(编号:222300420515);河南省精神病院重点实验室开放课题(编号:ZDSYS2020004);河南省大学生创新创业训练计划项目(编号:202210472006);新乡医学院基础医学院科研培育项目(编号:JCYX-YKY202116)。
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FFAs 代谢物显著减少[6]。短链脂肪酸(short-chain fatty acids,SCFAs)含有 2 ~6 个碳原子,是肠道微生物代谢的主要产物。临床研究发现,PD 患者粪便中 SCFAs 水平明显降低,并具有性别依赖性,且 PD 发病年龄与 SCFAs 呈正相关[7];CHEN 等[8]研究也发现,PD 患者粪便中 SCFAs 水平明显降低,但血浆中 SCFAs 水平却呈上调趋势。SHIN 等[9]研究发现,血浆 SCFAs 在 PD 患者呈增加趋势,并与疾病的严重程度和抗 PD 药物相关。多不饱和脂肪酸(polyunsaturated fatty acids,PUFAs),尤其是 n-3 脂肪酸,是人体膳食中必需的营养脂肪酸,也是细胞膜的重要组成成分。研究发现,血浆中高水平 PUFAs 以及低饱和脂肪的饮食均可降低 PD 的风险,其中α-亚油酸和亚油酸水平与 PD 患者运动障碍严重程度呈负相关,而二十二碳六烯酸和花生四烯酸水平与 PD 非运动症状严重程度呈正相关,提示 PUFAs 与 PD 的发生发展有关[10]。HERNANDO 等[11]研究发现,PD 动物模型补充 n-3 PUFAs,可对抗神经炎症和氧化应激,表明 n-3 PUFAs 的摄入可降低 PD 发生。总之,多种 FFAs 可能参与 PD 的发生。

1.2　甘油酯与 PD 的发生

三酰甘油(triacylglycerol,TAG)由 1 分子甘油和 3 分子脂肪酸组成。来自荷兰的一项研究使用多基因风险评分来评估 PD 患者血液中 370 种脂质和脂质相关分子水平与 PD 发生风险的关系,结果显示,TAG 与 PD 发生风险呈负相关[12]。FU 等[13]对血清中胆固醇或 TAG 与 PD 发生风险之间的关系进行评估,结果显示,血清 TAG、胆固醇水平升高可能是 PD 发病的保护因素。2021 年,一项研究使用代谢组学分析方法对 PD 患者皮脂中的脂质变化进行追踪,结果发现,神经酰胺、TAG 和脂肪酰基类代谢物在 PD 患者中表达下调[14]。SÁNCHEZ CAMPOS 等[15]对经典的 PD 动物模型(ASN A53T 小鼠)的血清代谢物进行分析发现,血清中胆固醇、TAG 和非酯化脂肪酸水平显著下降。但 GUERREIRO 等[16]研究发现,大鼠多巴胺能神经元 N27 细胞中过表达 ASN A53T 可激活催化 TAG 合成的酰基辅酶 a 合成酶,导致 TAG 水平升高,这似乎相悖于 PD 患者体内的研究结果。

二酰基甘油(diacylglycerol,DAG)是细胞膜的重要组成成分,可以在 Ca^{2+} 的参与下激活蛋白激酶 C(protein kinase C,PKC),而活化 PKC 可磷酸化下游目标蛋白,参与包括神经元突触传递等许多重要的生理活动[17]。WOOD 等[18]对神经退行性疾病患者体内脂质分子水平进行检测发现,不仅 PD 患者大脑额叶皮质中 DAG 水平升高,阿尔茨海默病(Alzheimer′s disease,AD)及路易体病患者大脑额叶皮质中 DAG 水平同样也明显升高,表明,DAG 异常在疾病早期并伴随皮质功能性障碍的发生被放大。二酰甘油激酶 Q(diacylglycerol kinases,DGKs)可磷酸化 DAG,使其转变为磷脂酸(phosphatidic acid,PA)[19]。DGKs 家族共有 10 种亚型,其中二酰甘油激酶(diacylglycerol kinases theta,DGKQ)位于染色体 4p16.3 区,GAK/TMEM175/DGKQ 区域是全基因组关联分析发现的 PD 第三大风险位点,与 PD 的易感性相关[20],这可能与 DGKQ 活性的改变打破了 DAG 与 PA 之间的平衡有关,提示 DAG-PA 轴的异常可能是 PD 和 AD 的共同特征。

1.3　磷脂与 PD 的发生

磷脂既是组成生物膜的基本成分,又可作为重要的信号分子参与细胞信号转导,在多种疾病的病理生理过程中发挥重要作用[21-25]。LÓPEZ DE FRUTOS 等[26]研究发现,与健康对照组相比,葡糖脑苷脂酶(glucocerebrosidase,GBA)缺陷病和 PD 患者的血清磷脂水平均明显增加,表明磷脂在此类疾病发展中发挥一定作用,血清磷脂水平可能是 PD 的生物标志物。甘油磷脂(glycerophospholipids,GPL)是基于甘油的磷脂,包含至少 1 个连接到甘油部分的 O-酰基残基,如磷脂酰胆碱、磷脂酰乙醇胺(phosphatidylethanolamine,PE)和磷脂酰丝氨酸(phosphatidylserine,PS)等。这些甘油磷脂丰富并存在于哺乳动物细胞膜上,对大脑的结构形成和认知功能的发育至关重要[27]。研究发现,在精神分裂症、亨廷顿症和 AD 患者细胞膜中 GPL 水平明显升高[28-29];PD 患者额叶皮层和初级视觉皮质中 PS 和 PE 水平显著升高,但黑质中磷脂酰肌醇、PS 和 PE 水平显著降低[18,30-31]。WANG 等[32]研究发现,低水平 PE 具有促进脂质囊泡与 ASN 结合的作用。综上,磷脂水平改变可能与 PD 的发生相关。

1.4　鞘脂与 PD 的发生

细胞内鞘脂类和鞘糖脂物质既是细胞膜的重要组成成分,也参与许多细胞内信号通路调节,包括细胞增殖、凋亡等[33-35]。鞘脂类化合物的脂质部分为鞘氨醇,可被鞘氨醇激酶 1(sphingosine kinases 1,SK1)和鞘氨醇激酶 2(sphingosine kinases 2,SK2)磷酸化,转化为 1-磷酸鞘氨醇(sphingosine-1-phosphate,S1P)[35]。神经酰胺和 S1P 均是重要的生物活性鞘脂,共同参与神经元生存与死亡的调控,参与神经退行性疾病的生理病理过程[36]。PÉPIN 等[37]在细胞实验中发现,S1P 通过激活 S1P 受体 1 来增强线粒体生物生成,可保护多巴胺能神经元免受 1-甲基-4-苯基吡啶诱发的细胞死亡。另有研究发

现,PD 小鼠黑质中 SK2 表达显著下调,使用 S1P 激动剂可产生神经保护作用,提示,SK/S1P/S1P 可能是有希望的神经保护靶点[38-39]。ABBOTT 等[40]通过对 1 例去世的 PD 患者脑组织进行分析发现,前扣带皮层表现出显著的 PD 病理学改变,分布在该区域的神经酰胺合酶-1 基因表达显著上调。MIELKE 等[41]研究发现,PD 伴认知障碍患者血浆中多种神经酰胺(如 C16∶0、C18∶0、C22∶0、C24∶1)水平升高。

GBA 是 PD 的重要遗传风险因素,5% ~15% 的 PD 患者携带 GBA1 基因类型变异,这可能是由于 GBA 基因突变造成其底物葡萄糖神经酰胺(葡萄糖脑苷脂)在多种组织中贮积有关[42]。有研究报道,携带富亮氨酸重复激酶 2(leucine-rich repeat kinase 2,LRKK2)基因突变的 PD 患者脑脊液中神经鞘脂水平显著升高[42-43]。HU 等[44]采用非靶向代谢组学和蛋白质组学分析发现,PD 患者血浆中的差异代谢物中鞘脂类占 25%,参与鞘磷脂代谢的 6 种代谢物均显著增加,提示 PD 患者中鞘磷脂代谢通路被激活。

1.5 胆固醇与 PD 的发生

胆固醇是细胞膜中不可缺少的成分,大脑中胆固醇在人体总胆固醇中占比较高。有研究报道,胆固醇水平过高会增加患 PD 的风险,提示血清胆固醇水平与神经变性疾病相关[45]。但是,ASCHERIO 等[46]通过队列研究发现,高血清胆固醇患者罹患 PD 的风险较低。而一项 meta 分析对 8 项前瞻性研究和 13 项回顾性研究的数据进行分析发现,总胆固醇对 PD 具有保护作用[13]。出现结果不一致的原因可能与不同的研究招募研究对象的条件不同有关。

2 脂质失调促进 PD 发病的分子机制

2.1 脂质通过结合并促进 ASN 聚集参与 PD 发生发展

ASN 是广泛表达在突触前轴突末梢的可溶性蛋白,可通过与突触蛋白和突触前膜相互作用调节囊泡内神经递质的聚集和释放[47-49]。研究表明,ASN 的异常聚集可形成 PD 中常见的路易氏小体的主要蛋白质成分,单体 ASN 发生异常聚集并错误折叠成低聚物,从而形成路易小体,是典型的 PD 病理标志[50]。ASN 可结合带有负电荷的脂质促进自身异常聚集可能是其参与 PD 发生的机制之一。

ASN 由 140 个氨基酸残基组成,N 端(1 ~95 号氨基酸残基)脂质结合区域甘油酯、脂肪酸、磷脂、心磷脂、鞘脂和其他酸性磷脂(磷脂酸)均能与 ASN 结合,结合脂质后 ASN 的前 95 个氨基酸残基从无规则卷曲转变为 2 个两亲性 α 螺旋,这种结构转变导致 ASN 蛋白质的异常聚集[51-52]。在 PD 不同细胞和动物模型中已经证明,脂肪酸、鞘磷脂、胆固醇衍生物等特定脂质水平的变化与聚集性的 ASN 增多有关,而且脂质性质和水平的改变也对 ASN 的聚集倾向产生影响[53]。因此,在 PD 进程中,脂质可能是通过影响 ASN 异常折叠而参与 PD 进程。

2.2 ASN 掺入细胞膜导致脂质过氧化参与 PD 发生发展

不平衡的氧化还原状态会引起氧化应激,包括活性氧(reactive oxygen species,ROS)的过度生成或抗氧化系统功能障碍。大脑富含容易过氧化的磷脂及多不饱和脂肪酸,且对氧的需求量较高,抗氧化系统功能障碍时,神经元膜磷脂易受 ROS 攻击发生过氧化。磷脂酶 A 2γ(phospholipase A 2γ,PLA 2γ)是参与甘油磷脂分解的重要酶。研究发现,PLA 2γ 功能缺失可使线粒体 ROS 增加、脂质过氧化增强、ATP 合成减少、谷胱甘肽水平降低及线粒体膜缺陷等病理变化,从而参与 PD 的发生发展[54]。在在体及离体 PD 模型中也观察到聚集性 ASN 在细胞膜内产生 ROS 和脂质过氧化物[55-56]。因此,磷脂过氧化及抗氧化酶的活性降低或丧失,可能是中脑多巴胺能神经元脆弱和进行性运动功能障碍的原因。ANGELOVA等[57]研究发现,降低 PD 小鼠细胞内或线粒体 ROS 水平,可抑制小胶质细胞的激活和脂质过氧化,增加纹状体中酪氨酸羟化酶活性,表明降低 ROS 及抑制脂质过氧化可发挥神经保护作用。

3 结论

PD 患者存在不同程度、不同种类的脂质代谢差异,而脂质的种类以及构成可以调控 ASN 积聚。甘油磷脂、鞘磷脂、甾醇等不同种类的脂质是细胞膜、线粒体膜、内质网膜及高尔基复合体的主要成分。因此,细胞内膜组成中脂质成分的改变可能通过影响神经递质的囊泡运输、ASN 的聚集等重要过程参与 PD 的发生发展。总之,脂质代谢途径和膜脂组成中一些生物活性脂质的改变可能在 PD 发生发展中起着重要作用,关注 PD 患者脂质代谢途径及脂质组学变化可为 PD 的治疗提供潜在靶点和生物标志物。

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(本文编辑:周二强)

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(本文编辑:孟 月)