

血脑屏障功能障碍与精神疾病关系的研究进展

王 馨, 胡凌霄, 蒋文高*

重庆医科大学药学院分子生物学与生化药理学重点实验室, 重庆

收稿日期: 2026年1月5日; 录用日期: 2026年1月29日; 发布日期: 2026年2月4日

摘 要

血脑屏障(BBB)是外周血液和脑实质之间的动态界面, 控制物质进出脑的转运, 保护大脑免受血源性病原体和各种神经毒素的侵害。近年的研究提示BBB功能障碍与多种精神疾病的病理生理机制相关。本文综述了精神分裂、抑郁症和双相情感障碍等精神疾病发生发展过程中BBB功能障碍的临床和实验室研究证据, 探讨了在精神疾病中BBB破坏的不同分子机制及其对疾病的影响。

关键词

血脑屏障, 精神分裂症, 抑郁症, 双相情感障碍

Research Progress on the Relationship between Dysfunction of the Blood Brain Barrier and Psychiatric Diseases

Xin Wang, Lingxiao Hu, Wengao Jiang*

Laboratory of Molecular and Biochemical Pharmacology, School of Pharmacy, Chongqing Medical University, Chongqing

Received: January 5, 2026; accepted: January 29, 2026; published: February 4, 2026

Abstract

The blood brain barrier (BBB) represents the dynamic interface between the peripheral blood circulation and the central nervous system (CNS). It controls the substance transportation across the brain, protects the brain from external pathogens as well as inert neurotoxic substances from entering the CNS. Recent research has revealed the relevance of BBB dysfunction to the pathophysiology of several psychiatric diseases. The review describes the clinical and experimental evidence, possible

*通讯作者。

文章引用: 王馨, 胡凌霄, 蒋文高. 血脑屏障功能障碍与精神疾病关系的研究进展[J]. 国际神经精神科学杂志, 2026, 15(1): 10-18. DOI: 10.12677/ijpn.2026.151002

mechanisms and effects of the BBB dysfunction on schizophrenia, major depressive disorder and bipolar disorder.

Keywords

Blood Brain Barrier, Schizophrenia, Major Depressive Disorder, Bipolar Disorder

Copyright © 2026 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

血脑屏障(blood-brain barrier, BBB)是指脑毛细血管壁与神经胶质细胞形成的血浆与脑细胞之间的屏障,以及由脉络丛形成的血浆和脑脊液(cerebrospinal fluid, CSF)之间的屏障。BBB 能够有效且严格限制循环血液和脑微环境之间的分子交换,既能为脑细胞提供含氧血液和能量基质,同时也能清除大脑中的代谢废物,是大脑与外周进行物质交换的主要场所[1]。由于神经元再生能力有限, BBB 发挥精准的微环境调控作用来维持中枢神经系统(central nervous system, CNS)的恒定稳态对于保持大脑正常运作至关重要。在 CNS 病变的情况下,血液-CNS 屏障的屏障特性将发生改变,导致水肿形成和炎症细胞向 CNS 的聚集。近年研究表明 BBB 结构和通透性的病理生理变化可以先于或加速一系列精神疾病的进展,提示 BBB 功能障碍在精神疾病发病机制中发挥了重要作用[2][3]。基于精神分裂症、抑郁症、双相情感障碍三类疾病发病率与疾病负担的显著性、BBB 功能障碍相关研究的充分性以及病理机制的代表性,本文聚焦上述三类疾病,系统综述其 BBB 功能障碍的最新研究进展。

2. 精神分裂症

精神分裂症(schizophrenia, SCZ)是指以思维、情感、行为障碍及现实感知扭曲为特征的精神疾病。该病发病机制具有异质性,可由神经发育障碍或神经退行性变化或神经进行性变化所致[4]。各国荟萃分析显示 SCZ 患者的平均预期寿命比一般人群短 14.5 年,这与自杀,特别是心血管疾病密切相关[5]。SCZ 的血管假说认为神经血管单元(neurovascular unit, NVU)功能障碍和 BBB 高通透性是 SCZ 的重要病理生理因素之一[6]-[8]。

2.1. 精神分裂症患者存在 BBB 结构受损和功能障碍

Cheng Y 等人首次通过 DCE-MRI 技术发现 SCZ 患者丘脑的 BBB 通透性显著升高,这与疾病持续时间和 PANSS 评分呈正相关,并可能导致患者脑结构异常[9]。与上述观点一致,系统评价和荟萃分析发现, SCZ 患者 BBB 功能标志物 S100 β 水平随病程延长升高,白蛋白商(albumin quotient, QAlb)显著高于健康对照组,提示 BBB 结构受损和功能障碍可能随疾病进展而加重[10]。超微结构研究进一步证实, SCZ 患者前额叶皮层(prefrontal cortex, PFC)和视觉皮层存在基底膜增厚、星形胶质细胞终足肿胀和空泡化等 BBB 结构病理改变。毛细血管及其周围微环境损伤可能通过干扰脑血流灌注和代谢稳态参与 SCZ 的病理生理机制[11]。

2.2. 转录组分析揭示 BBB 功能障碍的关键基因和信号通路

转录组分析发现, SCZ 患者血管内皮相关基因(如 VEGF、CLDN5)和信号通路(如 WNT、Notch)表达异常,涉及血管生成、紧密连接(tight junction, TJ)和线粒体功能等关键通路[12]。在特定神经元类型如 PFC

的小清蛋白(parvalbumin, PV)神经元, 线粒体功能障碍和氧化磷酸化相关基因的表达下调尤为突出, 可能与 BBB 的代谢支持不足有关。此外, PV 神经元中细胞外基质相关基因的异常表达可能影响 BBB 的稳定性[13]。这些转录因子的变化不仅反映了 BBB 的结构和功能异常, 还可能通过 NVU 的失调加剧 SCZ 的病理进程。血管内皮生长因子(vascular endothelial growth factor, VEGF)被发现在 CNS 炎症状态下, 通过特异性下调脑微血管内皮细胞(brain microvascular endothelial cells, BMEC)中紧密连接蛋白 Claudin-5 的表达, 直接破坏 BBB 的结构完整性并诱导其功能受损[14]。Fulzele S 等人发现 SCZ 患者背外侧前额叶皮层(dorsolateral prefrontal cortex, DLPFC)中 VEGF mRNA 表达降低[15]。然而, 另一项研究显示, 患者血清 VEGF 水平显著升高, 且 PFC 体积显著减少, 二者呈负相关[16]。推测 VEGF 可能通过诱导 BBB 通透性改变, 导致脑内自由水增加和低灌注, 进而与 PFC 体积减少及功能异常相关。随着研究深入, SCZ 中 BBB 功能障碍的其他证据被逐渐挖掘。研究发现, 患者 CSF 中升高的血管细胞黏附分子 sVCAM-1 与 QAlb 显著相关, 表明免疫激活可能损害 BBB 完整性[17]。此外, 难治性 SCZ 患者血浆中基质金属蛋白酶 9(matrix metalloproteinase, MMP-9)水平异常升高[18]。MMP-9 作为一种与细胞外基质降解相关的蛋白酶, 其水平升高可能暗示 BBB 功能紊乱。生物信息学分析发现, PFC 中水通道蛋白 4(aquaporin, AQP4)表达上调与星形胶质细胞功能障碍相关[19]。

2.3. 紧密连接蛋白 Claudin-5 介导的 BBB 功能障碍参与 SCZ 病理生理机制

SCZ 的神经遗传学机制研究发现, 22q11.2 缺失综合征(22q11DS)患者因 22 号染色体的微缺失而表现出高 SCZ 风险和多系统异常[20]。研究表明, 22qDS 会导致 Claudin-5 表达下调及分布紊乱、ICAM-1 表达增加、单核细胞激活/迁移增加以及星形胶质细胞活化等病理变化, 同时伴随跨内皮电阻(transendothelial electrical resistance, TEER)显著降低的 BBB 功能受损现象[21]。CLDN5 基因的 rs10314 变异与 SCZ 风险微弱相关。研究发现, CLDN5 基因突变会进一步使 22q11DS 患者 Claudin-5 总表达量仅为正常水平的 25%。动物模型进一步揭示, 靶向抑制 Claudin-5 会破坏 BBB 完整性, 并诱发类似 SCZ 的行为表型。值得注意的是, 常用抗精神病药物(如氟哌啶醇、氯丙嗪)可剂量依赖性地上调 Claudin-5, 提示 Claudin-5 介导的 BBB 功能障碍既参与 SCZ 的病理进程也是潜在的治疗靶点[22]。未明确遗传因素情况下, Claudin-5 的失调源于 cAMP/PKA 通路异常激活与 5-HT_{1A} 受体信号紊乱。SCZ 患者 PFC 中, PKA 激活可磷酸化 Claudin-5 的 Thr207 位点, 导致蛋白功能破坏及 BBB 对小分子的选择性屏障受损[23]。Sugimoto 等人研究表明, cAMP 除了通过 PKA 依赖途径磷酸化 Claudin-5 蛋白导致其功能下降, 还能通过 PKA 非依赖途径诱导 CLDN5 基因表达; 血清素则通过 5-HT_{1A} 受体增强 BMEC 中 Claudin-5 蛋白的表达, 维持 BBB 完整性[24]。上述结论与一项关于新型非 D₂ 受体结合抗 SCZ 药物 SEP-363856 的治疗原理一致, 该药物可能通过激动微量胺相关受体 1(trace amine-associated receptor 1, TAAR1)和 5-HT_{1A} 受体来调节多巴胺和血清素系统改善 SCZ 症状, 为 SCZ 的靶向治疗提供了新思路[25]。

3. 抑郁症

抑郁症既是一种心理疾病, 也是一种普遍由遗传基因和环境应激的累积效应引起的精神疾病, 其特征是持续的抑郁情绪、认知功能受损以及复杂的病理生理和神经内分泌改变[26]。慢性压力持续应激会激活外周和中枢免疫系统, 导致促炎细胞因子水平升高、单核细胞浸润和神经炎症, 从而增加情绪障碍的风险[27]。值得注意的是, BBB 功能障碍可能先于或加剧这种由慢性压力和炎症介导的神经紊乱, 与抑郁症的病理进程密切相关。

3.1. 抑郁患者存在 BBB 结构破坏和功能障碍

重度抑郁症(major depressive disorder, MDD)作为抑郁症谱系障碍中最典型、症状最严重的临床亚型,

以显著的功能损害和高自杀风险为特征性临床表现。抑郁症患者海马体(情绪相关脑区)存在 TJs 表达紊乱,其灰质区 Claudin-5 水平显著降低,且海马体灰白质间存在血管形态差异[28]。类似地,两个研究团队先后发现,未接受抗抑郁治疗的 MDD 患者伏隔核中 Claudin-5 mRNA 水平及蛋白表达均显著降低,而抗抑郁治疗可部分逆转该异常变化[29] [30]。BBB 特异性葡萄糖转运蛋白 1 (glucose transporter, GLUT1) 缺乏可导致 BBB 早期破坏[31]。临床研究发现, MDD 患者的 GLUT1 甲基化水平显著升高,且治疗后缓解患者的甲基化水平恢复正常,而未缓解者则进一步升高。GLUT1 甲基化异常可能导致能量代谢障碍、BBB 稳态失衡,并与抑郁的持续状态相关[32]。在神经胶质细胞方面,尸检发现, MDD 患者海马体中胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)免疫反应性星形胶质细胞密度呈现区域特异性降低,提示星形胶质细胞丢失或萎缩[33]。另一项研究在 MDD 患者眶额叶灰质中观察到血管周围 AQP4 定位缺失。星形胶质细胞终足(尤其是 AQP4 阳性终足)与血管的功能性接触异常,可能通过水稳态失衡、脑血流量异常调节等影响 BBB 正常功能[34]。此外,一项涵盖 48 项研究的荟萃分析证实,脑小血管病变(白质高信号、微出血、微梗死)和内皮功能障碍标志物(如 sICAM-1、sVCAM-1)与抑郁症显著相关。微血管功能障碍可能通过 BBB 破坏导致慢性缺血、炎症和氧化应激,进而影响情绪调节网络[35]。该研究强调脑血管病变是晚年抑郁的独立风险因素,支持了“血管性抑郁”假说。

3.2. 动物模型研究提示 NVU 失衡导致的 BBB 异常可能是抑郁症的关键致病因素

慢性不可预测的轻度应激(chronic unpredictable mild stress, CUMS)暴露导致小鼠出现典型的抑郁样行为,并伴随 BBB 通透性显著增加,表现为荧光素钠泄漏增加和血清 S100 β 水平升高[36]。束缚应激模型中,应激大鼠 BBB 结构和功能出现时间依赖性变化,包括紧密连接蛋白 Claudin-5 和 Occludin 表达和分布改变、能量代谢异常(GLUT-1 表达异常)、星形胶质细胞功能障碍(GFAP 减少、AQP-4 增加)及毛细血管超微结构损伤(如内皮细胞损伤、基底膜增厚)。值得注意的是, PFC、杏仁核和海马等不同脑区面对应激时会出现不同的病理变化,提示 BBB 应激反应存在脑区特异性[37] [38]。Hattori 等人还在慢性束缚应激小鼠中发现血清及海马 VEGF 水平升高,并伴随 BBB 通透性增加(涉及 TJ 结构破坏和囊泡介导的跨细胞运输增强)。进一步研究发现,通过 VEGFR2 抑制剂干预可逆转 BBB 损伤并改善抑郁症状,提示 VEGF 介导的 BBB 功能障碍是抑郁症的重要病理机制[39]。此外,最新研究表明,慢性不可预测应激可能通过炎症或激素途径促进海马分子层 NG2+周细胞增殖,进而影响屏障功能[40]。神经炎症可能影响 BBB 功能,也与抑郁症的病理机制相关[41]。研究发现,慢性脂多糖(lipopolysaccharide, LPS)注射通过增加中脑甲醛水平,激活小胶质细胞并减少 Claudin-5 的表达,触发神经炎症和抑郁行为[42]。芬维 A 胺和逍遥散等药物被发现通过不同机制抑制 LPS 介导的神经炎症反应,从而改善 BBB 功能障碍并缓解抑郁样行为[43] [44]。

3.3. 血脑屏障功能障碍与抑郁症应激适应性和性别差异有关

慢性社会挫败应激(chronic social defeat stress, CSDS)会通过降低雄性小鼠伏隔核中 Claudin-5 的表达导致 BBB 完整性破坏,使外周细胞因子 IL-6 渗入脑内,诱发抑郁样行为。有趣的是,将 Claudin-5 敲低后,亚阈值社会应激即可诱导小鼠出现抑郁样行为,表明 Claudin-5 异常在应激诱导抑郁的病理过程中起关键作用[29]。值得注意的是,研究人员发现部分 CSDS 模型小鼠存在应激适应性,即应激抗性(resilient, RES)小鼠,与另一部分应激易感(stress-susceptible, SS)小鼠形成对比。研究发现,RES 小鼠通过表观遗传调控(如启动子组蛋白乙酰化增强、甲基化减弱)和抑制性转录因子 FoxO1 表达降低,来维持 Claudin-5 表达并保护 BBB 功能。而在 SS 小鼠 NAc 内皮细胞中, TNF α /NF κ B 信号通路被激活,且组蛋白去乙酰化酶 1 (histone deacetylase 1, HDAC1)表达上调,后者通过抑制 Claudin-5 加剧 BBB 渗漏[30]。上述研究从 BBB 的分子适应性的角度很好地解释了抑郁症存在的异质性和个体差异。此外,全国合并症调查发现女

性抑郁症终生患病率更高且症状更复杂[45]，然而抑郁症和 BBB 功能障碍的关联在雌性动物中的研究尚不充分。最近有研究发现，慢性应激导致雌性小鼠 PFC 中 Claudin-5 表达下降，BBB 通透性增加，并伴随焦虑和抑郁样行为，这些变化在雄性小鼠中未观察到，提示 BBB 对应激的反应性存在性别差异[46]。

4. 双相情感障碍

双相情感障碍(bipolar disorder, BD)是一种以躁狂/抑郁反复发作作为特征的重性精神疾病，全球患病率 1%~2%，患者自杀风险是普通人群的 20~30 倍[47] [48]。炎症水平升高是 BD 核心的病理生理学特征之一[49]。现有证据表明，遗传因素、表观遗传调控及 HPA 轴功能异常可通过炎症介导的分子机制加剧 BD 患者的 BBB 功能障碍，形成恶性循环，最终导致神经元损伤和疾病进展[50]-[52]。因此，BBB 功能障碍似乎是 BD 多系统病理变化的枢纽。

4.1. BD 患者 BBB 功能障碍与病情严重程度有关

DCE-MRI 结果表明，BBB 渗漏程度与 BD 的慢性化、抑郁和焦虑症状严重程度以及功能损害呈正相关[53]。荟萃分析显示，在疾病急性期(BD 躁狂/抑郁发作)患者血清 S100 β 水平较健康对照组显著升高，在缓解期趋于正常，提示 S100 β 可能是心境障碍急性期的潜在生物标志物[54]。躁狂/轻躁狂症状的长期累积负担已被证实与内皮功能异常相关[55]。临床研究显示，BD 患者的心血管死亡风险显著增加，且躁狂/轻躁狂症状负荷是这一死亡风险的独立预测因素[56]。另外，Zetterberg 等人发现，BD 患者(尤其是 BD-I 型)的 QAlb 显著高于健康对照者和 BD-II 型患者。尽管抗精神病药物治疗可能是 QAlb 升高的驱动因素，但研究仍无法排除疾病本身的影响[57]。综合现有证据，BD 患者的 BBB 功能障碍可能同时涉及长期稳定性异常(如 QAlb 升高)和急性期动态变化(如 S100 β 水平随发作状态波动) [58]。

4.2. 双相情感障碍中 BBB 屏障功能障碍的分子机制

Lizano 等通过诱导多能干细胞分化的 BMEC 模型首次证实，部分 BD 患者存在 BMEC 固有功能缺陷，表现为屏障完整性破坏及小分子通透性增加，这些异常与 MMP-1 活性升高显著相关[59]。值得注意的是，与抑郁症和 SCZ 患者主要表现为海马区 Claudin-5 表达下调不同，BD 患者的 Claudin-5 水平与发病年龄呈正相关，与病程呈负相关。BD 组表现为海马区血管密度呈非显著性增加，眶额皮质血管直径显著增大，提示其 BBB 异常可能伴随血管形态变化[28]。与脑实质内的变化不同，血清 Zonulin 和 Claudin-5 水平升高被发现独立于疾病分期(躁狂或缓解)持续存在[60]。除了 TJ 的变化外，研究发现超过 50% 的 BD 患者存在胰岛素抵抗(insulin resistance, IR)，且 IR 与 BBB 通透性增加相关[9] [51]。在神经炎症机制方面，研究显示，BD 患者在首次躁狂发作时，ICAM、VCAM 水平显著高于疾病缓解期及健康人群，且缓解期时分子水平可恢复至正常范围[61]。此外，BD 患者血清 IL-6 水平显著升高，TNF- α 水平呈现非显著性升高趋势[62]，提示外周炎症因子可能透过 BBB 侵入 CNS，参与神经炎症相关病理过程。ZhuY 等人发现 BD 高炎症亚组存在血管生成素 2 (ANGPT2)翻译后调控失调的血管生成素信号通路紊乱现象，与异常的星形胶质细胞一起导致 BBB 稳定性下降，而炎症驱动的纤溶酶原激活物抑制因子 1 (SERPINE1) 上调可促进血管重塑、免疫细胞浸润等，会进一步加重 BBB 损伤[52]。

5. SCZ、MDD、BD 三种精神疾病 BBB 功能障碍现有研究对比

通过整合现有临床研究、动物模型实验及分子机制研究结果，三种精神疾病均存在 BBB 功能障碍，但不同疾病 BBB 的病理生理特征存在差异。Claudin-5 作为 BBB 屏障功能的核心分子，在 SCZ、MDD、BD 中均存在表达或功能异常，是介导 BBB 通透性增加的共同关键因子。另一方面，现有研究发现 SCZ 与 MDD 患者均主要表现为脑内 Claudin-5 表达降低，而 BD 患者脑内 Claudin-5 表达与发病年龄、病程

相关，血清水平持续升高。此外，IL-6、TNF- α 等促炎细胞因子及 sICAM-1、sVCAM-1 等免疫粘附分子在三类疾病中均有不同程度上调，提示免疫激活与神经炎症是 BBB 功能障碍的共同驱动因素。在 BBB 功能标志物方面，S100 β 均与病情严重程度或病程相关；QAlb 在 SCZ、MDD 中与病程/病情相关，在 BD 中虽升高，但可能受抗精神病药物影响，二者均可作为反映 BBB 损伤的共性指标。三类疾病中 BBB 功能障碍的已有研究对比如表 1 所示。

Table 1. Comparison of BBB dysfunction among three psychiatry diseases including SCZ, MDD and BD
表 1. SCZ、MDD、BD 三种精神疾病 BBB 功能障碍的研究对比

对比维度	精神分裂症	抑郁症	双相情感障碍
BBB 通透性变化	显著升高，与疾病持续时间和 PANSS 评分呈正相关	普遍升高，呈脑区特异性，受应激类型、性别及应激适应性调控	急性期显著升高，伴随长期稳定性异常
脑区	丘脑、前额叶皮层、视觉皮层	前额叶皮层、海马、伏隔核、杏仁核	海马、眶额皮质
病理生理机制	NVU 失调、Claudin-5 磷酸化降解、VEGF 信号通路局部失调、MMP-9 升高、免疫激活	TJ 蛋白损伤、星形胶质细胞终足功能异常、VEGFR2 通路激活、GLUT1 甲基化异常、TNF α /NF κ B 通路激活、表观遗传调控	BMEC 固有缺陷、Claudin-5 表达异常、胰岛素抵抗、炎症驱动的血管重塑、ANGPT2 信号紊乱、ICAM/VCAM 及 IL-6 介导的神经炎症
证据类型	临床影像学、临床研究、荟萃分析、转录组学、动物模型实验	临床尸检、临床研究、荟萃分析、动物模型实验	临床影像学、临床研究

6. 总结

BBB 是维持 CNS 稳态的关键结构，虽然其结构和生理功能已经得到系统研究，但在精神疾病发生发展过程中的作用仍在很大程度上未知。现有的研究揭示了在多种精神疾病的患者和动物模型上存在 BBB 结构破坏，通透性增高和物质转运功能障碍。TJ 蛋白家族成员的基因变异和动态调控机制紊乱，NVU 失调和神经炎症反应是多种精神疾病病理生理机制的共同特征。此外，BBB 的损伤与病情严重程度相关，可能先于或加重精神疾病的进展。靶向 BBB 的保护或修复可能成为治疗精神疾病的新方向，未来需进一步探索在不同精神疾病中 BBB 功能障碍的分子机制和临床转化潜力。

基金项目

国家自然科学基金青年基金(Grant No.31600827)。

参考文献

[1] Iadecola, C. (2017) The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. *Neuron*, **96**, 17-42. <https://doi.org/10.1016/j.neuron.2017.07.030>

[2] Harrison, P.J., Geddes, J.R. and Tunbridge, E.M. (2018) The Emerging Neurobiology of Bipolar Disorder. *Trends in Neurosciences*, **41**, 18-30. <https://doi.org/10.1016/j.tins.2017.10.006>

[3] Simpson, J.E. (2023) Potential Mechanisms Underlying the Dysfunction of the Blood-Brain Barrier. *International Journal of Molecular Sciences*, **24**, Article No. 8184. <https://doi.org/10.3390/ijms24098184>

[4] Bora, E. (2014) Neurodevelopmental Origin of Cognitive Impairment in Schizophrenia. *Psychological Medicine*, **45**, 1-9. <https://doi.org/10.1017/s0033291714001263>

[5] Hjorthøj, C., Stürup, A.E., McGrath, J.J. and Nordentoft, M. (2017) Years of Potential Life Lost and Life Expectancy in

- Schizophrenia: A Systematic Review and Meta-Analysis. *The Lancet Psychiatry*, **4**, 295-301. [https://doi.org/10.1016/s2215-0366\(17\)30078-0](https://doi.org/10.1016/s2215-0366(17)30078-0)
- [6] Puvogel, S., Palma, V. and Sommer, I.E.C. (2022) Brain Vasculature Disturbance in Schizophrenia. *Current Opinion in Psychiatry*, **35**, 146-156. <https://doi.org/10.1097/ycp.0000000000000789>
 - [7] Najjar, S., Pahlajani, S., De Sanctis, V., Stern, J.N.H., Najjar, A. and Chong, D. (2017) Neurovascular Unit Dysfunction and Blood-Brain Barrier Hyperpermeability Contribute to Schizophrenia Neurobiology: A Theoretical Integration of Clinical and Experimental Evidence. *Frontiers in Psychiatry*, **8**, Article No. 83. <https://doi.org/10.3389/fpsy.2017.00083>
 - [8] Stanca, S., Rossetti, M., Bokulic Panichi, L. and Bongioanni, P. (2024) The Cellular Dysfunction of the Brain-Blood Barrier from Endothelial Cells to Astrocytes: The Pathway towards Neurotransmitter Impairment in Schizophrenia. *International Journal of Molecular Sciences*, **25**, Article No. 1250. <https://doi.org/10.3390/ijms25021250>
 - [9] Cheng, Y., Wang, T., Zhang, T., Yi, S., Zhao, S., Li, N., *et al.* (2022) Increased Blood-Brain Barrier Permeability of the Thalamus Correlated with Symptom Severity and Brain Volume Alterations in Patients with Schizophrenia. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, **7**, 1025-1034. <https://doi.org/10.1016/j.bpsc.2022.06.006>
 - [10] Futtrup, J., Margolinsky, R., Benros, M.E., Moos, T., Routhé, L.J., Rungby, J., *et al.* (2020) Blood-Brain Barrier Pathology in Patients with Severe Mental Disorders: A Systematic Review and Meta-Analysis of Biomarkers in Case-Control Studies. *Brain, Behavior, & Immunity—Health*, **6**, Article ID: 100102. <https://doi.org/10.1016/j.bbih.2020.100102>
 - [11] Uranova, N.A., Zimina, I.S., Vikhрева, O.V., Krukov, N.O., Rachmanova, V.I. and Orlovskaya, D.D. (2010) Ultrastructural Damage of Capillaries in the Neocortex in Schizophrenia. *The World Journal of Biological Psychiatry*, **11**, 567-578. <https://doi.org/10.3109/15622970903414188>
 - [12] Katsel, P., Roussos, P., Pletnikov, M. and Haroutunian, V. (2017) Microvascular Anomaly Conditions in Psychiatric Disease. Schizophrenia—Angiogenesis Connection. *Neuroscience & Biobehavioral Reviews*, **77**, 327-339. <https://doi.org/10.1016/j.neubiorev.2017.04.003>
 - [13] Enwright III, J.F., Huo, Z., Arion, D., Corradi, J.P., Tseng, G. and Lewis, D.A. (2017) Transcriptome Alterations of Prefrontal Cortical Parvalbumin Neurons in Schizophrenia. *Molecular Psychiatry*, **23**, 1606-1613. <https://doi.org/10.1038/mp.2017.216>
 - [14] Argaw, A.T., Gurfein, B.T., Zhang, Y., Zameer, A. and John, G.R. (2009) Vegf-Mediated Disruption of Endothelial CLN-5 Promotes Blood-Brain Barrier Breakdown. *Proceedings of the National Academy of Sciences*, **106**, 1977-1982. <https://doi.org/10.1073/pnas.0808698106>
 - [15] Fulzele, S. and Pillai, A. (2009) Decreased VEGF mRNA Expression in the Dorsolateral Prefrontal Cortex of Schizophrenia Subjects. *Schizophrenia Research*, **115**, 372-373. <https://doi.org/10.1016/j.schres.2009.06.005>
 - [16] Pillai, A., Howell, K.R., Ahmed, A.O., Weinberg, D., Allen, K.M., Bruggemann, J., *et al.* (2015) Association of Serum VEGF Levels with Prefrontal Cortex Volume in Schizophrenia. *Molecular Psychiatry*, **21**, 686-692. <https://doi.org/10.1038/mp.2015.96>
 - [17] Meixensberger, S., Kuzior, H., Fiebich, B.L., Süß, P., Runge, K., Berger, B., *et al.* (2021) Upregulation of sICAM-1 and sVCAM-1 Levels in the Cerebrospinal Fluid of Patients with Schizophrenia Spectrum Disorders. *Diagnostics*, **11**, Article No. 1134. <https://doi.org/10.3390/diagnostics11071134>
 - [18] Yamamori, H., Hashimoto, R., Ishima, T., Kishi, F., Yasuda, Y., Ohi, K., *et al.* (2013) Plasma Levels of Mature Brain-Derived Neurotrophic Factor (BDNF) and Matrix Metalloproteinase-9 (MMP-9) in Treatment-Resistant Schizophrenia Treated with Clozapine. *Neuroscience Letters*, **556**, 37-41. <https://doi.org/10.1016/j.neulet.2013.09.059>
 - [19] Nie, F., Jin, R., Wu, S., Yuan, W., Wu, Y., Xue, S., *et al.* (2024) AQP4 Is Upregulated in Schizophrenia and Its Inhibition Attenuates Mk-801-Induced Schizophrenia-Like Behaviors in Mice. *Behavioural Brain Research*, **475**, Article ID: 115220. <https://doi.org/10.1016/j.bbr.2024.115220>
 - [20] Gur, R.E., Bassett, A.S., McDonald-McGinn, D.M., Bearden, C.E., Chow, E., Emanuel, B.S., *et al.* (2017) A Neurogenetic Model for the Study of Schizophrenia Spectrum Disorders: The International 22q11.2 Deletion Syndrome Brain Behavior Consortium. *Molecular Psychiatry*, **22**, 1664-1672. <https://doi.org/10.1038/mp.2017.161>
 - [21] Crockett, A.M., Ryan, S.K., Vásquez, A.H., Canning, C., Kanyuch, N., Kebir, H., *et al.* (2021) Disruption of the Blood-brain Barrier in 22q11.2 Deletion Syndrome. *Brain*, **144**, 1351-1360. <https://doi.org/10.1093/brain/awab055>
 - [22] Greene, C., Kealy, J., Humphries, M.M., Gong, Y., Hou, J., Hudson, N., *et al.* (2017) Dose-Dependent Expression of Claudin-5 Is a Modifying Factor in Schizophrenia. *Molecular Psychiatry*, **23**, 2156-2166. <https://doi.org/10.1038/mp.2017.156>
 - [23] Nishiura, K., Ichikawa-Tomikawa, N., Sugimoto, K., Kunii, Y., Kashiwagi, K., Tanaka, M., *et al.* (2017) PKA Activation and Endothelial Claudin-5 Breakdown in the Schizophrenic Prefrontal Cortex. *Oncotarget*, **8**, 93382-93391. <https://doi.org/10.18632/oncotarget.21850>
 - [24] Sugimoto, K., Ichikawa-Tomikawa, N., Nishiura, K., Kunii, Y., Sano, Y., Shimizu, F., *et al.* (2020) Serotonin/5-HT1A Signaling in the Neurovascular Unit Regulates Endothelial CLDN5 Expression. *International Journal of Molecular*

- Sciences, 22, Article No. 254. <https://doi.org/10.3390/ijms22010254>
- [25] Koblan, K.S., Kent, J., Hopkins, S.C., Krystal, J.H., Cheng, H., Goldman, R., *et al.* (2020) A Non-D2-Receptor-Binding Drug for the Treatment of Schizophrenia. *New England Journal of Medicine*, **382**, 1497-1506. <https://doi.org/10.1056/nejmoa1911772>
- [26] Alexopoulos, G.S. (2005) Depression in the Elderly. *The Lancet*, **365**, 1961-1970. [https://doi.org/10.1016/s0140-6736\(05\)66665-2](https://doi.org/10.1016/s0140-6736(05)66665-2)
- [27] Ménard, C., Pfau, M.L., Hodes, G.E. and Russo, S.J. (2016) Immune and Neuroendocrine Mechanisms of Stress Vulnerability and Resilience. *Neuropsychopharmacology*, **42**, 62-80. <https://doi.org/10.1038/npp.2016.90>
- [28] Greene, C., Hanley, N. and Campbell, M. (2020) Blood-Brain Barrier Associated Tight Junction Disruption Is a Hallmark Feature of Major Psychiatric Disorders. *Translational Psychiatry*, **10**, Article No. 373. <https://doi.org/10.1038/s41398-020-01054-3>
- [29] Menard, C., Pfau, M.L., Hodes, G.E., Kana, V., Wang, V.X., Bouchard, S., *et al.* (2017) Social Stress Induces Neurovascular Pathology Promoting Depression. *Nature Neuroscience*, **20**, 1752-1760. <https://doi.org/10.1038/s41593-017-0010-3>
- [30] Dudek, K.A., Dion-Albert, L., Lebel, M., LeClair, K., Labrecque, S., Tuck, E., *et al.* (2020) Molecular Adaptations of the Blood-Brain Barrier Promote Stress Resilience vs. Depression. *Proceedings of the National Academy of Sciences*, **117**, 3326-3336. <https://doi.org/10.1073/pnas.1914655117>
- [31] Zheng, P., Romme, E., Spek, P.J.v.d., Dirven, C.M.F., Willemsen, R. and Kros, J.M. (2010) Glut1/SLC2A1 Is Crucial for the Development of the Blood-Brain Barrier in Vivo. *Annals of Neurology*, **68**, 835-844. <https://doi.org/10.1002/ana.22318>
- [32] Kahl, K.G., Georgi, K., Bleich, S., Muschler, M., Hillemacher, T., Hilfiker-Kleinert, D., *et al.* (2016) Altered DNA Methylation of Glucose Transporter 1 and Glucose Transporter 4 in Patients with Major Depressive Disorder. *Journal of Psychiatric Research*, **76**, 66-73. <https://doi.org/10.1016/j.jpsychires.2016.02.002>
- [33] Cobb, J.A., O'Neill, K., Milner, J., Mahajan, G.J., Lawrence, T.J., May, W.L., *et al.* (2016) Density of GFAP-Immunoreactive Astrocytes Is Decreased in Left Hippocampi in Major Depressive Disorder. *Neuroscience*, **316**, 209-220. <https://doi.org/10.1016/j.neuroscience.2015.12.044>
- [34] Rajkowska, G., Hughes, J., Stockmeier, C.A., Javier Miguel-Hidalgo, J. and Maciag, D. (2013) Coverage of Blood Vessels by Astrocytic Endfeet Is Reduced in Major Depressive Disorder. *Biological Psychiatry*, **73**, 613-621. <https://doi.org/10.1016/j.biopsych.2012.09.024>
- [35] van Agtmaal, M.J.M., Houben, A.J.H.M., Pouwer, F., Stehouwer, C.D.A. and Schram, M.T. (2017) Association of Microvascular Dysfunction with Late-Life Depression: A Systematic Review and Meta-Analysis. *JAMA Psychiatry*, **74**, 729-739. <https://doi.org/10.1001/jamapsychiatry.2017.0984>
- [36] Shi, W., Zhang, S., Yao, K., Meng, Q., Lu, Y., Ren, Y., *et al.* (2024) Breakdown of the Blood-Brain Barrier in Depressed Mice Induced by Chronic Unpredictable Mild Stress. *Journal of Psychiatric Research*, **180**, 138-146. <https://doi.org/10.1016/j.jpsychires.2024.10.004>
- [37] Sántha, P., Veszelska, S., Hoyk, Z., Mészáros, M., Walter, F.R., Tóth, A.E., *et al.* (2016) Restraint Stress-Induced Morphological Changes at the Blood-Brain Barrier in Adult Rats. *Frontiers in Molecular Neuroscience*, **8**, Article No. 88. <https://doi.org/10.3389/fnmol.2015.00088>
- [38] Xu, G., Li, Y., Ma, C., Wang, C., Sun, Z., Shen, Y., *et al.* (2019) Restraint Stress Induced Hyperpermeability and Damage of the Blood-Brain Barrier in the Amygdala of Adult Rats. *Frontiers in Molecular Neuroscience*, **12**, Article No. 32. <https://doi.org/10.3389/fnmol.2019.00032>
- [39] Matsuno, H., Tsuchimine, S., O'Hashi, K., Sakai, K., Hattori, K., Hidese, S., *et al.* (2022) Association between Vascular Endothelial Growth Factor-Mediated Blood-Brain Barrier Dysfunction and Stress-Induced Depression. *Molecular Psychiatry*, **27**, 3822-3832. <https://doi.org/10.1038/s41380-022-01618-3>
- [40] Treccani, G., Schlegelmilch, A., Schultz, N., Herzog, D.P., Bessa, J.M., Sotiropoulos, I., *et al.* (2020) Hippocampal NG²⁺ Pericytes in Chronically Stressed Rats and Depressed Patients: A Quantitative Study. *Stress*, **24**, 353-358. <https://doi.org/10.1080/10253890.2020.1781083>
- [41] Almeida, P.G.C., Nani, J.V., Osés, J.P., Brietzke, E. and Hayashi, M.A.F. (2020) Neuroinflammation and Glial Cell Activation in Mental Disorders. *Brain, Behavior, & Immunity—Health*, **2**, Article ID: 100034. <https://doi.org/10.1016/j.bbih.2019.100034>
- [42] Zhao, D., Wu, Y., Zhao, H., Zhang, F., Wang, J., Liu, Y., *et al.* (2024) Midbrain FA Initiates Neuroinflammation and Depression Onset in both Acute and Chronic LPS-Induced Depressive Model Mice. *Brain, Behavior, and Immunity*, **117**, 356-375. <https://doi.org/10.1016/j.bbi.2024.02.004>
- [43] Li, T., Zheng, L. and Han, X. (2020) Fenretinide Attenuates Lipopolysaccharide (LPS)-Induced Blood-Brain Barrier (BBB) and Depressive-Like Behavior in Mice by Targeting Nrf-2 Signaling. *Biomedicine & Pharmacotherapy*, **125**, Article

- ID: 109680. <https://doi.org/10.1016/j.biopha.2019.109680>
- [44] Liu, X., Liu, H., Wu, X., Zhao, Z., Wang, S., Wang, H., *et al.* (2024) Xiaoyaosan against Depression through Suppressing LPS Mediated TLR4/NLRP3 Signaling Pathway in “Microbiota-Gut-Brain” Axis. *Journal of Ethnopharmacology*, **335**, Article ID: 118683. <https://doi.org/10.1016/j.jep.2024.118683>
 - [45] Kessler, R. (1993) Sex and Depression in the National Comorbidity Survey I: Lifetime Prevalence, Chronicity and Recurrence. *Journal of Affective Disorders*, **29**, 85-96. [https://doi.org/10.1016/0165-0327\(93\)90026-g](https://doi.org/10.1016/0165-0327(93)90026-g)
 - [46] Dion-Albert, L., Cadoret, A., Doney, E., Kaufmann, F.N., Dudek, K.A., Daigle, B., *et al.* (2022) Vascular and Blood-brain Barrier-Related Changes Underlie Stress Responses and Resilience in Female Mice and Depression in Human Tissue. *Nature Communications*, **13**, Article No. 164.
 - [47] Carvalho, A.F., Firth, J. and Vieta, E. (2020) Bipolar Disorder. *New England Journal of Medicine*, **383**, 58-66. <https://doi.org/10.1056/nejmra1906193>
 - [48] Kessing, L.V., Ziersen, S.C., Andersen, P.K. and Vinberg, M. (2021) A Nation-Wide Population-Based Longitudinal Study on Life Expectancy and Cause Specific Mortality in Patients with Bipolar Disorder and Their Siblings. *Journal of Affective Disorders*, **294**, 472-476. <https://doi.org/10.1016/j.jad.2021.07.065>
 - [49] Fries, G.R., Walss-Bass, C., Bauer, M.E. and Teixeira, A.L. (2019) Revisiting Inflammation in Bipolar Disorder. *Pharmacology Biochemistry and Behavior*, **177**, 12-19. <https://doi.org/10.1016/j.pbb.2018.12.006>
 - [50] Barbosa, I.G., Bauer, M.E., Machado-Vieira, R. and Teixeira, A.L. (2014) Cytokines in Bipolar Disorder: Paving the Way for Neuroprogression. *Neural Plasticity*, **2014**, Article ID: 360481. <https://doi.org/10.1155/2014/360481>
 - [51] Calkin, C., McClelland, C., Cairns, K., Kamintsky, L. and Friedman, A. (2021) Insulin Resistance and Blood-Brain Barrier Dysfunction Underlie Neuroprogression in Bipolar Disorder. *Frontiers in Psychiatry*, **12**, Article ID: 636174. <https://doi.org/10.3389/fpsyt.2021.636174>
 - [52] Zhu, Y., Webster, M.J., Mendez Victoriano, G., Middleton, F.A., Massa, P.T. and Weickert, C.S. (2024) Molecular Evidence for Altered Angiogenesis in Neuroinflammation-Associated Schizophrenia and Bipolar Disorder Implicate an Abnormal Midbrain Blood-Brain Barrier. *Schizophrenia Bulletin*, **51**, 1146-1161. <https://doi.org/10.1093/schbul/sbae184>
 - [53] Kamintsky, L., Cairns, K.A., Veksler, R., Bowen, C., Beyea, S.D., Friedman, A., *et al.* (2020) Blood-Brain Barrier Imaging as a Potential Biomarker for Bipolar Disorder Progression. *NeuroImage: Clinical*, **26**, Article ID: 102049. <https://doi.org/10.1016/j.nicl.2019.102049>
 - [54] Schroeter, M.L., Abdul-Khaliq, H., Krebs, M., Diefenbacher, A. and Blasig, I.E. (2008) Serum Markers Support Disease-Specific Glial Pathology in Major Depression. *Journal of Affective Disorders*, **111**, 271-280. <https://doi.org/10.1016/j.jad.2008.03.005>
 - [55] Fiedorowicz, J.G., Coryell, W.H., Rice, J.P., Warren, L.L. and Haynes, W.G. (2012) Vasculopathy Related to Manic/Hypomanic Symptom Burden and First-Generation Antipsychotics in a Sub-Sample from the Collaborative Depression Study. *Psychotherapy and Psychosomatics*, **81**, 235-243. <https://doi.org/10.1159/000334779>
 - [56] Fiedorowicz, J.G., Solomon, D.A., Endicott, J., Leon, A.C., Li, C., Rice, J.P., *et al.* (2009) Manic/Hypomanic Symptom Burden and Cardiovascular Mortality in Bipolar Disorder. *Psychosomatic Medicine*, **71**, 598-606. <https://doi.org/10.1097/psy.0b013e3181acee26>
 - [57] Zetterberg, H., Jakobsson, J., Redsäter, M., Andreasson, U., Pålsson, E., Ekman, C.J., *et al.* (2014) Blood-Cerebrospinal Fluid Barrier Dysfunction in Patients with Bipolar Disorder in Relation to Antipsychotic Treatment. *Psychiatry Research*, **217**, 143-146. <https://doi.org/10.1016/j.psychres.2014.03.045>
 - [58] Wakonigg Alonso, C., McElhatton, F., O'Mahony, B., Campbell, M., Pollak, T.A. and Stokes, P.R.A. (2024) The Blood-Brain Barrier in Bipolar Disorders: A Systematic Review. *Journal of Affective Disorders*, **361**, 434-444. <https://doi.org/10.1016/j.jad.2024.06.032>
 - [59] Lizano, P., Pong, S., Santarriaga, S., Bannai, D. and Karmacharya, R. (2023) Brain Microvascular Endothelial Cells and Blood-Brain Barrier Dysfunction in Psychotic Disorders. *Molecular Psychiatry*, **28**, 3698-3708. <https://doi.org/10.1038/s41380-023-02255-0>
 - [60] Kılıç, F., Işık, Ü., Demirdaş, A., Doğuç, D.K. and Bozkurt, M. (2020) Serum Zonulin and Claudin-5 Levels in Patients with Bipolar Disorder. *Journal of Affective Disorders*, **266**, 37-42. <https://doi.org/10.1016/j.jad.2020.01.117>
 - [61] Turan, Ç., Kesebir, S. and Süner, Ö. (2014) Are ICAM, VCAM and E-Selectin Levels Different in First Manic Episode and Subsequent Remission? *Journal of Affective Disorders*, **163**, 76-80. <https://doi.org/10.1016/j.jad.2014.03.052>
 - [62] Hochman, E., Taler, M., Flug, R., Gur, S., Dar, S., Bormant, G., *et al.* (2023) Serum Claudin-5 Levels among Patients with Unipolar and Bipolar Depression in Relation to the Pro-Inflammatory Cytokine Tumor Necrosis Factor-Alpha Levels. *Brain, Behavior, and Immunity*, **109**, 162-167. <https://doi.org/10.1016/j.bbi.2023.01.015>