综 述

2型糖尿病共病焦虑症的神经病理生理机制研究进展

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[中图分类号] R749.2+4 [文献标志码] A [DOI] 10.11855/j.issn.0577-7402.0404.2023.1121
[声明] 本文所有作者声明无利益冲突
[引用本文] 梁华素, 杨会军, 杨莹. 2型糖尿病共病焦虑症的神经病理生理机制研究进展[J]. 解放军医学杂志, 2023, 48(7): 828-833.
[收稿日期] 2022-02-24 [录用日期] 2022-06-09 [上线日期] 2022-11-21

[摘要] 2型糖尿病(T2DM)常伴发焦虑症，临床发现T2DM与焦虑症之间存在复杂的相互作用，但是对于其重叠的机制仍然知之甚少。T2DM和焦虑症的特征均为中枢神经系统功能发生改变，在神经生化、脑源性神经营养因子(BDNF)、免疫炎症和下丘脑-垂体-肾上腺(HPA)轴间存在共同的生物学机制，但目前尚不清楚是否为其重叠的机制。本文主要针对T2DM、焦虑症与神经生化相关因子[γ-氨基丁酸(GABA)、谷氨酸(Glu)、5-羟色胺(5-HT)、多巴胺(DA)等]、BDNF、免疫炎症、HPA轴之间是否存在相关性进行综述，旨在探讨T2DM和焦虑症共病的潜在神经病理生理重叠机制，为共病的治疗提供参考。

[关键词] 糖尿病，2型；焦虑症；神经病理；神经生理

Research progress on the neuropathophysiological mechanism of co-morbid anxiety disorder in type 2 diabetes

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This work was supported by the National Natural Science Foundation of China (81760734), the Science Research Foundation of Education Department of Yunnan Province (2021J0018), the Provincial Innovation Team of Prevention, Diagnosis and Treatment of Diabetic Vascular Diseases, the Second People's Hospital of Yunnan Province (2019HC002), and the Postgraduate Innovation Fund of Kunming Medical University (2021S283)

[**Abstract**] Type 2 diabetes mellitus (T2DM) is often associated with anxiety disorders. It has been found that there is a complex pathogenic interaction between T2DM and anxiety disorders, but little is known about the mechanism of their overlap. Both T2DM and anxiety disorders are characterized by changes in the function of the central nervous system, share a common biological mechanism on neurobiochemistry, brain-derived neurotrophic factor (BDNF), immune inflammation, and hypothalamus-pituitary-adrenal (HPA) axis, but it is not clear whether it is the mechanism of overlap. The present article mainly reviews whether there is a correlation between T2DM and anxiety disorders in neurobiochemical-related mechanisms such as γ-aminobutyric acid (GABA), glutamate (Glu), 5-hydroxytryptamine (5-HT), dopamine (DA), BDNF, immune inflammation, and HPA axis, in order to explore the potential neuropathophysiological overlap mechanism of T2DM and anxiety disorders and to provide a reference for the treatment of the comorbidity.

[**Key words**] diabetes mellitus, type 2; anxiety disorder; neuropathology; neurophysiology

[基金项目] 国家自然科学基金(81760734)；云南省教育厅科学研究基金(2021J0018)；云南省第二人民医院糖尿病血管病变预防及诊疗省创新团队项目(2019HC002)；昆明医科大学硕士研究生创新基金(2021S283)

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近年来，全球糖尿病患病率明显增高，2021年成人糖尿病患病率为10.5%，其中2型糖尿病(type 2 diabetes mellitus，T2DM)占90%[1]。T2DM作为一种慢性进行性代谢性疾病，常与抑郁症和焦虑症并存[2]。然而，糖尿病人群中的焦虑症状往往未被发现，也未得到及时治疗。多项研究发现糖尿病与焦虑症可相互影响：糖尿病可增加焦虑症的风险高达48%[3]，且糖尿病并发症患者的焦虑风险更高[2]；同时，焦虑症状是T2DM的重要危险因素，焦虑症患者罹患糖尿病的风险是普通人群的2倍[4]。1990—2019年，这两种疾病的伤残调整寿命年明显增加，增幅位于369种疾病的前10位，已成为全球主要的公共卫生问题[5]。当糖尿病与焦虑症共病时，患者的自控力、依从性差，其血糖水平和精神状态更难控制，可显著加重患者的疾病负担[6-7]。以上研究表明糖尿病与焦虑症之间存在复杂的相互作用，但它们之间潜在的重叠机制目前仍知之甚少。有研究发现，神经生化、脑源性神经营养因子(brain-derived neurotrophic factor，BDNF)、免疫炎症、下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal，HPA)轴的异常均参与了T2DM和焦虑症两种疾病的发生发展，但这些机制是否为其重叠的机制仍不清楚[8-11]。本文主要针对T2DM和焦虑症相关的神经生化、BDNF、免疫炎症、HPA轴的神经病理生理机制等进行综述，旨在探讨T2DM和焦虑症共病的潜在神经病理生理重叠机制，以期为防治T2DM和焦虑症共病提供参考。

1 神经生化失调与T2DM和焦虑症的关系

中枢神经递质主要包括氨基酸类、吲哚类、单胺类及其他类神经递质。其中，氨基酸类抑制性神经递质γ-氨基丁酸(γ-aminobutyric acid，GABA)及兴奋性神经递质谷氨酸(glutamic acid，Glu)、吲哚类神经递质5-羟色胺(5-hydroxytryptamine，5-HT)、单胺类神经递质多巴胺(dopamine，DA)等的异常表达均参与了T2DM和焦虑症的发生发展。

1.1 GABA　GABA作为抑制性神经递质，与GABA受体结合后可介导多种神经疾病和精神疾病。GABA受体包括离子型(GABAA和GABAC)和代谢型(GABAB)受体，其中GABAA和GABAB受体的表达及功能改变与焦虑的调节有关。GABAA受体的正变构调节剂苯二氮䓬类药物是使用最广泛的抗焦虑药物，可激动GABAA受体从而发挥抗焦虑作用[12]，而GABAB1或GABAB2受体亚基功能的丧失则可增强先天焦虑[13-14]，因此增加中枢神经系统GABA浓度可缓解焦虑症状[15]，是治疗焦虑症的主要靶标。除中枢神经系统外，GABA可发挥免疫调节作用并诱导胰岛β细胞再生[16]。T2DM患者体内GABA合成减少，腹腔注射GABA可使葡萄糖转运蛋白4水平升高，减少糖异生途径，并降低胰高血糖素受体基因表达水平，从而改善T2DM小鼠的胰岛素抵抗[17]。链脲佐菌素诱导的糖尿病可通过GABA系统对嗅球神经产生不利影响，导致嗅觉功能受损、GABA减少[18]。因此，增加GABA表达的药物有望在这两种疾病中发挥治疗作用。

1.2 Glu　Glu是与焦虑相关的兴奋性神经递质[19]，焦虑症患者的Glu水平可异常升高[20]。Glu以谷氨酰胺(glutamine，Gln)形式存储于神经胶质细胞中，而焦虑大鼠海马Glu和Gln水平均明显升高[21]。因此，降低谷氨酸能神经传递的药物被认为具有抗焦虑作用。同时，T2DM患者血浆Glu水平升高[22]，Glu受体信号可能与糖尿病的发病机制有关。临床研究发现，糖尿病患者脑高Glu水平可作为糖尿病脑并发症的早期标志物[23]。对于胰岛β细胞来说，Glu是一把双刃剑：在细胞内水平，Glu可增强Ca^{2+}信号，从而触发胰岛素分泌[24]；在细胞外水平，Glu可激活N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid receptor，NMDA)受体，降低细胞内Ca^{2+}浓度，从而降低胰岛素的胞吐速率[25]，还可导致胰岛β细胞死亡[26]。因此，胰腺NMDA受体可作为糖尿病治疗的潜在靶标。Glu升高与焦虑症和糖尿病均呈正相关，推测降低Glu水平有望延缓二者的发生发展。

1.3 5-HT　5-HT分布于中枢神经系统和周围神经系统。大脑表达7种类型的5-HT受体，包括18个不同的亚型。5-HT与不同亚型受体结合的作用不同，激活5-HT1A、5-HT2B、5-HT4、5-HT6、5-HT7受体和拮抗5-HT2A、5-HT2C、5-HT3受体可发挥抗焦虑作用，提示突触间隙高浓度的5-HT与焦虑症的发生有关[27]。有研究发现，在小鼠胰岛细胞中存在5-HT，且可通过作用于5-HT2C受体抑制基础胰岛素和葡萄糖刺激的胰岛素分泌(glucose-stimulated insulin secretion，GSIS)[28]。此外，还有研究发现，在健康人群中的5-HT可抑制胰岛素和胰高血糖素的分泌，而在T2DM患者中5-HT1D、5-HT2A受体的过表达则明显增加了GSIS[29]。这可能反映了糖尿病前期的一种代偿机制，即通过增加GSIS来降低血糖，表现为高胰岛素血症，但从长远来看，则可能导致β细胞衰竭，进而发展为T2DM。同时，临床研究显示，不同剂量及类型的5-HT2A受体拮抗剂对血糖有不同的影响[30-31]。在高脂饮食诱导的T2DM大鼠模型中，大鼠的高血糖和糖耐量降低与其焦虑样行为相关，这可能是由于背缝5-HT1A自身受体的敏感性增加所致[32]。中枢及外周5-HT浓度增加与糖尿病和焦虑症均呈正相

关，这为二者共病患者提供了潜在的治疗方向，但具体机制仍有待进一步研究。

1.4 DA DA是一种重要的神经递质，与DA受体(dopamine receptor，DR)结合后在外周和中枢神经系统中发挥作用。DR可分为兴奋性受体(D1R、D5R)和抑制性受体(D2R、D3R、D4R)。因此，DA诱导的生物反应取决于DR亚型、受体密度、细胞类型和受体所在的大脑区域[33]。患者眼眶额叶皮质D2R[34]及腹侧纹状体中的D2R、D3R水平[35]异常升高均与焦虑症呈正相关；另有研究发现，将D1R激动剂注入前额叶皮质可缓解大鼠的焦虑症状[36]。同时，突触间隙的DA可被突触前膜的DA转运体重吸收，使突触间隙DA浓度降低，增加焦虑的发生风险。有研究发现，杏仁核和海马中DA转运体增多的患者焦虑症状更严重[37]，杏仁核内D1R的高多巴胺能状态可能使糖尿病大鼠的焦虑症状加重[8]。除中枢神经系统外，周围神经系统突触间隙的DA也在葡萄糖代谢和能量平衡中发挥关键作用。DA参与GSIS调节，通过依赖D2R的机制减少胰岛素分泌[38]，这可能是避免胰岛β细胞耗竭的一种保护机制。小鼠D1R[39]、D2R[40]受体被抑制后可表现出高胰岛素血症及葡萄糖耐量异常。目前，D2R激动剂溴隐亭已被FDA批准用于治疗T2DM，该药可增加肝脏中酪氨酸羟化酶水平，从而提高胰岛素敏感性，并改善T2DM患者的代谢状况[41]。综上，推测D2R异常可能是糖尿病和焦虑症患者共病的机制之一。

2 BDNF下降对T2DM和焦虑症的促进作用

BDNF是一种可促进神经元增殖、成熟的神经营养因子。BDNF表达于中枢神经系统以及骨骼和内分泌系统等外周组织。成熟的BDNF可与酪氨酸激酶受体B(tyrosine kinase receptor B，TrkB)结合，但在中枢及外周组织的表现不同。在中枢神经系统中，BDNF参与调节抗焦虑药物的行为反应[42]。在焦虑症患者、焦虑动物模型及糖尿病大鼠相关的焦虑样行为中，BDNF的表达水平及*BDNF*基因多态性降低[18,43-44]。而在外周组织中，BDNF与糖尿病密切相关。研究发现，糖尿病患者体内的BDNF水平降低[45]；BDNF与TrkB结合后可增加胰岛素的敏感性[46]；接受BDNF治疗的糖尿病患者血糖水平明显降低，体重减轻，食物摄入量减少，且葡萄糖和能量代谢增强[47]，提示BDNF对循环血糖水平具有正向调节作用。但是，也有研究发现T2DM患者的血清BDNF水平明显升高[48]，推测可能与T2DM患者早期可通过增加BDNF的表达来改善新陈代谢，减少食物摄入量[49]有关，提示BDNF对糖尿病和焦虑症是有益的。然而，由于生物利用度低、半衰期短、对血脑屏障的透过性较差，BDNF在临床上的应用受到了限制[50]。因此，仍需进一步研究以明确BDNF的代谢及作用。

3 免疫炎症对T2DM和焦虑症进展的影响

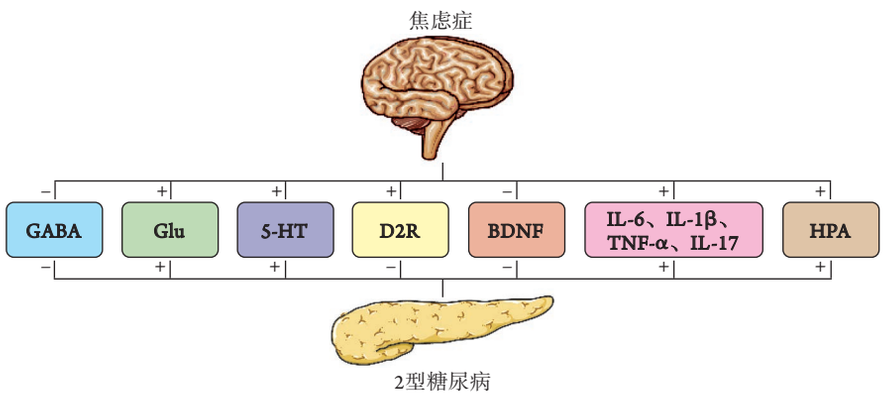
炎症细胞因子是一种小分子蛋白，由免疫细胞合成、分泌。炎症细胞因子除了调节免疫系统，还参与生物体内神经信号的传递。焦虑症和糖尿病似乎均与炎性细胞因子有关[51-52]，炎症不仅可诱导疾病的发生，而且可使疾病恶化，因此，糖尿病与焦虑症是彼此的危险因素。糖尿病及焦虑患者均可出现慢性低度炎症[10]，表现为外周和中枢炎性细胞因子、炎性介质增加，同时全身的炎症会触发以小胶质细胞持续激活为特征的神经炎性反应[53]，产生神经毒性作用，并影响神经内分泌和神经递质的活性。有研究发现，糖尿病合并焦虑小鼠的中枢促炎细胞因子白细胞介素(interleukin，IL)-6、IL-1β、肿瘤坏死因子-α(tumor necrosis factor，TNF-α)水平升高[54]；还有研究发现，母代大鼠的高糖饮食及新生大鼠血清IL-1β水平升高均可改变整个生命过程中的焦虑行为[55]。此外，在临床研究中也发现，糖尿病合并焦虑患者的血清IL-6、IL-17、TNF-α水平明显升高[56]。上述研究均证实了免疫炎症与焦虑症和糖尿病存在联系。

4 HPA轴过度激活在T2DM和焦虑症发生中的作用

HPA轴是哺乳动物中比较重要的神经内分泌系统，其分泌的糖皮质激素(皮质醇)可参与代谢、情绪、免疫、生殖的调节。HPA轴激活及皮质醇慢性增多可导致高血糖、胰岛素抵抗、炎症等糖尿病表现[57]。此外，HPA轴过度活动也被认为是焦虑症的基础生物学机制之一[58]，并可介导焦虑症患者糖尿病并发症的发生[11]。因此，过度活跃的HPA轴可能是焦虑症与糖尿病相关代谢异常之间的生物学联系。在动物模型中，长期服用皮质醇的小鼠焦虑相关行为明显增多[59]，而在临床研究中也发现，糖尿病[57]和焦虑症[60]患者的血清皮质醇水平明显升高。可见，患者的焦虑情绪可使糖皮质激素水平慢性持续性升高，进而出现HPA轴失调、胰岛素抵抗，最终促进糖尿病的发生发展。

综上，T2DM和焦虑症共病的神经病理生理机制与神经生化(Glu、5-HT、GABA、D2R)、BDNF、免疫炎症(IL-6、IL-1β、TNF-α、IL-17)和HPA轴失调等均有关(图1)。这些机制可相互作用，形成恶性循环。T2DM和焦虑症的特征均为中枢神经系统功能的改变，因而共同的神经病理机制

在两种疾病中经常被观察到。精神健康状况已被证实可增加与糖尿病相关的短期和长期并发症的发生风险，包括严重的低血糖或高血糖、体重增加、微血管疾病等[61-62]；而糖尿病与焦虑症共病对患者的生活质量、治疗和预后均可产生负面影响[63]。以上结果表明，对于T2DM等躯体疾病患者，适当监测并处理焦虑症共病是非常必要的，建议糖尿病患者尽早筛查及治疗焦虑症，从而减少并发症的发生，提高患者的生活质量。



GABA. γ-氨基丁酸；Glu. 谷氨酸；5-HT. 5-羟色胺；D2R. 多巴胺受体2；BDNF. 脑源性神经营养因子；IL. 白细胞介素；TNF-α. 肿瘤坏死因子-α；HPA. 下丘脑-垂体-肾上腺轴；+. 促进作用；–. 抑制作用

图1 T2DM与焦虑症相关的神经病理生理机制

Fig.1 Neuropathophysiological mechanisms associated with anxiety disorders and T2DM

5 总结与展望

T2DM是最常与焦虑症共病的躯体性疾病，大量证据证实二者在神经生化、BDNF、免疫炎症和HPA轴失调中存在共同的病理生理学机制，但对于机制中涉及的各种途径是否会相互作用尚不清楚。同时，目前对T2DM和焦虑症的机制研究主要停留在基础实验阶段，研究手段单一，缺乏对共病的系统性探讨。此外，焦虑症的诊断主要依靠焦虑量表，缺乏一定的客观性。因此，在未来的研究中，对于T2DM和焦虑症共病患者的临床研究可发挥辅助检查如神经影像技术的优势，再联合神经生化、BDNF、免疫炎症和HPA轴等指标的改变，对共病患者进行系统性分析，将有助于进一步探讨其共病机制，及早识别、治疗糖尿病患者的焦虑问题，减轻患者的疾病负担，改善其血糖水平和精神状态，从而降低并发症的发生风险。

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