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酒精滥用对阿尔茨海默病发病机制雏探

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摘　要

阿尔茨海默病(Alzheimer disease, AD)是一种神经退行性疾病，主要表现为认知障碍。酒作为日常饮品虽能给人体带来益处，但过度饮酒将损害机体健康，目前研究成果展示由于酒精滥用会增加患AD的风险。为了探讨酒精对AD的作用机制，本文将通过AD的发病机制与酒精滥用对机体产生的危害进一步阐明酒精滥用对AD的影响。结果显示，酒精滥用将会导致机体产生炎症和氧化应激，而氧化应激又将进一步加重机体的炎症反应。此外，酒精滥用还会危害人体肠道微生物的数量及比例分布等，进而导致微生物生态失衡，不仅如此，肠道微生物还因酒精滥用导致炎症，这也将进一步危害机体的健康。又因氧化应激、炎症反应等又会加快AD的发病，所以由酒精滥用引起的氧化应激、炎症反应、肠道微生物失调等因素也能促进AD的发展。因此，控制酒精的摄取可能会在一定程度上减缓AD的发病，起到预防AD的作用。

关键词

阿尔茨海默，酒精，氧化应激，炎症

A Preliminary Study on the Mechanism of Alcohol Abuse in Alzheimer's Disease

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Abstract

Alzheimer disease (AD) is a neurodegenerative disease, mainly manifested as cognitive impair-

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ment. Although alcohol as a daily drink can bring benefits to the human body, excessive drinking will damage the health of the body. The current research results show that alcohol abuse will increase the risk of AD. In order to explore the action mechanism of alcohol on AD, this article will further clarify the impact of alcohol abuse on AD through the pathogenesis of AD and the harm of alcohol abuse on the body. The results show that alcohol abuse will lead to inflammation and oxidative stress in the body, and oxidative stress will further aggravate the inflammatory reaction of the body. In addition, alcohol abuse will also harm the number and proportion of human intestinal microorganisms, which will lead to the imbalance of microbial ecology. In addition, intestinal microorganisms will also cause inflammation due to alcohol abuse, which will further endanger the health of the body. Because oxidative stress and inflammatory reaction will accelerate the onset of AD, factors such as oxidative stress, inflammatory reaction and intestinal microbial imbalance caused by alcohol abuse can also promote the development of AD. Therefore, controlling alcohol intake may slow down the onset of AD to a certain extent and play a role in preventing AD.

Keywords

Alzheimer's Disease, Alcohol, Oxidative Stress, Inflammation

1. 引言

随着人口老龄化，老年人的健康问题逐渐成为人们关注的焦点。AD 是最常见的神经退行性疾病。随着预期寿命的不断增加，认知障碍和全球 AD 负担正在增加。目前估计全世界有超过 5500 万人患有失智症，每 3 秒就有 1 例新发病例，预计到 2050 年，受影响的人数将增加到 1.39 亿[1]。对于 AD 这种神经退行性疾病过程的典型特征是两种标志性病理：淀粉样蛋白(Amyloid-beta, Aβ)斑块沉积和超磷酸化和 Tau 蛋白的神经原纤维缠结(neurofibrillary tangle, NFT) [2]。Aβ 和 tau 聚集会导致毒性聚集物(可溶性低聚物)，有效抑制聚集的早期步骤可能会阻止 AD 的进展[3]。AD 的特征是持续的神经炎症导致记忆力减退和认知能力下降，近期发现酒精滥用对于 AD 的发病也有着密切联系。在过去的几十年里，已有研究表明，饮酒会导致包括肝脏、肠道和大脑在内的重要器官过度炎症[4]，此外，酒精诱导的中枢神经系统(central nervous system, CNS)先天免疫激活已被证明可以介导神经毒性和乙醇诱导的行为，包括临床前和临床环境中的酒精成瘾和认知能力下降[5]。因此长期和大量饮酒会加速大脑衰老，并增加失智的风险，尤其是增加患 AD 的风险[6]。饮酒广泛存在，且是促进神经退行性疾病的环境因素之一。大脑是酒精行为的主要目标，长期以来，大量饮酒与脑损伤有关。长期饮酒会导致谷氨酸引起的兴奋性毒性、氧化应激和与营养不良相关的永久性神经元损伤[7]。因此饮酒会影响 AD 的发病进程，本文将通过探讨酒精对 AD 的关系展开综述。

2. AD 的发病机制

2.1. Aβ 假说

Aβ 发病机制始于淀粉样蛋白前体蛋白(Amyloid precursor protein, APP)通过 β 分泌酶和 γ 分泌酶改变切割，产生不溶性 Aβ 原纤维。然后 Aβ 寡聚化，扩散到突触裂隙中，并干扰突触信号传导[8]。Aβ 寡聚物是最具神经毒性的聚集物，通过导致功能性神经元死亡、认知损伤和失智，并在 AD 的发生和发展中

发挥关键作用[9]。此外，老化、氧化应激和基因突变等因素会破坏 Aβ 内稳态，导致 Aβ 积聚和聚集，形成低聚物和纤维，以及脑内斑块沉积[10]。这也将进一步加快 AD 的发病。“淀粉样蛋白级联假说”在过去 25 年中主导了 AD 领域。该假说认为 Aβ 的增加是 AD 中触发 Tau 病理学的关键事件，然后是神经元死亡，最终是疾病[11]。淀粉样蛋白假说的核心，即 Aβ 是 AD 的原因[12]。

2.2. Tau 蛋白假说

Tau 是一种轴突微管相关蛋白，具有众所周知的促进微管蛋白聚合成微管，稳定微管结构和维持神经元功能的功能[13]。微管是在内部支持神经元的结构，有助于将营养物质和分子从细胞引导到轴突和树突[14]。每当这些微管形成时，其长度可以延长也可以收缩，进而导致微管分崩离析。微管分崩离析的过程被称为微管灾难[15]。在非 AD 大脑中，Tau 蛋白在其磷酸化状态下将微管稳定在任何长度，并防止微管灾难[16]。AD 患者认知功能下降、突触和神经元丢失的程度与 Tau 病理学密切相关。使用氟哌啶标记 AD 患者脑组织的 PET 成像显示，脑萎缩最严重的部位正是 Tau 的集中部位[17]。因此正确的 Tau 亚型比例对于维持脑细胞稳态和预防神经退行性疾病是必要的[18]。Tau 蛋白的过度磷酸化被认为是 AD 神经病变和认知障碍的来源[19]。Tau 蛋白假说指出，AD 的进展和发展也是由于称为 Tau 的蛋白质的聚集，而 Tau 的异常积累称为 NFT，聚集在神经元内部[15]，进而造成 AD。因为过度磷酸化导致 Tau 蛋白对微管的亲和力降低，并且过度磷酸化的 Tau 形成 NFT 并沉积在细胞质中，不能再执行维持细胞结构的功能。并且这种沉积会影响正常的细胞功能，如突触传递、轴突运输、信号转导，细胞逐渐变性[20]。

2.3. 神经炎症

神经炎症由炎症小体复合物介导，炎症小体复合体是一种多蛋白复合物，可感知病原体和危险信号，导致前炎性 IL-1β 和 IL-18 的分解和释放[21]。神经炎症在 AD 的发病机制中起核心作用，急性炎症在防御脑损伤方面具有保护作用。然而，小胶质细胞的持续激活使其无法去除斑块，但其释放促炎细胞因子的能力得以保留，导致促炎细胞因子和抗炎细胞因子之间的不平衡[22]。进而导致 AD 的发生。在淀粉样斑块沉积时，小胶质细胞被募集到吞噬酶并在内溶酶体途径内处理 Aβ [23]。并且 Aβ 本身是小胶质细胞活化和神经炎症的诱导剂，被认为是 AD 发展的潜在和统一因素，在 Aβ 积累，活化的小胶质细胞和小胶质细胞炎症介质之间形成了炎症的恶性循环，并增强了 Aβ 的沉积和神经炎症[24]。神经胶质细胞是 CNS 的非兴奋细胞。这些细胞是一个高度异质的群体，负责许多重要的大脑功能[25]。并且对任何类型的脑损伤都有反应被激活，产生广泛的促炎或抗炎介质[26]。所以神经胶质细胞与神经炎症有莫大的联系，进而对 AD 产生影响。越来越多的证据表明 AD 炎症机制的复杂性，以及这些机制如何通常由神经胶质细胞功能的改变驱动[27]。并且炎症反应会伴随着 AD 发生、发展的各个阶段，炎症反应机制与 Aβ、Tau 等机制有着密切的联系，会共同损伤神经系统，进而促进 AD 病情的加深。

3. 酒精的危害

3.1. 酒精与神经炎症的关系

酒精会引起多个器官的炎症反应，包括肠道、肝脏、胰腺和大脑[28]。其中神经炎症是慢性饮酒的标志性影响之一[29]。酒精暴露在大脑中产生促炎环境，导致细胞因子和趋化因子等免疫配体上调。这导致了小胶质细胞上免疫受体的激活，持续的转录组改变，结构可塑性，以及几种可以改变神经元功能的炎症介质的产生[29]。激活的小胶质细胞释放炎症因子刺激一种亚型星形胶质细胞分泌神经毒性因子，这被认为是几种人类神经退行性疾病的常见机制[30]。此外，酒精也是全身免疫信号传导的已知调节剂，并扰

乱几种免疫相关基因的表达[31]。小胶质细胞在感知和响应酒精摄入方面起着关键作用，并参与多种免疫信号通路[32]。酒精诱导的神经免疫激活的一个主要成分是脑内细胞因子的表达增加，包括 IL-1β、TNF-α、IL-6 和 CCL2 [21]。在机制水平上，酒精被认为主要通过 PRRs-TLR4 和 NLRP3 介导其免疫激活，这两者都主要在 CNS 的小胶质细胞中表达[33]。TLR4 是 toll 样受体家族的成员，是一种跨膜蛋白，主要通过 NF-kB 途径导致炎性细胞因子的产生来激活[34]。酒精滥用主要通过 TLR4、2 和 NLRP3 炎症小体导致小胶质细胞活化。因此，小胶质细胞显示出增殖，形态转化，细胞因子，趋化因子，EV 和免疫介质的释放，这将导致外周巨噬细胞浸润、神经毒性、突触丢失和乙醇诱导行为的调节[35]。而且已有实验证明酒精通过刺激神经胶质细胞中的 toll 样受体 4 信号传导来激活先天免疫系统，从而触发炎症介质的释放并引起神经炎症[36]。炎症损伤可能导致星形胶质细胞基因表达的离散或广泛改变，从而形成一个分级连续体，星形胶质细胞通过该连续体对中枢神经系统的各种病理状况作出反应[37]。此外星形胶质细胞结构复杂，有许多分支突起，可与血脑屏障(Blood Brain Barrier, BBB)、突触裂和其他胶质细胞进行功能性相互作用[38]。BBB 由脑血管内壁的特化内皮细胞组成，周围细胞和星形胶质细胞可以感知外周炎症并随后驱动脑实质中的神经炎症[39]。因此，内皮细胞和周细胞似乎介导酒精诱导的神经炎症机制[40]。且有研究表明，慢性酒精滥用导致全身炎症的增加，直接影响 BBB 的稳定性，并增加促炎介质流入脑实质[41]。这将进一步加快炎症作用对大脑的危害，促进 AD 的发展。此外，直接和间接酒精诱导的神经免疫反应，包括促炎细胞因子，对于酒精诱导的线粒体功能障碍与加速大脑衰老有关，并增加失智的风险，尤其会增加 AD 的发病概率[6]。

3.2. 酒精与肠道微生物的关系

人体肠道是一种厌氧生物反应器，具有多种微生物种群，包括细菌、酵母、古细菌、病毒、原生动物和蠕虫等寄生虫，统称为微生物群，且会占据胃肠道黏膜表面的不同生态位[42]。肠道微生物群通过调节小胶质细胞和星形胶质细胞的发育和功能，影响神经生理功能，包括神经发育、CNS 免疫激活和 BBB 完整性[43]。这些微生物组成和结构的变化可能通过释放炎性细胞因子和脂多糖、肠壁渗漏来促进肠道炎症，并可能影响对身体正常功能很重要的全身炎症和免疫机制。生态失调的这些神经毒性机制可能会增加对 AD 和其他神经退行性疾病的易感性[44]。肠道微生物组的减少与 CNS 和肠道中炎性体成分的表达增加有关[45]。并且肠道微生物群的失调会导致全身炎症、神经炎症、胰岛素抵抗，这些都与 AD 的发病机制有关[46]。越来越多的证据表明，酒精摄入会改变微生物群和微生物群－肠－脑轴[47]，因此酒精引起的微生物组改变可引起神经炎症并改变神经免疫功能的平衡。另一方面，过量的酒精与神经递质系统相互作用，增加 BBB 通透性，导致脑损伤和功能障碍，进而促进 AD 的发展[48]。大量证据表明，长期饮酒会导致肠道生物失调，从而导致酒精诱导的炎症和器官损伤[49]。然而肠道微生物群的促炎变化是饮酒的良好记录后果，这些变化包括被认为有益的细菌减少，同时增加的被认为是促炎的细菌[50]。并且有研究表明，微生物 Aβ 被证明能够激活 T 淋巴细胞并诱导促炎白细胞介素 IL-17A 和 IL-22 的产生。这些细胞因子能够穿透 BBB 并引起活性氧的产生，小胶质细胞和星形胶质细胞中 TLR2/1 和 NFB 信号通路的激活，而这与神经炎症和神经变性直接相关[51]。另外，酒精增加肠道通透性和细菌易位到外围[52]，诱导肝脏炎症反应，并促进促炎细胞因子的全身释放[53]。由于肠道通透性增加，导致酒精性肝病的肠道微生物群和及其产物的易位[54]。因此，过度饮酒导致肠道菌群失调和肠道通透性增加，且当酒精相关性肝病发生时，肠道微生物的数量和组成比例也会相应变化[55]。这时将会导致微生物生态失衡，进而影响 AD 发病进程。而且肠道微生物群在神经退行性疾病的发病机制中起重要作用，最近的研究表明，益生菌可以改善神经退行性疾病的症状，这表明胃肠道改变与 AD 的病因之间存在因果关系[56]。

3.3. 氧化应激

酒精代谢导致细胞应激、肝细胞损伤和肝脏中无菌危险信号的释放[57]。酒精通过直接作用增加氧化化学物质的产生或通过间接作用降低细胞的抗氧化能力来诱导氧化应激[58]。炎症是氧化应激最常见的结果之一，有人认为，氧化应激可能刺激趋化因子和细胞因子的表达[59]。如过量饮酒后，经历氧化应激诱导的细胞损伤和死亡的酒精暴露肝细胞会产生多种炎症介质，例如细胞因子、趋化因子和 DAMP，进而激活免疫反应和炎症[60]。DAMP 由 Toll 样受体和 NOD 样受体识别，后者在肝细胞和免疫细胞中表达[61]。AND 介导的这些受体激活可增强酒精性肝病中先天免疫相关炎症通路，同时增强细胞因子、趋化因子和粘附分子的表达，从而促进先天免疫细胞的浸润和/或活化[62]。此外，饮酒会增加 ROS 水平和脂质过氧化，促进丙二醛和 4-羟基壬烯醛蛋白质加合物的产生，丙二醛和 4-羟基壬烯醛可作为新抗原并激活 T 细胞和 B 细胞介导的适应性免疫[63]。此外，酒精代谢导致细胞内 NAD+/NADH 的比值发生变化。酒精的代谢主要分两步，首先，酒精脱氢酶将酒精转化为乙醛，乙醛是一种有毒的反应性分子。接下来，乙醛脱氢酶将乙醛转化为乙酸酯。每一个反应都会导致一个 NADH 分子的形成，从而提供更多的起始物质，从而增强呼吸链的活性，包括增强氧气的利用和 ROS 的形成[64]。因此又会造成对细胞的损害。酒精所导致的氧化应激在 AD 的发病机制中起着重要作用，并且大脑比其他器官更容易受到氧化应激的影响，神经元的大部分成分在 AD 中会因线粒体功能障碍、金属水平升高、炎症和 Aβ 肽而被氧化，所以酒精会间接导致 AD 的发展[65]。

4. 酒精滥用与 AD 的关系

4.1. 酒精对 AD 的影响

大量研究报告说，饮酒对健康有害，并导致认知缺陷和神经变性[66]，并增加患 AD 等神经退行性疾病的风险[67]。然而，越来越多的研究结果证明了低至中度饮酒具有神经保护作用，并降低与神经退行性疾病相关的风险[67]。乙醇浓度较低的酒精饮料，如啤酒，当以低或中等量服用时，可降低患 AD 的风险。啤酒中的嘌呤、烟酸、叶酸和其他酚类化合物等化合物被认为可以介导酒精的神经保护作用[68]。暴饮暴食，长期间歇性饮酒与酒精诱导的神经变性有关。同样，在人类中，饮用高乙醇含量的饮料与较高的认知能力下降率有关。鉴于上述证据表明神经炎症在 AD 中有作用，并且酒精会增加神经炎症，Aβ 病理学很可能通过共同途径直接或间接地受到酒精的影响[69]。酒精的间接全身效应可能直接导致小胶质细胞活化，并导致 Aβ 级联炎症过程的自我延续循环。这是由于小肠变化，肝脏变化和戒断效应以及由此产生的循环细胞因子释放和前列腺素和 iNOS 的内皮表达增加。通过循环细胞因子、前列腺素和一氧化氮对大脑的作用，这可能导致小胶质细胞活化和小胶质细胞倦怠，进一步驱动 Aβ 病理，并引起随后的神经炎症，最终导致神经元细胞死亡[69]。

4.2. 酒精滥用对大脑的危害

硫胺素，也称为维生素 B1，是对神经功能至关重要的重要辅助因子。主要负责碳水化合物和脂质代谢的几种酶的功能以及包括核酸和神经递质在内的几种必需分子的产生所必需的[70]。TPP 是硫胺的主要活性形式，是许多硫胺依赖酶的重要辅因子，如转酮醇酶、丙酮酸脱氢酶复合物和 α-酮戊二酸脱氢酶复合物。一旦人脑中的硫胺素水平降低，这些酶的活性就会受到影响，导致线粒体活性的改变，氧化代谢受损，能量状态下降和脑损伤[71]。此外，硫胺素缺乏会导致神经毒性，对认知功能产生负面影响[70]。一种假设，大脑皮层和白质的萎缩以及基底前脑区域的萎缩可能是由酒精的神经毒性作用引起的，硫胺素缺乏可能导致下丘脑部分受损。根据这一假设，易受酒精毒性影响的酗酒者可能出现与脑萎缩相关的永久性或短暂性认知缺陷[72]。对已故患者大脑进行的神经病理学研究以及活体大脑神经影像学研究得出

的发现表明，额叶大脑系统对酒精中毒相关损伤的易感性增加[72]。酒精通过酒精脱氢酶(Alcohol dehydrogenase, ADH)，CYP2E1 和过氧化氢酶的作用代谢为乙醛。已知乙醛是有毒的活性代谢物，且与酒精性心肌病的诱导有关[73]。此外，酒精性肝病进展期间的肝脏炎症与炎症细胞的浸润和活化有关[74]，并且氧化应激和炎症细胞活化经常相互影响。

5. 总结与展望

酒精和 AD 的全球负担正在增加。流行病学研究表明酒精是 AD 的重要危险因素之一。饮酒是全球最常见的习惯行为之一，适量饮酒可促进身体健康，而过度饮酒则将会对机体产生危害。然而，饮酒并非不可控制，可通过简单禁欲行为改变这种习惯。流行病学研究报告，酒精可作用于大脑，影响 AD 的发病进程。酒精具有双重性，适量饮酒的个体患 AD 风险下降，饮用低或中等浓度的酒可降低海马神经元中的 Aβ 毒性，过量饮酒将会增加 Aβ 和 Tau 磷酸化的积累，导致神经元细胞死亡和神经变性。此外，酒精会增加机体过度氧化应激，介导炎症的发生，破坏肠道微生物的平衡，进而影响大脑 CNS 的功能，并进一步引发 AD 的发生。酒精滥用在 AD 进展中的具体作用尚未阐明，酒精滥用背景下，更大规模的纵向流行病学研究和 AD 模型临床前研究还有待进行，现有临床研究表明控制酒精的摄入可能会在一定程度上降低 AD 的发病，因此探索酒精与 AD 的关系也将是未来科研的重要方向。

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参考文献

[1] ADI (2023) Dementia Facts & Figures. https://www.alzint.org/about/dementia-facts-figures

[2] Weller, J. and Budson, A. (2018) Current Understanding of Alzheimer's Disease Diagnosis and Treatment. *F*1000*Research*, **7**, 1161. https://doi.org/10.12688/f1000research.14506.1

[3] Chiti, F. and Dobson, C.M. (2017) Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress over the Last Decade. *Annual Review of Biochemistry*, **86**, 27-68. https://doi.org/10.1146/annurev-biochem-061516-045115

[4] Bishehsari, F., Magno, E., Swanson, G., *et al*. (2017) Alcohol and Gut-Derived Inflammation. *Alcohol Research*, **38**, 163-171.

[5] Crews, F.T. (2008) Alcohol-Related Neurodegeneration and Recovery: Mechanisms from Animal Models. *Alcohol Research & Health*, **31**, 377-388.

[6] León, B.E., Kang, S., Franca-Solomon, G., *et al*. (2021) Alcohol-Induced Neuroinflammatory Response and Mitochondrial Dysfunction on Aging and Alzheimer's Disease. *Frontiers in Behavioral Neuroscience*, **15**, Article ID: 778456. https://doi.org/10.3389/fnbeh.2021.778456

[7] Peng, B., Yang, Q., *et al*. (2020) Role of Alcohol Drinking in Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis. *International Journal of Molecular Sciences*, **21**, 2316. https://doi.org/10.3390/ijms21072316

[8] Crews, L. and Masliah, E. (2010) Molecular Mechanisms of Neurodegeneration in Alzheimer's Disease. *Human Molecular Genetics*, **19**, R12-R20. https://doi.org/10.1093/hmg/ddq160

[9] Huang, Y.R. and Liu, R.T. (2020) The Toxicity and Polymorphism of beta-Amyloid Oligomers. *International Journal of Molecular Sciences*, **21**, 4477. https://doi.org/10.3390/ijms21124477

[10] Selkoe, D.J. and Hardy, J. (2016) The Amyloid Hypothesis of Alzheimer's Disease at 25 Years. *EMBO Molecular Medicine*, **8**, 595-608. https://doi.org/10.15252/emmm.201606210

[11] Gulisano, W., Maugeri, D., Baltrons, M.A., *et al*. (2018) Role of Amyloid-beta and Tau Proteins in Alzheimer's Disease: Confuting the Amyloid Cascade. *Journal of Alzheimer's Disease*, **64**, S611-S631. https://doi.org/10.3233/JAD-179935

[12] Morris, G.P., Clark, I.A. and Vissel, B. (2014) Inconsistencies and Controversies Surrounding the Amyloid Hypothesis of Alzheimer's Disease. *Acta Neuropathologica Communications*, **2**, 135. https://doi.org/10.1186/s40478-014-0135-5

[13] Albayram, O., Herbert, M.K., Kondo, A., *et al*. (2016) Function and Regulation of Tau Conformations in the Development and Treatment of Traumatic Brain Injury and Neurodegeneration. *Cell & Bioscience*, **6**, 59. https://doi.org/10.1186/s13578-016-0124-4

[14] Mandelkow, E.M. and Mandelkow, E. (2012) Biochemistry and Cell Biology of Tau Protein in Neurofibrillary Degeneration. *Cold Spring Harbor Perspectives in Medicine*, **2**, a6247. https://doi.org/10.1101/cshperspect.a006247

[15] Mashal, Y., Abdelhady, H. and Iyer, A.K. (2022) Comparison of Tau and Amyloid-beta Targeted Immunotherapy Nanoparticles for Alzheimer's Disease. *Biomolecules*, **12**, 1001. https://doi.org/10.3390/biom12071001

[16] Illenberger, S., Zheng-Fischhofer, Q., Preuss, U., *et al*. (1998) The Endogenous and Cell Cycle-Dependent Phosphorylation of Tau Protein in Living Cells: Implications for Alzheimer's Disease. *Molecular Biology of the Cell*, **9**, 1495-1512. https://doi.org/10.1091/mbc.9.6.1495

[17] la Joie, R., Visani, A.V., Baker, S.L., *et al*. (2020) Prospective Longitudinal Atrophy in Alzheimer's Disease Correlates with the Intensity and Topography of Baseline tau-PET. *Science Translational Medicine*, **12**, 524. https://doi.org/10.1126/scitranslmed.aau5732

[18] Mroczko, B., Groblewska, M. and Litman-Zawadzka, A. (2019) The Role of Protein Misfolding and Tau Oligomers (TauOs) in Alzheimer's Disease (AD). *International Journal of Molecular Sciences*, **20**, 4661. https://doi.org/10.3390/ijms20194661

[19] Ando, K., Oka, M., Ohtake, Y., *et al*. (2016) Tau Phosphorylation at Alzheimer's Disease-Related Ser356 Contributes to Tau Stabilization When PAR-1/MARK Activity Is Elevated. *Biochemical and Biophysical Research Communications*, **478**, 929-934. https://doi.org/10.1016/j.bbrc.2016.08.053

[20] Huang, F., Wang, M., Liu, R., *et al*. (2019) CDT2-Controlled Cell Cycle Reentry Regulates the Pathogenesis of Alzheimer's Disease. *Alzheimer's & Dementia*, **15**, 217-231. https://doi.org/10.1016/j.jalz.2018.08.013

[21] Lippai, D., Bala, S., Petrasek, J., *et al*. (2013) Alcohol-Induced IL-1beta in the Brain Is Mediated by NLRP3/ASC Inflammasome Activation That Amplifies Neuroinflammation. *Journal of Leukocyte Biology*, **94**, 171-182. https://doi.org/10.1189/jlb.1212659

[22] Khan, S., Barve, K.H. and Kumar, M.S. (2020) Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease. *Current Neuropharmacology*, **18**, 1106-1125. https://doi.org/10.2174/1570159X18666200528142429

[23] Heneka, M.T., Carson, M.J., El, K.J., *et al*. (2015) Neuroinflammation in Alzheimer's Disease. *The Lancet Neurology*, **14**, 388-405. https://doi.org/10.1016/S1474-4422(15)70016-5

[24] Cai, Z., Hussain, M.D. and Yan, L.J. (2014) Microglia, Neuroinflammation, and Beta-Amyloid Protein in Alzheimer's Disease. *International Journal of Neuroscience*, **124**, 307-321. https://doi.org/10.3109/00207454.2013.833510

[25] Doens, D. and Fernandez, P.L. (2014) Microglia Receptors and Their Implications in the Response to Amyloid Beta for Alzheimer's Disease Pathogenesis. *Journal of Neuroinflammation*, **11**, 48. https://doi.org/10.1186/1742-2094-11-48

[26] Gundersen, V., Storm-Mathisen, J. and Bergersen, L.H. (2015) Neuroglial Transmission. *Physiological Reviews*, **95**, 695-726. https://doi.org/10.1152/physrev.00024.2014

[27] Steardo, L.J., Bronzuoli, M.R., Iacomino, A., *et al*. (2015) Does Neuroinflammation Turn on the Flame in Alzheimer's Disease? Focus on Astrocytes. *Frontiers in Neuroscience*, **9**, 259. https://doi.org/10.3389/fnins.2015.00259

[28] Gonzalez-Reimers, E., Santolaria-Fernandez, F., Martin-Gonzalez, M.C., *et al*. (2014) Alcoholism: A Systemic Proinflammatory Condition. *World Journal of Gastroenterology*, **20**, 14660-14671. https://doi.org/10.3748/wjg.v20.i40.14660

[29] Erickson, E.K., Grantham, E.K., Warden, A.S., *et al*. (2019) Neuroimmune Signaling in Alcohol Use Disorder. *Pharmacology Biochemistry and Behavior*, **177**, 34-60. https://doi.org/10.1016/j.pbb.2018.12.007

[30] Liddelow, S.A., Guttenplan, K.A., Clarke, L.E., *et al*. (2017) Neurotoxic Reactive Astrocytes Are Induced by Activated Microglia. *Nature*, **541**, 481-487. https://doi.org/10.1038/nature21029

[31] Neupane, S.P. (2016) Neuroimmune Interface in the Comorbidity between Alcohol Use Disorder and Major Depression. *Frontiers in Immunology*, **7**, 655. https://doi.org/10.3389/fimmu.2016.00655

[32] Qin, L. and Crews, F.T. (2012) NADPH Oxidase and Reactive Oxygen Species Contribute to Alcohol-Induced Microglial Activation and Neurodegeneration. *Journal of Neuroinflammation*, **9**, 5. https://doi.org/10.1186/1742-2094-9-5

[33] Zhang, Y., Chen, K., Sloan, S.A., *et al*. (2014) An RNA-Sequencing Transcriptome and Splicing Database of Glia, Neurons, and Vascular Cells of the Cerebral Cortex. *Journal of Neuroscience*, **34**, 11929-11947. https://doi.org/10.1523/JNEUROSCI.1860-14.2014

[34] Kawasaki, T. and Kawai, T. (2014) Toll-Like Receptor Signaling Pathways. *Frontiers in Immunology*, **5**, 461. https://doi.org/10.3389/fimmu.2014.00461

[35] Ramos, A., Joshi, R.S. and Szabo, G. (2022) Innate Immune Activation: Parallels in Alcohol Use Disorder and Alzheimer's Disease. *Frontiers in Molecular Neuroscience*, **15**, Article ID: 910298. https://doi.org/10.3389/fnmol.2022.910298

[36] Pascual, M., Balino, P., Aragon, C.M., *et al*. (2015) Cytokines and Chemokines as Biomarkers of Ethanol-Induced Neuroinflammation and Anxiety-Related Behavior: Role of TLR4 and TLR2. *Neuropharmacology*, **89**, 352-359. https://doi.org/10.1016/j.neuropharm.2014.10.014

[37] Zamanian, J.L., Xu, L., Foo, L.C., *et al*. (2012) Genomic Analysis of Reactive Astrogliosis. *Journal of Neuroscience*, **32**, 6391-6410. https://doi.org/10.1523/JNEUROSCI.6221-11.2012

[38] Vasile, F., Dossi, E. and Rouach, N. (2017) Human Astrocytes: Structure and Functions in the Healthy Brain. *Brain Structure and Function*, **222**, 2017-2029. https://doi.org/10.1007/s00429-017-1383-5

[39] Profaci, C.P., Munji, R.N., Pulido, R.S., *et al*. (2020) The Blood-Brain Barrier in Health and Disease: Important Unanswered Questions. *Journal of Experimental Medicine*, **217**, e20190062. https://doi.org/10.1084/jem.20190062

[40] Haorah, J., Knipe, B., Gorantla, S., *et al*. (2007) Alcohol-Induced Blood-Brain Barrier Dysfunction Is Mediated via Inositol 1,4,5-Triphosphate Receptor (IP3R)-Gated Intracellular Calcium Release. *Journal of Neurochemistry*, **100**, 324-336. https://doi.org/10.1111/j.1471-4159.2006.04245.x

[41] Alikunju, S., Abdul, M.P., Zhang, Y., *et al*. (2011) The Inflammatory Footprints of Alcohol-Induced Oxidative Damage in Neurovascular Components. *Brain*, *Behavior*, *and Immunity*, **25**, S129-S136. https://doi.org/10.1016/j.bbi.2011.01.007

[42] Cryan, J.F., O'riordan, K.J., Cowan, C., *et al*. (2019) The Microbiota-Gut-Brain Axis. *Physiological Reviews*, **99**, 1877-2013. https://doi.org/10.1152/physrev.00018.2018

[43] Milani, C., Duranti, S., Bottacini, F., *et al*. (2017) The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota. *Microbiology and Molecular Biology Reviews*, **81**, e00036-17. https://doi.org/10.1128/MMBR.00036-17

[44] Khan, M.S., Ikram, M., Park, J.S., *et al*. (2020) Gut Microbiota, Its Role in Induction of Alzheimer's Disease Pathology, and Possible Therapeutic Interventions: Special Focus on Anthocyanins. *Cells*, **9**, 853. https://doi.org/10.3390/cells9040853

[45] Lowe, P.P., Gyongyosi, B., Satishchandran, A., *et al*. (2018) Reduced Gut Microbiome Protects from Alcohol-Induced Neuroinflammation and Alters Intestinal and Brain Inflammasome Expression. *Journal of Neuroinflammation*, **15**, 298. https://doi.org/10.1186/s12974-018-1328-9

[46] Zhang, T., Han, Y., Wang, J., *et al*. (2018) Comparative Epidemiological Investigation of Alzheimer's Disease and Colorectal Cancer: The Possible Role of Gastrointestinal Conditions in the Pathogenesis of AD. *Frontiers in Aging Neuroscience*, **10**, 176. https://doi.org/10.3389/fnagi.2018.00176

[47] Hillemacher, T., Bachmann, O., Kahl, K.G., *et al*. (2018) Alcohol, Microbiome, and Their Effect on Psychiatric Disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **85**, 105-115. https://doi.org/10.1016/j.pnpbp.2018.04.015

[48] Gushcha, V.K., Lelevich, S.V. and Sheibak, V.M. (2019) Neurotransmitter Disturbances in Some Parts of the Rat Brain and Their Correction under Chronic and Intermittent Alcohol Intoxication. *Biomeditsinskaya Khimiya*, **65**, 21-27. https://doi.org/10.18097/PBMC20196501021

[49] Shukla, P.K., Meena, A.S., Dalal, K., *et al*. (2021) Chronic Stress and Corticosterone Exacerbate Alcohol-Induced Tissue injury in the Gut-Liver-Brain Axis. *Scientific Reports*, **11**, Article No. 826. https://doi.org/10.1038/s41598-020-80637-y

[50] Frausto, D.M., Engen, P.A., Naqib, A., *et al*. (2022) Impact of Alcohol-Induced Intestinal Microbiota Dysbiosis in a Rodent Model of Alzheimer's Disease. *Frontiers in Aging*, **3**, Article ID: 916336. https://doi.org/10.3389/fragi.2022.916336

[51] Perriard, G., Mathias, A., Enz, L., *et al*. (2015) Interleukin-22 Is Increased in Multiple Sclerosis Patients and Targets Astrocytes. *Journal of Neuroinflammation*, **12**, 119. https://doi.org/10.1186/s12974-015-0335-3

[52] Adachi, Y., Moore, L.E., Bradford, B.U., *et al*. (1995) Antibiotics Prevent Liver Injury in Rats Following Long-Term Exposure to Ethanol. *Gastroenterology*, **108**, 218-224. https://doi.org/10.1016/0016-5085(95)90027-6

[53] Crews, F.T., Lawrimore, C.J., Walter, T.J., *et al*. (2017) The Role of Neuroimmune Signaling in Alcoholism. *Neuropharmacology*, **122**, 56-73. https://doi.org/10.1016/j.neuropharm.2017.01.031

[54] Bjarnason, I., Peters, T.J. and Wise, R.J. (1984) The Leaky Gut of Alcoholism: Possible Route of Entry for Toxic Compounds. *The Lancet*, **1**, 179-182. https://doi.org/10.1016/S0140-6736(84)92109-3

[55] Chi, X., Pan, C.Q., Liu, S., *et al*. (2020) Regulating Intestinal Microbiota in the Prevention and Treatment of Alcohol-Related Liver Disease. *Canadian Journal of Gastroenterology and Hepatology*, **2020**, Article ID: 6629196.

https://doi.org/10.1155/2020/6629196

[56] Quigley, E. (2017) Microbiota-Brain-Gut Axis and Neurodegenerative Diseases. *Current Neurology and Neuroscience Reports*, **17**, 94. https://doi.org/10.1007/s11910-017-0802-6

[57] Petrasek, J., Iracheta-Vellve, A., Saha, B., *et al*. (2015) Metabolic Danger Signals, Uric Acid and ATP, Mediate Inflammatory Cross-Talk between Hepatocytes and Immune Cells in Alcoholic Liver Disease. *Journal of Leukocyte Biology*, **98**, 249-256. https://doi.org/10.1189/jlb.3AB1214-590R

[58] Shield, K.D., Parry, C. and Rehm, J. (2013) Chronic Diseases and Conditions Related to Alcohol Use. *Alcohol Research*, **35**, 155-173.

[59] Reuter, S., Gupta, S.C., Chaturvedi, M.M., *et al*. (2010) Oxidative Stress, Inflammation, and Cancer: How Are They Linked? *Free Radical Biology and Medicine*, **49**, 1603-1616. https://doi.org/10.1016/j.freeradbiomed.2010.09.006

[60] Cai, Y., Xu, M.J., Koritzinsky, E.H., *et al*. (2017) Mitochondrial DNA-Enriched Microparticles Promote Acute-on-Chronic Alcoholic Neutrophilia and Hepatotoxicity. *JCI Insight*, **2**, e92634. https://doi.org/10.1172/jci.insight.92634

[61] Jo, E.K., Kim, J.K., Shin, D.M., *et al*. (2016) Molecular Mechanisms Regulating NLRP3 Inflammasome Activation. *Cellular & Molecular Immunology*, **13**, 148-159. https://doi.org/10.1038/cmi.2015.95

[62] Kim, A., Bellar, A., Mcmullen, M.R., *et al*. (2020) Functionally Diverse Inflammatory Responses in Peripheral and Liver Monocytes in Alcohol-Associated Hepatitis. *Hepatology Communications*, **4**, 1459-1476. https://doi.org/10.1002/hep4.1563

[63] Mottaran, E., Stewart, S.F., Rolla, R., *et al*. (2002) Lipid Peroxidation Contributes to Immune Reactions Associated with Alcoholic Liver Disease. *Free Radical Biology and Medicine*, **32**, 38-45. https://doi.org/10.1016/S0891-5849(01)00757-2

[64] Wu, D. and Cederbaum, A.I. (2003) Alcohol, Oxidative Stress, and Free Radical Damage. *Alcohol Research & Health*, **27**, 277-284.

[65] Chen, Z. and Zhong, C. (2014) Oxidative Stress in Alzheimer's Disease. *Neuroscience Bulletin*, **30**, 271-281. https://doi.org/10.1007/s12264-013-1423-y

[66] Crews, F.T. and Nixon, K. (2009) Mechanisms of Neurodegeneration and Regeneration in Alcoholism. *Alcohol and Alcoholism*, **44**, 115-127. https://doi.org/10.1093/alcalc/agn079

[67] Liu, R., Guo, X., Park, Y., *et al*. (2013) Alcohol Consumption, Types of Alcohol, and Parkinson's Disease. *PLOS ONE*, **8**, e66452. https://doi.org/10.1371/journal.pone.0066452

[68] Sánchez-Muniz, F.J., Macho-González, A., Garcimartín, A., *et al*. (2019) The Nutritional Components of Beer and Its Relationship with Neurodegeneration and Alzheimer's Disease. *Nutrients*, **11**, 1558. https://doi.org/10.3390/nu11071558

[69] Venkataraman, A., Kalk, N., Sewell, G., *et al*. (2017) Alcohol and Alzheimer's Disease—Does Alcohol Dependence Contribute to Beta-Amyloid Deposition, Neuroinflammation and Neurodegeneration in Alzheimer's Disease? *Alcohol and Alcoholism*, **52**, 151-158. https://doi.org/10.1093/alcalc/agw092

[70] Nutt, D., Hayes, A., Fonville, L., *et al*. (2021) Alcohol and the Brain. *Nutrients*, **13**, 3938. https://doi.org/10.3390/nu13113938

[71] Thomson, A.D., Guerrini, I. and Marshall, E.J. (2012) The Evolution and Treatment of Korsakoff's Syndrome: Out of Sight, out of Mind? *Neuropsychology Review*, **22**, 81-92. https://doi.org/10.1007/s11065-012-9196-z

[72] Oscar-Berman, M. and Marinkovic, K. (2003) Alcoholism and the Brain: An Overview. *Alcohol Research & Health*, **27**, 125-133.

[73] Guo, R. and Ren, J. (2010) Alcohol and Acetaldehyde in Public Health: From Marvel to Menace. *International Journal of Environmental Research and Public Health*, **7**, 1285-1301. https://doi.org/10.3390/ijerph7041285

[74] Nguyen, G.T., Green, E.R. and Mecsas, J. (2017) Neutrophils to the ROScue: Mechanisms of NADPH Oxidase Activation and Bacterial Resistance. *Frontiers in Cellular and Infection Microbiology*, **7**, 373. https://doi.org/10.3389/fcimb.2017.00373