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高脂饮食诱导情绪障碍及药物干预研究进展*

王慧^{1,2} 周佳^{1,2} 夏振江³ 王路路^{1,2} 尚靖^{1,2,Δ}

(1 中国药科大学天然药物活性组分与药效国家重点实验室 江苏 南京 210009 ;

2 中国药科大学江苏省中药评价与转化重点实验室 江苏 南京 211198 ;

3 中国科学院藏药研究重点实验室,中国科学院西北高原生物研究所 青海 西宁 810008)

摘要 近年来代谢性疾病和抑郁症的发病率逐渐上升,临床研究表明代谢紊乱疾病与抑郁症之间存在共病现象。富含高糖高脂的西方饮食通常可造成肥胖、糖尿病、代谢综合征等代谢紊乱性疾病,近期研究发现高脂饮食是情绪障碍发病的危险因素,然而具体高脂饮食对情绪紊乱的影响机制尚未明确,其可能机制包括胰岛素抵抗、瘦素抵抗、炎症、氧化应激、神经凋亡、大脑奖赏回路系统等。本文对近年来报道的高脂饮食诱发情绪障碍可能机制及药物研究进行阐述。

关键词 高脂饮食;代谢紊乱;情绪障碍;药物干预

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Emotional Disorder Induced by High Fat Diet and Progress in Drug Intervention*

WANG Hui^{1,2}, ZHOU Jia^{1,2}, XIA Zhen-jiang³, WANG Lu-lu^{1,2}, SHANG Jing^{1,2,Δ}

(1 State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing, Jiangsu, 210009, China;

2 Jiangsu Key Laboratory of TCM Evaluation and Translational Research, China Pharmaceutical University, Nanjing, Jiangsu, 211198, China; 3 Key Laboratory of Tibetan Medicine Research, Northwest Institute of Plateau Biology,

Chinese Academy of Sciences, Xining, Qinghai, 810008, China)

ABSTRACT: Recently, the incidence of metabolic disorder and depression gradually increases and clinical research demonstrated that metabolic disorder and depression often related to comorbidity. Western diet enriched in fat and refined sugar commonly results in some metabolic diseases in modern life, such as obesity, type 2 diabetic (T2DM) and metabolism syndrome. Moreover, it was found to be the risk factor for emotional disorder. But the exact mechanism underlying emotional disorder induced by high fat diet is still not fully elucidated, the probable mechanism including insulin and leptin resistant, inflammation, oxidative stress, neuronal apoptosis and brain rewarding circuitry. This paper reviews the potential mechanism of emotional disorder induced by high fat diet and the research progress on drug intervention.

Key words: High fat diet; Metabolic disorder; Emotional disorder; Drug intervention

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前言

据一项长达三十年(1980-2013年)涉及到188个国家的全球肥胖调查显示,全球肥胖或超重人群已经达到了近21亿人^[1]。而快节奏的生活导致一般人群普遍存在焦虑情绪,严重时可能产生抑郁症等精神疾病。Meta分析调查显示抑郁症和糖尿病存在着并发现象^[2],抑郁症可使糖尿病患病风险增加,而另一方面糖尿病患者相对于健康人而言,其抑郁症患病概率要高出2倍以上^[3]。近5年来国内外大量报道了高脂饮食(High fat diet, HFD)对动物情绪状态的影响,在动物研究层面上证实了代谢性疾病可诱发焦虑、抑郁症等情绪障碍性疾病^[4-6]。临床

meta分析结合动物研究表明高脂饮食诱导的代谢紊乱与后续诱发的情绪障碍是存在直接联系的,如何改善高脂饮食诱导的焦虑抑郁样行为已经成为当前研究热点。

1 高脂饮食诱发情绪障碍

多项临床及实验类研究对饮食脂肪含量、成分与人体健康之间的关系进行探讨发现,低脂肪饮食无法提供人体足够的营养物质;而持续高脂饮食则可能促进肥胖、2型糖尿病等代谢紊乱疾病的发生发展^[7]。代谢性疾病又可以进一步诱导情绪障碍损伤,其可能的机制包括炎症、大脑奖赏环路、氧化应激、神经细胞凋亡、胰岛素抵抗及瘦素抵抗等^[8]。

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作者简介:王慧(1992-),硕士研究生,主要研究方向:糖脂代谢紊乱, E-mail: wanghui92hou@163.com

Δ通讯作者:尚靖(1967-),博士生导师,教授,主要研究方向:代谢药理, E-mail: shangjing21cn@163.com, 电话: +86-025-83271142

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高脂饮食诱发情绪障碍可能与脑内能量平衡和炎症反应有关。Sophie Dutheil 等人研究发现给予 16 周以上的高脂饮食后,小鼠出现焦虑和无休止的行为,长达 4 个月的高脂饮食会使得突触可塑性、胰岛素/葡萄糖稳态相关的细胞内级联反应(如 Akt、ERK、P70S6K)中断,皮质酮水平增加,固有免疫系统激活,多种炎症因子水平增加。长期高脂饮食可能对体内能量平衡、与突触可塑性相关的胰岛素/mTORC1 信号转导通路、Toll 样受体的表达及促炎细胞因子生成等多个过程产生影响^[4]。

长期摄入高脂饮食可诱使大脑奖赏回路的神经适应效应,进而促进消极情绪和焦虑、绝望样行为。高脂饮食和肥胖引起的抑郁样行为与大脑奖赏回路的突触可塑性改变有关。Sharma S 等人对 C57 雄鼠分别以高脂饮食、成分匹配或低脂饮食饲喂 12 周,发现高脂小鼠在高架十迷宫和强迫游泳实验中表现出明显的焦虑、抑郁样行为,其体内皮质酮水平显著升高;D2R、BDNF 和 Δ FosB 显著上调,但伏隔核中 D1R 受体表达下调,伏隔核、纹状体中 BDNF 表达及纹状体中 p CREB 表达与小鼠行为绝望呈正相关^[9]。

长期高脂饮食干预后,机体处于一种氧化应激状态,此时体内大量的活性氧簇(ROS)可引起细胞内脂质、蛋白质和核酸氧化损伤^[10],这些过氧化产物进一步影响神经元功能。丙二醛(MDA)作为一种脂质过氧化产物,能够显著抑制海马神经前体细胞增殖,进而影响神经认知或情绪功能^[11]。氧化应激还可促使线粒体功能失调进而产生更多的 ROS,最终线粒体膜通透性增加,神经元细胞启动凋亡过程。JC Moraes 等人报道称膳食脂肪可诱导神经元细胞的凋亡,减少突触传入下丘脑弓状核和下丘脑外侧区,其诱导神经凋亡的作用与炎症信号转导、瘦素胰岛素抵抗及氧化应激等有关^[12]。

胰岛素抵抗是肥胖、2 型糖尿病等代谢紊乱疾病与抑郁症之间共同的病理生理机制^[13-15]。报道称高脂喂养仅 1-3 周即可在心脏、骨骼肌、肝脏和脂肪组织等多个组织器官产生胰岛素抵抗^[16]。胰岛素可穿过血脑屏障进入中枢,通过调控神经膜上的兴奋性和抑制性受体的表达调节突触传递节律,进而调控突触可塑性影响神经回路功能^[17]。在外周胰岛素功能障碍情况下,中枢神经细胞内胰岛素受体底物(IRS)/磷脂酰肌醇 3 激酶(PI3K)及 Shc/Raf/MAPK(促分裂原活化蛋白激酶)信号转导途径发生异常,进而与神经细胞凋亡、炎症反应、氧化应激有关^[18]。

高脂饮食还可使下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA)功能亢进,基础饮食及应激刺激后的皮质酮水平显著上调^[9,19]。胰岛素抵抗、瘦素抵抗、炎症、神经元凋亡及大脑奖赏回路系统等均可能作为药物研发的潜在靶点。

2 基于高脂饮食诱发情绪障碍的药物干预

2.1 他汀类

他汀类作为一种羟甲基戊二酰辅酶 A(HMG-CoA)还原酶抑制剂,近年研究发现其不仅可以有效地降低血清胆固醇水平,还能在一定程度上降低抑郁症患病风险甚至改善抑郁症患者预后功能^[20,21]。代谢紊乱性疾病常与情绪障碍伴发或继发出现,心脏病患者抑郁症患病风险较健康人群偏高,而服用他汀类的心脏病患者其抑郁症的患病风险相对降低^[22]。

以辛伐他汀为例,作为一种亲脂性他汀类药物,辛伐他汀一方面通过血脑屏障或可对神经元产生直接不利作用,另一方面又可以通过多种机制对认知功能产生有益作用,如改善内皮功能、减少自由基生成、改善炎症等^[23]。Lee CY 等人研究也显示辛伐他汀可使高脂饮食动物的血清甘油三酯恢复至正常水平,显著改善高脂饮食诱导的焦虑/抑郁样行为及认知功能障碍,并对正常饮食的动物显示出抗焦虑、抗抑郁和“益智”的作用^[24]。辛伐他汀对慢性应激刺激动物的抑郁样行为也有一定改善作用^[25],再次表明辛伐他汀的抗抑郁效应在某种程度上可能是独立于其降脂作用的。

2.2 降糖药物

高脂饮食通过改变饮食结构,可一定程度上模拟葡萄糖耐量受损及早期 2 型糖尿病症状,而研究报道称高脂饮食诱发的糖代谢紊乱与后续个体中出现的行为异常紧密相关^[5]。二甲双胍是临床上用于治疗 2 型糖尿病一线用药,尤其适用于肥胖的 2 型糖尿病,可有效减少肝糖产生,降低肠道对糖吸收并通过增加外周葡萄糖的摄取和利用从而提高胰岛素敏感性。然而近年来越来越多研究发现,二甲双胍(Metformin, MET)不仅具有降血糖作用,还具有降血脂、抗炎、抗衰老、抗肿瘤、延长寿命等作用^[26,27]。国内外多项研究报道称二甲双胍对阿尔兹海默症的认知功能障碍有一定改善作用, MET 可迅速透过血脑屏障产生抗炎及神经保护作用^[28]。Miller 等人研究发现小鼠服用二甲双胍后新生神经元产生增加,在空间学习迷宫测试中表现更佳,二甲双胍可以促进神经干细胞修复大脑,进而发挥改善认知功能作用^[29]。Hofmann P 等人报道称二甲双胍和米那普仑可用于抑郁、糖尿病合并症患者的治疗^[30]。但其对神经系统的有益作用与体内维生素 B12 状态有关,长期服用二甲双胍可导致维生素 B12 水平显著下降,进而导致甲基基团缺乏,同型半胱氨酸代谢异常浓度增加,反而会进一步诱发神经和血管毒性^[31,32]。

除了二甲双胍以外,吡格列酮作为一种胰岛素增敏剂,可通过高选择性经氧化物酶增殖体受体- γ (PPAR- γ)进而发挥其降糖作用。近年临床研究发现吡格列酮不仅具有降糖效应,对于重度抑郁症患者还显示出一定的抗抑郁效应^[33]。Hu Y 等人对于 118 例 2 型糖尿病脑卒中患者进行了为期 3 个月的追踪调查研究,在吡格列酮干预后重度抑郁组汉密尔顿量表评分远低于二甲双胍组,药物治疗期间空腹胰岛素水平显著下降,提示吡格列酮对于 2 型糖尿病合并脑卒中后抑郁患者可能有效^[34]。然而后续研究显示其抗抑郁效应与胰岛素增敏作用无关,其具体机制仍待进一步深入研究^[35]。

2.3 抗抑郁药物

抗抑郁药物种类繁多,而临床常用药物主要分为三类:三环类、单胺氧化酶抑制剂及四环类。现有关于高脂饮食诱导行为学异常的药物干预研究主要集中于 5-HT 重摄取抑制剂,如氟西汀、艾司西普肽兰等。Elsa Isingrini 等人发现同时给予大鼠高脂饮食并予以慢性不可预计应激(Chronic unpredictable mild stress, CUMS)刺激后,此时抗抑郁药物氟西汀对其抑郁样症状无明显改善作用,然而氟西汀对常规饮食合并 CUMS 刺激所产生的抑郁样症状有效,文中将这一复合模型称为“氟西汀耐药模型”^[36]。

艾司西普肽兰, 同样作为一种选择性 5-HT 再摄取抑制剂对高脂饮食诱发的行为学异常有效, 具体机制未明。Juliane 等人给予动物 12 或 16 周高脂饮食, 发现 16 周时动物出现的代谢紊乱与相应个体中出现的行为异常是直接相关的, 且高脂饮食进一步损害 5-HT 功能, 在给予 5-HT 重摄取抑制剂艾司西普肽兰可以显著逆转高脂饮食诱发的代谢紊乱及行为异常^[5]。

此外报道称氯胺酮可改善 HFD 诱发的焦虑样行为, 其作用机制与前额皮质中 Akt、ERK 及 P70S6K 磷酸化有关^[4]。吴秀萍等人对文拉法辛(5-羟色胺、多巴胺、去甲肾上腺素重摄取抑制剂)和帕罗西汀(5-羟色胺再摄取抑制剂)对糖尿病伴发抑郁障碍的患者进行对照研究发现, 二者均可改善汉密尔顿量表评分及体内糖代谢情况, 在控制患者血糖的同时有利于控制患者焦虑抑郁伴发情况^[37]。其他抗抑郁药物能否对高脂饮食诱发的情绪障碍行为或高脂应激复合模型中的抑郁样症状有一定效用仍值得进一步探究。

2.4 5-羟色胺(5-hydroxy tryptamine, 5-HT)受体调节剂

5-HT 是一种单胺类神经递质, 广泛参与调解中枢及外周的多项生命活动, 其调节作用与受体亚型的多样性相关, 目前文献报道已发现共有 15 种亚型^[38]。近年来针对改善饮食诱导情绪障碍的药物研究主要集中于 5-HT₃ 受体^[39], 5-HT₃ 受体作为一种离子门控通道受体广泛表达于海马、杏仁体和极后区中。多项临床前研究表明 5-HT₃ 拮抗剂具有抗抑郁、抗焦虑效应, 而后续 Yeshwant 等人^[40] 发现一种 5-HT₃ 受体拮抗剂 QCM-4 可显著改善高脂饮食诱导动物体内产生的血清 HPA 轴亢进、瘦素抵抗及脑内氧化应激状态, 并显著改善动物出现的焦虑、抑郁样行为。

昂丹司琼, 作为一种高选择性的 5-HT₃ 受体拮抗剂, 临床上主要用于预防或治疗肿瘤患者在接受化疗及放射治疗所引起的剧烈呕吐。Yeshwant Kurbe 等人研究发现 HFD 合并 CUMS 模型小鼠在给予昂丹司琼后, 强迫游泳实验中的不动时间及高架十字迷宫等行为学参数显著改善, 此外血糖、血脂水平等代谢参数也较模型显著下调^[41]。该课题组后续研究发现昂丹司琼改善抑郁肥胖共病模型行为学参数, 改善大鼠葡萄糖耐量及外周瘦素、抵抗素、皮质酮及 5-HT 水平。

2.5 天然植物活性成分

多项研究表明天然植物提取物中的某些有效成分可显著改善高脂饮食诱导的情绪障碍, 如茶叶、竹子、莴苣等。Ai Yoto 等人报道称经由茶叶中提取的 L-茶氨酸可显著降低高脂组小鼠血压值并改善其焦虑状态, 其中 L-茶氨酸被常用于多种减肥保健品中^[42]。Singapura Nagesh Harsha 等人以 70% 甲醇对菊科植物莴苣进行提取, 有趣的是将提取物给予小鼠后显示出一定的抗氧化和抗焦虑效应^[43]。Adeline Del Rosario 等人发现竹子提取物也对高脂诱发焦虑抑郁模型中焦虑样行为有显著改善作用^[44]。

传统中药复方中也有对高脂饮食诱发的抑郁模型有一定疗效的方剂, 杨利等人以百合知母汤提取物给予高脂饲料喂养的抑郁模型大鼠, 结果显示百合知母汤能显著改善抑郁样行为, 其机制可能与调节大鼠神经递质作用有关^[45]。因此进一步发掘并从整体水平观察传统中医药的疗效及治疗作用, 对于改

善高脂饮食诱发情绪障碍药物的发展和应用具有重大意义。

2.6 其他

Weina Liu 等人利用高脂饮食和糖皮质激素成功诱导建立抑郁-胰岛素抵抗模型 (Depression-like and insulin resistant, DIR), AICR 作为一种可通透细胞膜的 AMP 激活的蛋白激酶 (Adenosine 5'-monophosphate activated protein kinase, AMPK) 激动剂, 对于 DIR 模型显示出显著的抗抑郁活性, 且相对于传统药物可减弱长期高脂饲喂造成的骨骼肌胰岛素作用^[46]。适度运动、早期中断高脂饮食并调整饮食结构也被证明对改善高脂饮食诱发的情绪^[5,46]。Jasmin A 等人发现踏转轮运动 (wheel-running) 可显著改善在 C57 小鼠中高脂饮食诱导的胰岛素抵抗和体重增长等糖尿病症状, 并改善小鼠在旷场及明暗箱实验中的抑郁样行为学参数^[47]。

3 结语

研究表明长期高脂饮食可诱发情绪障碍, 而介导这一作用的机制可能包括胰岛素抵抗、炎症、氧化应激、神经细胞凋亡及大脑奖赏回路系统等。目前靶向作用于不同机制的药物主要分为他汀类降脂药物、降糖药物、抗抑郁药物、5-HT 受体调节剂、天然产物等, 但多数药物仍停留在临床前探索研究阶段, 寻找一种在改善体内代谢紊乱的同时又对焦虑、抑郁样症状有效的药物十分必要, 这对代谢性疾病合并抑郁症临床用药有重要指导意义。

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