

代谢性疾病对情绪和认知功能的影响及其可能机制研究进展

刘琼珍^{1,2}, 吕文婷^{1,2}, 蔡旻煊^{1,3}, 吴华丽^{2,3}, 尚 靖^{1,2,3}

(1.中国药科大学新药筛选中心, 江苏 南京, 210009; 2.天然药物活性组分与药效国家重点实验室, 江苏 南京, 210009; 3.江苏省中药评价与转化重点实验室, 江苏 南京, 210009)

摘要:近年来,大量流行病学和动物实验研究表明,代谢性疾病如肥胖、2型糖尿病和代谢综合征对大脑功能有不良影响,会引起情绪障碍和认知损伤。代谢性疾病诱导情绪障碍和认知损伤涉及多种中枢功能异常,并与外周信号的介导密切相关。这些异常的中枢功能包括大脑萎缩和神经营养功能削弱、中枢胰岛素抵抗、中枢氧化应激、中枢瘦素抵抗、多巴胺奖赏环路失调等,外周介导信号涉及高甘油三酯/游离脂肪酸血症、炎症和下丘脑-垂体-肾上腺轴失调等。另一方面,初步研究表明,抑郁症会增加代谢性疾病发生的风险,精神应激会影响机体糖脂代谢。代谢性疾病和大脑功能的相互影响已成为科学研究的热点之一。本文重点讨论肥胖及相关的代谢性疾病诱导情绪障碍和认知损伤的可能机制。

关键词:高脂饮食; 代谢性疾病; 抑郁症; 阿尔茨海默病

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代谢性疾病如肥胖、2型糖尿病和代谢综合征是世界范围内的重大公共卫生问题。超重和肥胖往往伴随其他病理性代谢问题如胰岛素抵抗、高血压和动脉粥样硬化,导致2型糖尿病、代谢综合征、冠心病及卒中等并发疾病。近年来,临床调查数据还发现,肥胖及相关的代谢性疾病患者并发抑郁症^[1-4]、痴呆和阿尔茨海默病^[5-9]的风险增高。

抑郁症以显著而持久的心境低落为临床表征,阿尔茨海默病则以记忆和认知障碍为突出特点。此外,抑郁症患者往往还存在学习、记忆和执行功能的减退,增加阿尔茨海默病发病的风险。动物实验研究发现,给予高脂饮食的小鼠或大鼠不但有抑郁样行为,且学习记忆功能会受到削弱。可见,情绪障碍和认知损伤在一定程度上是相互联系的,两者并不完全分割。

普遍的观点认为,肥胖及相关的代谢性疾病诱导情绪障碍和认知损伤是由于两者具有诸多相通的神经生物学机制。结合目前大量的动物实验资料,发现其中可能的介导机制包括下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA轴)失调、炎症、氧化应激、凋亡、胰岛素抵抗、瘦素

抵抗和大脑奖赏环路异常等。另一方面,初步研究表明,抑郁症和阿尔茨海默病对糖脂代谢会产生异常影响。然而,由于动物模型的局限性,糖脂代谢的改变往往被归咎于机体的应激反应,目前对此尚无较成熟的机制阐述。本文重点讨论肥胖及相关的代谢性疾病诱导情绪障碍和认知损伤的可能机制。

1 代谢性疾病导致的中枢神经系统功能异常

情绪和认知是大脑功能的体现,发生情绪障碍和认知损伤时往往伴随着中枢功能的异常改变。大脑的功能是和其结构相互依存的,大脑结构的器质性改变是导致不良情绪和认知的重要病理形成基础。突触可塑性和神经元再生对大脑结构和功能的维持有重要意义。此外,大脑还具有奖惩机制,直接参与情绪和情感的调控。

1.1 大脑萎缩和神经营养功能削弱

研究发现,肥胖患者大脑整体体积缩小^[10],灰质萎缩^[11-12],其他脑区和部位如额叶、前扣带回、海马和丘脑以及白质基底神经节和放射冠也存在萎缩的现象^[13]。研究还发现,体质指数(body mass index, BMI)越高者,大脑体积缩小的速度越快^[14]。因此,肥胖造成的大脑萎缩可直接影响情绪和认知功能。

大脑萎缩与神经营养因子尤其是脑源性神经

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作者简介:刘琼珍, 硕士, 主要从事糖脂代谢紊乱研究。

通讯作者:尚 靖, E-mail: shangjing21cn@163.com,

Tel: (025)83271516

营养因子(brain-derived neurotrophic factor, BDNF)介导的突触可塑性和神经元再生能力受损密不可分。研究显示,高脂饮食使海马和大脑皮质 BDNF 含量减少, BDNF 下游效应因子突触素 I 和环磷酸腺苷效应元件结合蛋白[cyclic adenosine monophosphate (cAMP) - response element binding protein, CREB]的基因和蛋白表达以及磷酸化受抑制^[15-19],引起海马树突棘密度降低和长时程增强效应(long-term potentiation, LTP)削弱^[19],造成学习和认知功能损伤。高脂饮食导致的 BDNF 含量减少往往与中枢炎症、氧化应激和胰岛素抵抗相伴发生^[17, 20-25];若改善炎症、氧化应激和胰岛素抵抗的状态,则能逆转高脂饮食诱导的 BDNF 含量减少,从而改善认知功能^[21-22]。说明在代谢紊乱的情况下,认知功能受损与海马和大脑皮质 BDNF 含量减少有直接关系。

此外,在抑郁症患者的海马和前额皮质中, BDNF 含量也异常减少;使用抗抑郁制剂后,这些脑区的 BDNF 含量增加^[26-28]。同样,在应激性抑郁样动物的海马和前额皮质中, BDNF 含量减少,严重时引起海马锥体神经元树突萎缩进而导致海马萎缩^[29-31]。因此,海马和皮质 BDNF 介导的神经营养功能削弱时也会对情绪产生不良影响,成为高脂饮食诱导抑郁样行为的可能机制之一。

1.2 中枢胰岛素抵抗

胰岛素抵抗是肥胖、2 型糖尿病和代谢综合征等代谢性疾病的共同病理生理机制,并与阿尔茨海默病^[32-37]和抑郁症^[38-40]密切相关。

胰岛素由胰岛β细胞分泌,能穿过血脑屏障,通过调控神经元膜上的兴奋性和抑制性受体的表达而调节突触传递的节律^[41]。胰岛素受体在突触小体处含量丰富,并与轴突末梢标志物突触蛋白和突触素 I 共定位^[42]。通过在突触的胰岛素信号,中枢胰岛素可调控突触可塑性而影响神经回路的功能,这与学习和记忆是紧密联系的^[43]。长期高脂饮食显著抑制大鼠海马 CA1 区域外源性胰岛素刺激诱导的胰岛素受体、胰岛素受体底物 1 和丝氨酸-苏氨酸激酶(serine/threonine kinase, Akt)/蛋白激酶 B (protein kinase B, PKB)的磷酸化,并且该区域突触传递的长时程抑制效应(long-term depression, LTD)减弱^[44]。同样,在高脂饮食的条件下,小鼠海马和皮质区域多磷酸肌醇激酶(inositol polyphosphate multikinase, IPMK)减少,磷脂酰肌醇 3-激酶(phosphatidylinositol 3-kinase, PI3K)-Akt-哺乳动物西罗莫司(雷帕霉素)靶分子[mammalian target

of sirolimus (Rapamycin), mTOR]胰岛素信号通路被抑制,在海马区域第 616 位丝氨酸残基磷酸化的胰岛素受体底物 1 (IRS1-pS616, 胰岛素抵抗的标志物)表达增加;伴随着胰岛素抵抗, PSD-95 (富含于突触后的支架蛋白)和突触极蛋白(synaptopodin, 富含于树突棘的肌动蛋白相关蛋白)表达减少,突触可塑性的削弱导致小鼠空间记忆功能受损^[45]。若施加干预使高脂饮食诱导的外周和中枢胰岛素抵抗得以显著改善,则能提高高脂饮食小鼠脑皮质和海马区域突触素 I 和 PSD-95 的含量,从而改善小鼠空间记忆功能^[22]。对于高脂饮食和皮质酮注射联合建立的小鼠抑郁样-胰岛素抵抗疾病模型,给予 AICAR (一种 AMPK 激动剂)在显著改善全身胰岛素抵抗的同时缓解抑郁样行为^[46]。

胰岛素不仅与突触可塑性有关,还会影响β淀粉样蛋白(amyloid-beta protein, Aβ)的代谢过程以及 tau 蛋白的磷酸化。目前,β淀粉样斑块和神经纤维缠结是阿尔茨海默病患者特别常见的病变,是造成神经元退化引起记忆和认知障碍的重要原因之一。早期报道, PI3K/Akt 激活能使糖原合酶激酶-3(glycogen synthase kinase-3, GSK-3)第 9 位丝氨酸残基磷酸化,从而抑制 GSK-3α 和 GSK-3β^[47]。其中 GSK-3α 调控 Aβ 的形成^[48],而 GSK-3β 参与了 tau 蛋白过度磷酸化^[49]。其他报道还表明,胰岛素通过 PI3K 依赖性途径调控可溶性 Aβ 的前体物质淀粉样前体蛋白(amyloid precursor protein, APP)的释放^[50],加速 APP/Aβ 从高尔基网络向浆膜的转运,减少 Aβ 在神经元内的堆积^[51]。人神经元体外培养时,给予胰岛素刺激能使 tau 蛋白磷酸化降低并促进 tau 蛋白与微管的结合^[49],从而防止 tau 蛋白过度磷酸化形成双螺旋而导致神经纤维缠结。

1.3 中枢氧化应激

机体在肥胖时处于氧化应激状态,体内大量的活性氧簇(reactive oxygen species, ROS)会增加脂质过氧化、蛋白质氧化和 DNA 损伤^[52]。据文献报道,高脂饮食时氧化应激先于胰岛素抵抗出现^[53],采用抗氧化剂减轻氧化应激则可有效地改善高脂饮食诱导的胰岛素抵抗^[54]。在阿尔茨海默病患者的大脑中,尤其是在 Aβ 聚集沉淀处,存在大量的自由基氧化应激的现象,且自由基氧化应激与 Aβ 聚集沉淀之间有着互为因果的复杂关系^[55-57]。

长期高脂饮食诱导形成肥胖和 2 型糖尿病时,大脑皮质和海马区域的氧化应激和脂质过氧化增加^[58-60]。脂质过氧化产物丙二醛(malondialdehyde, MDA)能抑制海马神经前体细胞的增殖^[23],对

记忆和认知功能产生不良影响。此外,高脂饮食诱导的中枢氧化应激往往伴随着 BDNF 含量减少,使神经元再生受损,从而可能导致记忆和认知功能障碍^[20,23]。采用抗氧化剂能缓解高脂饮食诱导的海马氧化应激^[21],逆转高脂饮食诱导的海马 DG 区域 LTP 抑制^[61],从而改善高脂饮食诱导的学习记忆缺陷。

氧化应激引起脂质、蛋白质和核酸氧化损伤时,会导致线粒体功能失调并进而产生更多的 ROS,最终使线粒体膜通透性增加而诱使细胞启动“自杀式”凋亡机制^[62]。实际上,氧化应激还和内质网应激、炎症信号转导形成错综复杂的三角联系,它们均参与凋亡信号通路^[63]。文献报道,应激致大鼠抑郁样行为时,海马、去甲肾上腺素能蓝斑系统、5-羟色胺能中缝核和多巴胺能腹侧被盖区的神经元凋亡增加^[62,64]。高脂饮食也能诱导下丘脑和海马神经元凋亡^[63,65-66]。这种凋亡机制可能参与了高脂饮食诱导的情绪障碍和认知损伤。

在氧化应激的条件下,细胞还可能出现过度自噬的现象。自噬是细胞通过单层或双层膜包裹待降解物形成自噬体,然后运送到溶酶体形成自噬溶酶体并进行多种酶的消化和降解,以实现细胞本身的代谢需要和细胞器的更新。自噬在正常细胞内处于一个相当低的水平,它作为一种防御机制可清除某些毒素和病原体以及变性的胞浆成分以维持细胞自身稳态。当细胞内存在大量 ROS 时,自噬被过度激活,可导致细胞 II 型程序性死亡,即有别于凋亡和坏死形式的细胞主动性死亡。目前的研究表明,自噬参与多种神经退行性疾病如阿尔茨海默病、帕金森病和亨廷顿病等。在抑郁症的研究中也发现神经元的自噬现象,并与神经元形态结构的改变和大脑萎缩有关。因此,过度自噬也可能是高脂饮食和代谢性疾病诱导情绪障碍和认知损伤的机制之一。

1.4 中枢瘦素抵抗

瘦素是机体重要的厌食性信号,它主要作用于下丘脑,具有抑制食欲和增加能量代谢的功能。当瘦素受体信号缺陷或者下丘脑瘦素抵抗时(如瘦素缺乏的 *ob/ob* 小鼠和瘦素受体缺乏的 *db/db* 小鼠、*fa/fa* 大鼠),会导致肥胖和 2 型糖尿病^[67]。除了下丘脑外,在海马、小脑、脑干和杏仁核等脑区也有瘦素受体分布。瘦素和瘦素受体在结构和功能上与调控 LTP 的白细胞介素 6 家族类似,因此,瘦素很可能参与突触可塑性的调节而影响学习记忆功能。

研究显示,在海马区域瘦素能激活 PI3K、丝裂

原活化蛋白激酶(mitogen-activated protein kinase, MAPK)和 Src 酪氨酸激酶,从而快速增强 *N*-甲基-*D*-天冬氨酸(*N*-methyl-*D*-aspartic acid, NMDA)诱导的胞内 Ca^{2+} 浓度并将 NMDA 受体介导的突触传递从短时程增强效应(short-term potentiation, STP)转化为 LTP;当上述过程受到削弱时可导致认知缺陷^[68]。对瘦素受体缺乏的 *db/db* 小鼠和 *fa/fa* 大鼠的研究发现,海马 CA1 区域 Ca^{2+} /钙调素依赖性蛋白激酶 II 活性降低,LTD 和 LTP 受到削弱,并在水迷宫实验中表现出空间记忆功能受损^[69-70]。值得注意的是,瘦素对海马突触可塑性的调控呈剂量依赖性,当静脉注射的瘦素达到 $1 \text{ pmol} \cdot \text{L}^{-1}$ 时反而会抑制大鼠海马的突触可塑性^[71]。对于高脂饮食诱导的空间认知障碍和异常的海马形态,瘦素也可能参与其中^[72]。

此外,中枢瘦素还具有抗抑郁的效应。瘦素能显著缩短正常小鼠和 *ob/ob* 小鼠在强迫游泳实验中的不动时间(抑郁样行为),瘦素过表达的转基因小鼠在强迫游泳实验中的不动时间也显著减少,而对于瘦素抵抗的饮食所致的肥胖小鼠瘦素不能缓解其抑郁样行为^[73]。

1.5 多巴胺奖赏环路失调

多巴胺奖赏环路在解剖结构上分别起止于产生多巴胺的腹侧被盖区(ventral tegmental area, VTA)和多巴胺敏感的伏隔核(nucleus accumbens, NAc),亦称作中脑-边缘多巴胺系统,是大脑重要的奖赏机制之一。

肥胖患者纹状体的多巴胺 D2 受体(dopamine D2 receptor, D2 受体)数量显著降低^[74],这种现象亦见于对乙醇、可卡因和鸦片成瘾的患者^[75],意味着肥胖患者具有暴饮暴食倾向,加重肥胖。动物实验研究亦证实,肥胖倾向的大鼠中脑-边缘多巴胺系统胞外多巴胺浓度减少,多巴胺合成和转运削弱,这导致摄食产生的满足感和愉悦感降低,从而引起摄食过量以作为补偿^[76],增加肥胖发生风险。可见,多巴胺奖赏环路失调与肥胖症的病理生理形成密切相关。

除了多巴胺和多巴胺受体外, ΔFosB 、BDNF 和 CREB 也是多巴胺奖赏环路内重要且必需的生物分子。自发活动降低、快感/兴趣缺乏(如糖水嗜好消失或减弱)、社交退缩、性行为减退等抑郁症症状被认为与多巴胺奖赏环路内上述生物分子的异常变化有关^[77]。NAc 内 BDNF 水平增高和 CREB 磷酸化增强具有促抑郁效应,即产生抑郁相关的糖水嗜好降低,行为绝望增强^[78-79]。研究显示,给予高脂饮

食喂养的小鼠中脑-边缘多巴胺系统内多巴胺合成减少, Δ FosB 含量升高, 引起摄食过量; 同时 NAc 内 BDNF 含量升高且 CREB 磷酸化增强, 小鼠表现出抑郁样行为^[80]。此外, 高脂饮食还能快速改变小鼠中脑-边缘多巴胺系统以外脑区(如前额叶皮质、海马、下丘脑)的多巴胺代谢, 诱导焦虑样行为和学习/记忆功能减退^[81]。也有报道, 对于母婴分离应激的幼年大鼠, 给予高脂饮食能缓解焦虑样/抑郁样行为^[82], 这可能与高脂饮食是一种天然的奖赏刺激因子有关^[83-84]。

2 介导中枢神经系统功能异常的外周信号

大脑的功能在很大程度上受到躯体外周状态的影响。当外周参与糖脂代谢的关键组织如脂肪、胰、肝和骨骼肌等发生病变时, 循环血液中甘油三酯/游离脂肪酸、炎症细胞因子和糖皮质激素等的含量异常升高。现有研究表明, 这些外周病变信号介导了代谢性疾病诱导的中枢功能异常。

2.1 高甘油三酯/游离脂肪酸血症

肥胖的形成直接与脂质过度蓄积相关, 肥胖患者血浆中往往含有高水平的甘油三酯和游离脂肪酸。游离脂肪酸的大量增加会直接阻断胰岛素信号转导, 并诱导氧化应激和炎症, 从而可能间接地增强胰岛素抵抗^[85-86]。胰岛素抵抗时, 脂肪细胞内激素敏感性脂肪酶的活性相对不被抑制, 脂解作用增强, 游离脂肪酸的生成增加, 从而形成恶性循环^[87]。迄今为止, 大量证据表明, 高甘油三酯/游离脂肪酸介导了肥胖相关的情绪障碍和认知损伤。

早期临床报道, 高甘油三酯血症会导致认知功能减退^[88], 而降低甘油三酯则能显著改善认知功能^[89]。动物实验研究结果表明, 肥胖小鼠认知功能削弱, 选择性地降低甘油三酯则能显著缓解肥胖小鼠的大脑氧化应激状态并改善认知功能; 若直接向小鼠大脑注射甘油三酯三油精则能抑制海马 LTP, 意味着小鼠的学习/记忆功能受到削弱^[90]。研究还发现, 肥胖状态下的高甘油三酯血症还会削弱瘦素和胰岛素在血脑屏障的转运, 导致中枢瘦素抵抗和胰岛素抵抗^[91-93], 从而间接地对情绪和认知功能产生不良影响。甘油三酯在体内能降解成游离脂肪酸, 其中的饱和脂肪酸也可能是甘油三酯诱导认知功能障碍的机制之一。例如, 软脂酸(又称棕榈酸, 是脂肪细胞释放的主要饱和脂肪酸)和硬脂酸虽然不能直接改变大鼠原代皮质神经元 tau 蛋白的磷酸化程度, 但是上述脂肪酸与星形胶质细胞作

用后的基质能显著引起大鼠原代皮质神经元 tau 蛋白过度磷酸化, 若同时给予抗氧化剂则能逆转上述脂肪酸诱导的 tau 蛋白过度磷酸化^[94]。

事实上, 膳食来源的脂肪对认知功能的影响取决于脂肪酸的类型。饱和脂肪酸(而非单不饱和脂肪酸和多不饱和脂肪酸)会导致认知功能减退^[95]。 Ω -3 不饱和脂肪酸尤其是二十二碳六烯酸(docosahexaenoic acid, DHA)具有神经保护作用, 能够抑制 A β 的产生和聚集以及 tau 蛋白过度磷酸化和神经纤维缠结, 从而预防痴呆^[96]。膳食中增加鱼油这类富含单不饱和脂肪酸和多不饱和脂肪酸的脂质的摄取能预防抑郁样和痴呆样的症状^[97-99]。因此, 在一定程度上高脂饮食导致肥胖、肥胖相关的代谢性疾病以及情绪-认知障碍性疾病的危害源于饱和脂肪酸, 所谓的高脂饮食是基于富含饱和脂肪酸的脂质, 如猪油等。

2.2 炎症

肥胖症被认为是一种“代谢性炎症”, 这种慢性、低度的炎症涉及多种代谢器官包括脂肪组织、肝、肌肉、胰以及大脑^[100]。研究显示, 炎症对情绪和认知功能具有重要的影响^[101-103], 并且炎症是抑郁症、认知功能障碍、痴呆以及痴呆相关疾病如阿尔茨海默病等的重要的病理生理机制^[104-106]。

动物实验研究结果表明, 给予小鼠腹腔注射脂多糖(lipopolysaccharide, LPS)能增加海马和大脑皮质 A β 生成, 削弱记忆功能并促进阿尔茨海默病的病理进程^[107]。另外, 小鼠腹腔注射 LPS 或肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)能增强 NAc 和内侧前额叶皮质 5-羟色胺和多巴胺转运体的活性, 增强上述两种神经递质的代谢, 削弱奖赏环路而导致抑郁相关的快感缺乏^[108-109]。LPS 还能激活中枢吲哚胺-2, 3-双加氧酶, 下调海马 BDNF 水平, 从而可能减弱中枢 5-羟色胺合成并增加色氨酸-犬尿氨酸生物途径中神经毒物质的生成, 减弱海马神经元再生, 最终诱导抑郁样行为^[110-111]。因此, 在肥胖状态下, 外周循环中大量的促炎细胞因子如 LPS 和 TNF- α 可穿过血脑屏障, 通过上述机制诱导认知功能障碍和抑郁样行为。

此外, 由于下丘脑的弓状核和其他室周器官如穹隆下器官、后极区等缺乏有效的血脑屏障保护, 外周循环的饱和脂肪酸可直接激活上述区域的 Toll 样受体-4(Toll-like receptor-4, TLR-4)产生中枢炎症效应, 如上调下丘脑 I κ B 激酶- β (I-kappa-B-kinase beta, IKKB)和 NF- κ B 的表达, 使 IL-1 β , IL-6 和 TNF- α 的表达增加^[112]。除下丘脑外, 大脑皮质和海马等脑

区在高脂饮食或基因突变(*db/db*小鼠)诱导的代谢失常状态下也会出现炎症,表现为 IL-1 β , IL-6 和 TNF- α 的表达显著增加^[24-25,110,113],这些中枢炎症反应与焦虑样/抑郁样行为和认知功能障碍等精神异常症状直接相关。

2.3 HPA 轴失调

皮质酮/糖皮质激素是 HPA 轴分泌的激素之一,是 HPA 轴活性的标志物。HPA 轴主要包含下丘脑室旁核、垂体前叶和肾上腺皮质 3 个部分,并且上述边缘脑区含有 5-羟色胺能神经元和多巴胺能神经元的投射。当 HPA 轴功能失调时可能诱导中枢 5-羟色胺系统和多巴胺系统的异常变化,后者是抑郁症的重要病理生理形成机制^[114]。

在慢性应激诱导的抑郁症动物模型中,HPA 轴功能亢进,血皮质酮水平显著增高^[31]。由于皮质酮对 HPA 轴的负反馈调节作用,外周给予皮质酮可用于建造抑郁症动物模型^[115]。给予啮齿类动物高脂饮食能使基础和应激诱导的皮质酮浓度显著高于正常对照组^[80,116],高脂饮食模型也在一定程度上被认为是一种慢性应激^[116]。因此,HPA 轴亢进很可能是高脂饮食诱导抑郁样行为的机制之一。若动物在围生期给予高脂饲料喂养,其后代仍可出现 HPA 轴的信号异常,并引起焦虑样行为的增加^[117]。在庫欣综合征患者,过高的糖皮质激素可使海马体积缩小,引起记忆功能减退^[118]。海马作为糖皮质激素受体最为丰富的脑区,过度暴露于高水平的糖皮质激素会导致海马神经元树突萎缩、神经元数量损失和突触可塑性病变^[119],这可能是庫欣综合征患者记忆功能减退的病理机制之一。

3 结语

目前,代谢性疾病对大脑功能的影响已成为科学研究的热点之一。突触可塑性和神经元再生受损以及由此导致的神经元凋亡或者萎缩、大脑结构改变等器质性病变是情绪障碍和认知损伤的病理形成基础,BDNF、胰岛素、自由基、皮质酮/糖皮质激素、促炎细胞因子、瘦素、甘油三酯/游离脂肪酸等都是影响突触可塑性和神经元再生的重要因素。他汀类药物^[120-126]和罗格列酮^[127-130]均显示出抗抑郁效应,为临床的用药指导、药物的二度开发和新药的研发策略提供了启示。

另一方面,大脑功能也会影响外周代谢性疾病的发生发展。荟萃分析显示,肥胖及相关的代谢性疾病和情绪障碍之间是双向联系的^[1,4,40],意味着抑

郁症会增加肥胖、2 型糖尿病和代谢综合征发病的风险。动物实验研究结果表明,精神应激不仅会诱导动物抑郁样行为,还会上调肝胆固醇逆转运相关基因的表达^[131],改变大脑不同脑区的葡萄糖代谢^[132],上调肠道糖脂转运体 *slc5a1* 和 *slc2a2* 的表达^[133],影响机体糖脂代谢。在精神应激下,HPA 轴激活,HPA 轴各部分分泌的激素对食欲的作用不同,其中下丘脑室旁核和垂体前叶分泌的促肾上腺皮质激素释放因子和肾上腺皮质激素是厌食性的,而糖皮质激素有直接的促食欲效应和间接的厌食性效应,这就意味着 HPA 轴激活会改变摄食行为进而影响未来的胖瘦^[134]。此外,精神应激可能诱导外周炎症引起胰岛素抵抗,并进而造成肥胖、动脉粥样硬化和 2 型糖尿病^[135]。

总之,大量的临床和动物实验研究表明,肥胖及相关的代谢性疾病和大脑功能之间是相互影响的。在未来的研究中,神经免疫学机制、肠道微生物菌群等可能会成为连接神经精神疾病与外周其他疾病如肥胖、2 型糖尿病和代谢综合征的重要桥梁。

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Effect of metabolic diseases on emotional and cognitive functions and its potential mechanisms: research progress

LIU Qiong-zhen^{1,2}, LYU Wen-ting^{1,2}, CAI Min-xuan^{1,3}, WU Hua-li^{2,3}, SHANG Jing^{1,2,3}

(1. Center for Drug Screening, China Pharmaceutical University, Nanjing 210009, China; 2. State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, China; 3. Jiangsu Key Laboratory of TCM Evaluation and Translational Research, China Pharmaceutical University, Nanjing 210009, China)

Abstract: In recent years, a considerable number of epidemiological investigations and animal studies have confirmed that metabolic diseases, such as obesity, type 2 diabetes mellitus and metabolic syndrome, have adverse effects on brain functions, inducing mood disorders and cognition impairment. Brain dysfunctions induced by obesity and related complications are associated with numerous central abnormalities, involving brain shrinkage and neurotrophic function impairment, brain insulin resistance, brain oxidative stress, and brain leptin resistance, as well as dysfunctioned dopamine motivation and the reward system. Moreover, these brain dysfunctions are mediated by several peripheral factors, such as triglycerides/free fatty acids, proinflammatory cytokines, and corticosterone/glucocorticoid. On the other hand, metabolic disturbances correlated with emotional-cognitive disorders are evident, but the mechanisms remain obscure. Because of the drawbacks of animal models, the majority of researches focus on the impact of mental stress on the metabolism of lipid and glucose. The interrelationship between metabolic diseases and brain functions has become one of the hot spots for research. In this review, we mainly discussed the potential mechanisms underlying mood disorders and cognition impairment induced by obesity and related complications.

Keywords: high-fat diet; metabolic diseases; depression; Alzheimer's disease

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Corresponding author: SHANG Jing, Tel.: (025)83271516, E-mail: shangjing21cn@163.com

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