·综 述·

东莨菪碱的中枢药理机制研究进展

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[摘 要] 东莨菪碱(scopolamine)是一种天然莨菪烷生物碱,于1880年从东莨菪中分离纯化,是最早发现的竞争性胆碱能受体拮抗剂之一。相比于阿托品等同类药物,东莨菪碱对血脑屏障的通透性更强,且在中枢神经系统中可长期滞留并发挥药理作用。东莨菪碱被广泛用于晕动症、麻醉镇痛等,并在抑郁症等疾病中有广阔的应用前景。另一方面,东莨菪碱在一定剂量下会损伤认知、学习记忆和注意力等中枢神经系统功能,限制其临床用药。东莨菪碱的中枢神经系统毒性亦被广泛应用于健忘症和谵妄等动物模型研究,成为研究中枢胆碱能系统的重要工具。文章梳理了东莨菪碱的化学结构与分类,总结了其在中枢神经系统中的临床用药与毒性,讨论了其在胆碱能功能研究和临床前研究中的应用,以及中枢神经系统毒性所引发的争议,并针对东莨菪碱在中枢系统疾病的应用前景做了展望。

[关键词] 东莨菪碱;中枢神经系统;胆碱能;认知障碍;谵妄

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Advances in the central pharmacological mechanism of scopolamine

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[**Abstract**] Scopolamine, a natural tropane alkaloid, was isolated in 1880 from *Scopolia japonica* and is considered one of the earliest discovered competitive cholinergic receptor antagonists. Compared to other drugs with similar effects, such as atropine, scopolamine exhibits greater permeability across the blood-brain barrier and can remain in the central nervous system longer to exert pharmacological effects. Scopolamine is widely utilized in the treatment of motion sickness, anesthesia, and pain relief, and may be broadly applied to diseases, such as depression. On the other hand, scopolamine can impair central nervous system functions, such as cognition, learning and memory, and attention, which limits its clinical use. Additionally, the neurotoxicity of scopolamine has been widely used in animal models of amnesia and delirium and has become an important tool for studying the central cholinergic system. This review outlines the chemical structure and classification of scopolamine, summarizes its clinical use and toxicity in the central nervous system, discusses its application in cholinergic function research and preclinical studies, as well as the controversy surrounding its central nervous system toxicity. We also provided an outlook for the potential use of scopolamine in central nervous system diseases.

[**Key words**] scopolamine; central nervous system; cholinergic; cognitive disorder; delirium

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东莨菪碱是一种广泛用于临床的莨菪烷生物碱,通过非选择性、竞争性地拮抗毒蕈碱乙酰胆碱受体(muscarinic acetylcholine receptor, mAChR),在外周和中枢神经系统发挥广泛的抗胆碱能效应[1]。相较于其他胆碱能受体拮抗剂,东莨菪碱具有良好的血脑屏障透过性,因此能够更好地作用于中枢神经系统[1-2],是中枢胆碱能系统功能研究的重要工具。胆碱能系统参与前庭中枢的信号转导,从而调节视知觉与体感知觉的平衡并与晕动症的发生有关,因此东莨菪碱是临床治疗晕动症的一线疗法[3]。胆碱能系统也参与情绪的控制,特别是杏仁核的胆碱能信号参与焦虑和抑郁等情绪的调节[4],而东莨菪

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碱已被证明具有快速的抗抑郁作用[5]。乙酰胆碱(acetylcholine,ACh)也是运动神经元的主要调控因子之一,在控制机体运动中至关重要[6]。最近的研究也表明,不同的行为状态(面部运动、躯体运动和静止)与ACh波动的不同时空模式和增加的大规模网络同步有关,东莨菪碱给药选择性地降低了运动皮层的活动[7]。除了对大脑高级功能的调节,东莨菪碱还被广泛用于缓解有机磷农药中毒、术后恶心呕吐、晕动症等外周与中枢系统共同作用的症状。

尽管东莨菪碱的药用价值已经得到广泛认可,其对中枢神经系统广泛的神经毒性也一直备受关注。1907年,Karl Gauss等首次报道了产妇术前使用高剂量东莨菪碱后产生健忘症,而后的研究发现,在正常临床剂量下,东莨菪碱也可能会诱发短暂的记忆缺失[8],并损害学习能力[9]。过量东莨菪碱诱发谵妄[10]、光恐惧症与声音恐惧症等[11]。在注意力方面,东莨菪碱干扰了毒蕈碱胆碱能系统介导的注意力处理[12]。单细胞电信号记录显示,恒河猴在执行空间注意力任务时,ACh处理可显著增强注意力水平,而东莨菪碱处理会损害注意力的调节[13]。此外,由于较强的副交感神经系统抑制作用,东莨菪碱还会引起心率加快、腺体分泌受抑、支气管扩张、散瞳、面部潮红和体温升高等外周反应[11,14]。这一系列的不良反应极大限制了东莨菪碱的临床应用。

在临床前研究中,东莨菪碱已被证明可以阻断胆碱能神经元向海马的投射,还可升高啮齿动物脑内乙酰胆碱酯酶(acetylcholinesterase,AChE)的活性,降低ACh水平,产生中枢神经系统毒性,进而诱发啮齿类等动物空间认知与工作记忆的显著损伤[15]。东莨菪碱已被广泛应用于认知与记忆、意识障碍等相关疾病的动物模型构建,应用于健忘症和谵妄等疾病发病机制研究以及药物筛选等领域[16-17]。

本文综合探讨东莨菪碱的中枢系统药理学特征,从以东莨菪碱为代表的莨菪烷生物碱的组成、分类及相关性质出发,总结了东莨菪碱在中枢神经系统的临床适应证和不良反应,综述了东莨菪碱的中枢神经系统药理机制和毒理机制,并着重讨论了东莨菪碱在中枢神经系统疾病造模中的应用,以期通过对东莨菪碱的系统性分析,阐述东莨菪碱在临床及临床前的重要作用,并为东莨菪碱的未来应用提供参考。

1　莨菪烷生物碱与胆碱能受体拮抗剂

东莨菪碱是一种提取自天仙子(又名莨菪)、曼陀罗和颠茄等茄科植物中的天然生物碱。这类植物在两千余年前即被作为致幻剂和麻醉剂使用[18]。19世纪科学家开始尝试从这类药用植物中提取有效成分,并于1832年首先分离出阿托品[19],随后又成功分离出东莨菪碱和山莨菪碱等物质。进一步,科学家发现这类物质均含有一个相同的基团,即8-氮杂双环[3.2.1]辛烷,并将其命名为莨菪烷环,由此定义了一类新的生物碱,即莨菪烷生物碱[20]。

天然的莨菪烷生物碱绝大多数是以莨菪烷衍生的醇类和不同的有机酸生成的酯,目前已发现近200种。莨菪烷生物碱包含了3类化合物:第一类为莨菪碱及东莨菪碱类,包含阿托品、莨菪碱、东莨菪碱和山莨菪碱等,具有显著的胆碱能受体拮抗作用,药用价值最高[21];第二类为可卡因类,包含可卡因及其衍生物,通过抑制多巴胺、去甲肾上腺素和5-羟色胺等神经递质的再摄取刺激中枢神经系统兴奋,但受限于其高成瘾性,成药用途较少;第三类为打碗花精类,是一类选择性糖苷酶抑制剂,于1990年首次发现并分离[22],目前的药理研究较少。

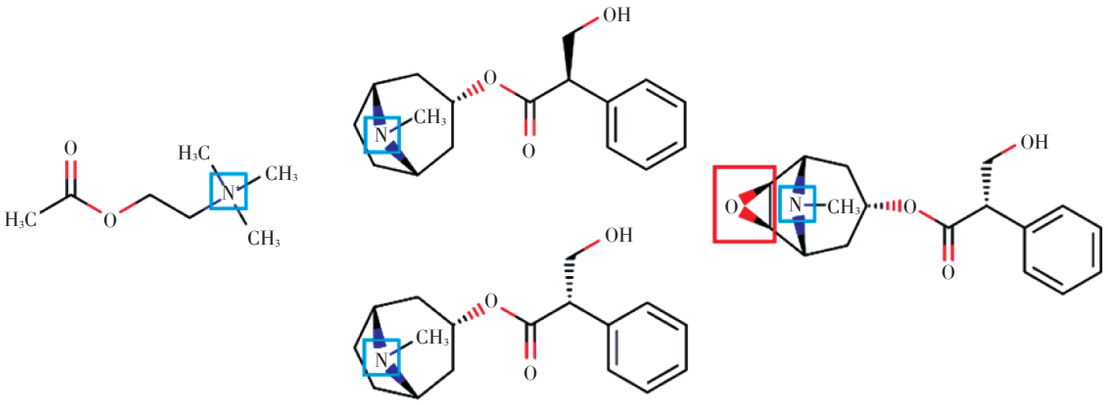
莨菪碱与东莨菪碱类化合物在结构和功能上高度相似[23]。在莨菪烷环结构基序外,均包含一个苯环和一个含手性中心的热带酸[S-(-)-托品酸]组分。其中阿托品与莨菪碱互为手性分子,莨菪碱的左旋异构体不稳定,会迅速消旋为稳定的阿托品[18]。相较于二者,东莨菪碱额外含有一个环氧环,具有独特的弱碱性和良好的脂溶性,这使得东莨菪碱具有良好的血脑屏障透过性。阿托品与东莨菪碱的活性中心是其分子中的季铵盐结构,当药物分子靠近乙酰胆碱受体(acetylcholine receptor,AChR)时,其中的氮原子会与受体特定位点形成氢键等化学键,竞争性拮抗ACh与AChR的结合,从而阻断ACh的下游效应[18,24](图1)。

ACh广泛分布于外周神经系统及中枢神经系统,参与多种神经系统功能的调节,是人体中最重要的兴奋性神经递质之一[25-26]。AChR主要分布在外周自主神经系统(以副交感系统为主)、神经肌肉接头和中枢神经系统中。除ACh外,AChR也可与其他分子结合,根据对不同分子的相对亲和力和敏感性差异可分为mAChR和烟碱乙酰胆碱受体(nicotinic acetylcholine receptor,nAChR)。一般来说,神经肌肉接头处多为nAChR;外周副交感神经处多为mAChR,两种受体均广泛分布在中枢神经系统中[27-28]。因此,此类药物的药理作用与mAChR的分布直接相关。

在外周神经系统中,ACh是副交感神经系统的

主要神经递质，参与呼吸、心率控制、消化和能量代谢等生命活动，维持机体的生理平衡。副交感神经系统包括动眼神经、面神经、舌咽神经、骶2/骶4神经和迷走神经等，它们控制瞳孔括约肌与睫状肌活动、泪腺与唾液腺等腺体的活动、生殖活动和绝大多数内脏的活动。因此，莨菪碱与东莨菪碱类化合物可用于多种相关疾病的治疗(图2)。阿托品可引发瞳孔扩张，进而治疗和控制近视[29-31]。东莨菪碱则常用于手术麻醉前给药，通过抑制胃肠道广泛分布的迷走神经引起平滑肌舒张，继而预防术后恶心呕吐[32]；东莨菪碱也可抑制唾液腺的分泌，用于流涎症的治疗[33]；东莨菪碱还可以通过抑制上呼吸道分泌，缓解临终喉鸣[34]，在姑息医学中有一定的药用价值。

在中枢神经系统中，莨菪碱与东莨菪碱类化合物可直接阻滞ACh的神经信号传递，也可通过神经连接间接影响其他神经递质传递，最终影响突触可塑性及神经网络连接，从而对注意力、认知功能、学习记忆、情绪和运动能力等大脑高级功能产



红框：东莨菪碱环氧环结构；蓝框：季铵盐结构氮原子中心。

图1　乙酰胆碱、(+,-)-阿托品(莨菪碱)和东莨菪碱的结构式

Figure 1　Structural formulas of acetylcholine, (+,-)-atropine (hyoscyamine) and scopolamine

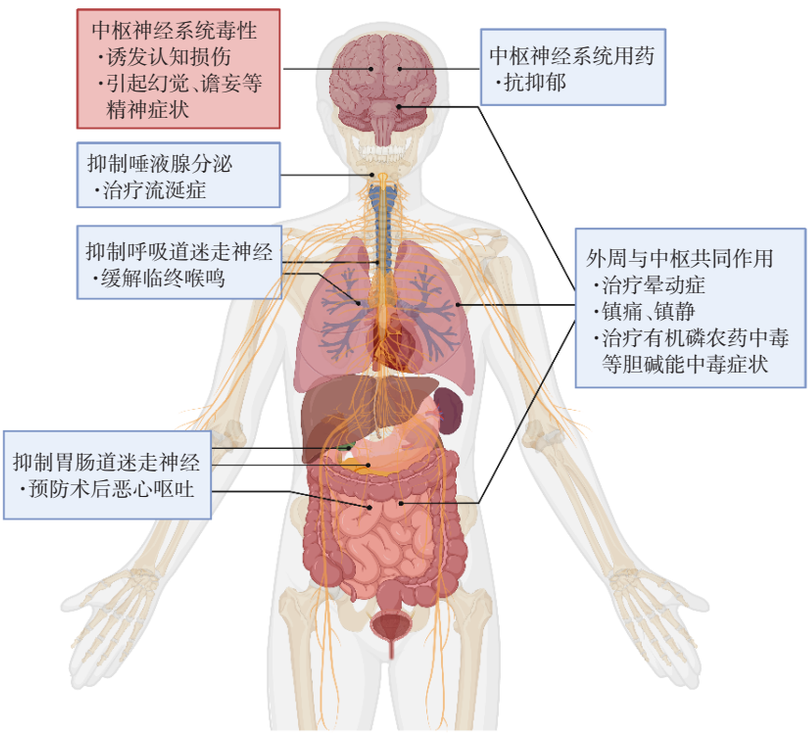


图2　东莨菪碱发挥药理及毒理作用的器官

Figure 2　Organs where scopolamine exerts pharmacological and toxicological effects

生影响[35]。作为典型的非选择性mAChR拮抗剂，东莨菪碱被认为对mAChR的5个亚型（M1~M5）均可产生拮抗效应[20,36-37]。成年人的多数脑区中至少表达一种mAChR亚型，其中，M1和M3在海马、扣带回和额叶各层（额叶下回、额叶上回、额叶眶回和额极等）中高表达；M2、M4和M5则在丘脑、脑桥、髓脑和中脑中高表达[38]。这些受体广泛分布在锥体神经元、颗粒神经元的突触前后和神经元胞体等区域[39-40]。因此，东莨菪碱用药后会表现出较强的认知和精神类中枢效应，在中枢神经系统相关疾病的临床治疗和基础研究中有着更为广泛的应用。

2　东莨菪碱的中枢系统用药及机制

2.1　晕动症

晕动症是由于人体暴露于异常的加速度环境引起的多系统生理反应，其以恶心和呕吐为核心症状，同时伴有头痛、昏睡、脸色苍白和流涎增多等表现[41]，是目前临床上东莨菪碱最常用的适应证之一。阿托品和东莨菪碱在上世纪初就被用于治疗晕动症[42]，多项临床试验已经证实了东莨菪碱在预防和治疗晕动症中的药效。目前，东莨菪碱贴片可弥特（国药准字H20091051）是临床上治疗晕动症的一线疗法之一[43]。

晕动症是中枢与外周系统共同作用的结果，其病理机制并不明确。其中，最被广泛接受的病理机制假说是视觉-前庭感觉冲突理论，即视觉输入、躯体知觉等感觉信息发生冲突后的复杂整合[44]。前庭系统是体感中枢，负责空间位置（本体感觉）和自我运动（运动感觉）的平衡，由位于内耳的前庭感受器，位于脑干、小脑和皮层的前庭中枢，以及连接二者的前庭神经元构成[45]。前庭感受器接收的感觉信息可通过胆碱能神经元直接传递到脑干前庭核，因此，东莨菪碱可能通过阻断感觉信息向中枢神经系统的传递缓解晕动症[46]。另一方面，前庭中枢之间也通过胆碱能神经环路互联。前庭神经核会向小脑投射胆碱能神经元，其释放的ACh会进一步诱发小脑ACh的释放，形成ACh在前庭中枢的正反馈释放，进一步激活脑干进而诱发晕动症，而东莨菪碱可以通过发挥抗胆碱能效应缓解晕动症[47]。

此外，影像学研究发现，除前庭中枢外，在晕动症发病前至发病中，患者的杏仁核等脑区存在广泛的神经活动增强[48]，东莨菪碱可以显著降低杏仁核等脑区的神经活动[49-50]。东莨菪碱对隔核-海马通路的明显阻断也会影响边缘系统，加之东莨菪碱通过抑制外周自主神经系统，可以缓解晕动症的胃肠道不适等外周症状[50]。

2.2　镇痛

作为常用的解痉药物，东莨菪碱（如丁溴东莨菪碱片，国药准字H20120523）被广泛应用于胃肠道痉挛、胆绞痛、肾绞痛等疾病的疼痛管理。东莨菪碱与吗啡联用镇痛，不仅可以改善吗啡产生的恶心、呕吐等不良反应，也可克服吗啡镇痛效果消失后的脱敏反应（如皮肤瘙痒和麻疹）[51]。通常认为东莨菪碱通过作用于外周神经系统辅助镇痛，也有研究指出东莨菪碱可独立于阿片能系统而单独通过毒蕈碱受体发挥镇痛效用[52]。动物实验显示，在高级中枢参与痛觉反应（如撕咬等）时，高剂量的东莨菪碱可提高痛觉阈值，起到抑制痛觉的效果，可维持2 d以上[52]。此外，有临床试验在研（NCT04240626）东莨菪碱参与术后多模态镇痛组合的可行性。需要注意的是，作为胆碱酯酶抑制剂，毒扁豆碱（physostigmine）也具有镇痛效果，说明胆碱能系统参与痛觉反应的机制较为复杂。

2.3　解毒

东莨菪碱也用于有机磷农药中毒的解毒，如临床常用的氢溴酸东莨菪碱注射液（国药准字H41021048）。有机磷农药会与AChE共价结合生成难水解的磷酸化乙酰胆碱酯酶，导致ACh在突触累积，进而诱发胆碱能中毒症状，中毒患者会出现毒蕈碱样症状（M样症状）、烟碱样症状（N样症状）和中枢神经系统症状。M样症状在有机磷农药中毒时出现较早，主要为副交感神经系统的过度兴奋，具体表现为唾液腺等腺体分泌增多、呼吸困难、腹泻等症状；N样症状在有机磷农药中毒时出现较晚，主要包括全身肌肉痉挛、血压升高、心律失常等症状[53]。东莨菪碱不仅能缓解有机磷农药中毒引起的M样症状，也能消除中枢性呼吸抑制及躁动、惊厥和震颤等中枢神经系统症状，与阿托品联用可明显缩短昏迷患者恢复清醒的时间，还可避免阿托品过量引起的呼吸肌麻痹[53]。类似地，在治疗急性重度杀虫双中毒患者时，东莨菪碱对中枢神经系统的作用也有助于控制惊厥，缓解呼吸衰竭和休克[54]。

2.4　抑郁症

抑郁症是以绝望、快感缺失、动机缺乏为核心症状的严重精神疾病[55]。关于抑郁症发病机制的假说，经典的单胺理论认为，抑郁症患者神经元突触间隙可有效利用的5-羟色胺等单胺类物质减少，升高突触间隙的5-羟色胺浓度可以改善抑郁症[56]。

除此之外，在抑郁症患者及动物模型的多个脑区中还存在突触丢失、神经元数量减少及神经连接的改变[57-58]。基于单胺理论的抗抑郁药物，如选择性5-羟色胺再摄取抑制剂等已取得了很大疗效，但仍存在起效慢、不良反应多、疗效不稳定等缺陷[59]。近年来，有研究发现东莨菪碱有强效的快速抗抑郁作用，是一种非常有希望的候选药物[5]。

M1、M3和M5受体可以通过蛋白激酶C-三磷酸肌醇(protein kinase C-inositol 1，4，5-triphosphate，PKC-IP_3)信号通路调节胞内Ca^{2+}水平，因此东莨菪碱可能通过作用于抑制性神经元的PKC-IP_3-Ca^{2+}信号通路，通过降低胞内Ca^{2+}水平发挥抗抑郁作用[60]。此外，动物实验揭示，东莨菪碱抗抑郁的机制可能并非通过直接作用于效应锥体神经元，而是借由γ-氨基丁酸(gamma amino-butyricacid，GABA)能中间神经元发挥作用。前额叶皮层的GABA能神经元可抑制谷氨酸释放，东莨菪碱通过拮抗GABA能神经元的M1和M2受体，调节其强直性放电，从而解除对谷氨酸能神经元的抑制，间接增加谷氨酸的释放，引起谷氨酸爆发，进而激活单胺中心释放5-羟色胺，升高突触间隙可利用的5-羟色胺浓度，改善抑郁症状[61-62]。谷氨酸还会激活α-氨基-3-羟基-5-甲基-4-异恶唑丙酸(α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid，AMPA)受体，进而激活电压依赖性钙离子通道(voltage-dependent calcium channel，VDCC)，引起脑源性神经营养因子(brain derived neurotrophic factor，BDNF)释放，作用于酪氨酸激酶受体B(tyrosine kinase receptor B，TrkB)，激活蛋白激酶B(protein kinase B，PKB，又称AKT)-哺乳动物雷帕霉素靶蛋白复合体(mammalian target of rapamycin complex 1，mTORC1)通路，促进AMPA受体1(AMPA receptor 1，AMPAR1，又称GluR1)、突触后致密蛋白95(postsynaptic density protein 95，PSD95)等突触功能蛋白的表达，从而促进突触数量及功能的恢复，改善突触可塑性以发挥抗抑郁效果[61,63]。

东莨菪碱的抗抑郁疗法大多仍处于临床试验阶段，且最近的几项临床试验得出了截然不同的结论。在轻至中度的抑郁患者(基线蒙哥马利抑郁量表评分25分以下)中，东莨菪碱表现出了良好的抗抑郁效果[64]；然而，东莨菪碱在重症患者(基线蒙哥马利抑郁量表评分30分以上)中疗效欠佳[65]。因此，患者症状的严重程度，以及耐药性水平等可能会影响东莨菪碱的抗抑郁效果。此外，有研究发现当对照组使用活性安慰剂(如格隆溴铵等血脑屏障透过性较差的抗毒蕈碱药物)时，东莨菪碱并未显现出差异[66]。因此东莨菪碱在临床试验中表现出的抗抑郁效果可能由其外周抗毒蕈碱作用介导，而非中枢神经系统的情绪调节作用[67]。不同研究中东莨菪碱组患者的不良反应表现不一，多温和且短期，如口干、嗜睡等[65]，其他如认知觉障碍、心率降低和谵妄等也有报道[66]。

2.5　其他

近年来，有病例报道称静脉注射东莨菪碱可迅速缓解帕金森(Parkinson's disease，PD)患者的抑郁和运动症状(震颤与强直)，且未见明显不良反应[68]。这也为未来PD的诊疗提供了参考。此外，东莨菪碱可改善毛果芸香碱大鼠癫痫模型中的自发性复发性癫痫发作，降低癫痫大鼠的兴奋性，同时减少其海马内异常苔藓纤维的出芽[69-71]。这些研究可能预示着东莨菪碱在癫痫治疗中的潜在应用价值。

3　东莨菪碱的中枢毒性

3.1　认知损伤、健忘症与阿尔兹海默病(Alzheimer's disease，AD)造模

在临床试验和多种动物实验(斑马鱼和啮齿动物等)中均观察到了东莨菪碱对学习和记忆的损伤作用[72-73]。东莨菪碱可阻断中部隔核胆碱能神经元向海马的投射，损害海马的正常功能，进而对学习和记忆产生负面影响[74-75]。向小鼠海马CA1区和内侧内嗅皮层注入东莨菪碱，会显著损害其对空间记忆和恐惧记忆的提取，并导致逆行性遗忘[76]。东莨菪碱可诱导小鼠海马髓鞘碱性蛋白发生降解，改变海马神经丝蛋白的表达水平，这可能是东莨菪碱致认知损伤的潜在病理机制[77-78]。更进一步地，针对记忆形成的不同阶段，有研究指出东莨菪碱仅影响记忆的提取[79]，但也有研究认为东莨菪碱对记忆的获取和巩固同样造成了损伤[78]。针对记忆的不同类型，狨猴实验揭示了东莨菪碱可能会损害自发物体位置识别和恐惧学习，提示东莨菪碱对空间记忆和恐惧记忆造成了一定损伤[80]。在啮齿动物实验中，东莨菪碱可能通过影响小鼠边界细胞编码，从而对空间记忆产生影响[81]。此外，东莨菪碱还会损害情境性恐惧记忆等[82]。

由于对认知和记忆造成的损伤，东莨菪碱被广泛用于健忘症造模[83-84]。健忘症是一种在没有其他实质性认知损伤(如痴呆或谵妄等)的情况下发生的记忆障碍，也被称作遗忘性障碍，其核心特征是记忆的损伤[85]。腹腔注射0.5~1.0 mg/kg东莨菪碱

会干扰大鼠在Y迷宫、莫里斯水迷宫等行为学范式中的工作记忆与空间认知损伤，被用于健忘症造模[83,86-90]。小鼠可在较广的剂量范围内用于健忘症模型构建，以满足健忘症药物开发需求。连续腹腔注射0.4 mg/kg东莨菪碱已经足以造成小鼠在目标定位、目标识别和情景记忆中的记忆缺陷[15]，而单次腹腔注射较大剂量（4 mg/kg）的东莨菪碱则可以影响小鼠在被动逃避测试中的逃逸潜伏期，增加出错率[91]；连续5 d注射3 mg/kg的东莨菪碱后，小鼠则会在在莫里斯水迷宫中表现出显著的空间记忆损伤[92]。在斑马鱼中，常见的健忘症造模剂量为100~200 μmol/L，可以影响斑马鱼在新事物识别以及抑制性回避测试等多种行为学测试中的表现[93-95]。

AD是以慢性进行性认知能力下降为主要症状的神经退行性疾病，其主要病理特征为脑内淀粉样蛋白（amyloid β，Aβ）斑块的聚集和Tau蛋白过度磷酸化形成的神经原纤维缠结[96]，并表现出胆碱能系统的严重损伤[97]。在啮齿类动物中，腹腔注射东莨菪碱会升高啮齿动物脑内AChE活性，降低ACh水平[15,87-88]，连续多次注射会降低大鼠的皮层与海马中的M1受体表达水平[98]，进而损害中枢胆碱能信号的传递，并参与诱导氧化应激和记忆障碍等AD样病理变化，因此在部分研究中被用作AD的药理学模型[99-101]。然而，AD患者脑内的Aβ斑块与神经原纤维缠结均呈现出与病程进展相关的形态与分布特点，并伴随着神经元的变性丢失[35,96]；相反，连续多次注射东莨菪碱虽然会诱发啮齿动物脑内$A\beta_{1-42}$水平升高和Tau蛋白多位点的过度磷酸化，但均没有发现类似于临床病理的进行性变化[102-103]。而东莨菪碱暴露虽然会影响成年小鼠神经元的增殖、分化和迁移，但并不会导致神经元的死亡[57]。此外，东莨菪碱造成的认知障碍通常是可逆的，且病程较短[104]。因此，东莨菪碱诱导的病理与行为表型似乎并不能体现临床AD的复杂性与进行性。

3.2 注意力损伤、幻觉与谵妄造模

基底前脑的胆碱能输入是介导持续注意力的关键，激活的胆碱能输入通过增强皮层对感觉信息的处理促进了“前注意力系统”的激活[105]。临床试验证明，东莨菪碱显著损害了受试者在双耳听觉测试中对信息处理施加的主动注意力控制水平，还会减少受试者对于高概率空间位置的目标检测能力，表明东莨菪碱损害了注意力的维持与分配[106]。与认知功能相比，注意力对东莨菪碱的毒性更加敏感，较低剂量的东莨菪碱即可显著影响动物在注意力测试中的表现[2,107]。

莨菪碱与东莨菪碱类化合物通常具有显著的致幻作用。其会产生特征性的复杂视觉意象，导致视觉能力下降，产生知觉妄想，进而出现漂移、复视、振动和残像等幻觉意象[108-109]。病例报告显示东莨菪碱会使人类产生精神错乱等幻觉反应[110-112]。东莨菪碱会诱发啮齿动物的运动过度和刻板行走行为[113]，并剂量依赖性地降低了啮齿动物的脉冲前抑制[114]，提示东莨菪碱存在较强的致幻作用。

谵妄是一种混乱的精神状态，急性发作的注意力障碍、认知损伤和幻觉等都是谵妄的核心表型[115]。莨菪碱与东莨菪碱类化合物的胆碱能拮抗作用可诱发注意力损伤和幻觉等诸多谵妄核心表型，因此，有研究将其称为致谵妄剂[108]，广泛用于构建大鼠、小鼠和斑马鱼等多种谵妄动物模型[108,116-120]。相比于阿托品，东莨菪碱可以低剂量诱发大鼠谵妄样的行为特征，如注意力缺陷和警觉性降低[121]，成为构建谵妄动物模型的常用药物。

谵妄患者的脑电图显示出大脑活动的广泛衰减[122]。同样地，临床东莨菪碱中毒病例也呈现出脑电图的功率谱变慢，α波段和β波段频率的相干性降低等特征[123]，而中等剂量的东莨菪碱（3 mg/kg）可在30 min内导致小鼠大脑功能连接中断[124]，表明东莨菪碱会引发与谵妄相似的脑活动及功能连接变化。

在病程上，谵妄患者会在短期内表现出一过性的认知损伤[125]。类似地，东莨菪碱可以通过拮抗mAChR诱发动物短期工作记忆的损伤[126]。此外，谵妄患者常伴有神经精神症状，在活动亢进型谵妄中，患者会表现出兴奋、焦虑、不安、身体运动过度等症状[125]。同样，东莨菪碱也会导致啮齿动物在高架十字迷宫开放臂中停留的时间减少和在旷场实验中的运动距离增多，表现出类似于谵妄的焦虑和运动过度等症状[116]。

4 结论与展望

作为一种天然产物，东莨菪碱具有悠久的药用历史和与之相对应的广泛的药理尝试，为多种疾病提供了治疗方案，至今仍然是晕动症缓解与镇静镇痛的一线药物。近年来，东莨菪碱潜在的抗抑郁作用得以开发，症状严重程度和治疗耐药性可能是药物起效的关键因素[65]。东莨菪碱具有重要的临床价值，同时，其不良反应也不容忽视。东莨菪碱显著的抗胆碱效应也带来了一系列中枢神经系统不良反应，成为其临床用药的限制性因素。如东莨菪碱在PD和

癫痫治疗中的潜力即受制于其在中枢神经系统中的不良反应,如导致谵妄等精神类效应[10],影响患者的精神管理,是此类研究中需要着重考虑的因素。因此,谨慎、合理地应用东莨菪碱,最大程度发挥其价值,同时规避不良反应是临床用药的关键点。

在临床前研究中,东莨菪碱在中枢神经系统的药效与毒性的双重作用也被分别开发用于胆碱能系统相关的基础研究与疾病造模,帮助了解认知损伤、幻觉和谵妄等中枢神经系统症状的机制,并为相关疾病的治疗提供新的思路。同时,由于胆碱能受体分布广泛,且与其他递质系统存在复杂的相互作用[127],东莨菪碱在中枢神经系统中作用的脑区和神经元特异性的研究较为困难,而要深入了解东莨菪碱的药理机制,目前还缺乏东莨菪碱与胆碱能受体结合的三维结构与下游的胞内反应研究。未来,结合结构生物学手段,借助全脑基因表达图谱与单细胞测序等技术将有助于探究东莨菪碱的药理作用,并为诸多胆碱能系统相关的科学问题和疾病治疗提供新的思路。

[参考文献]

[1] BOLDEN C, CUSACK B, RICHELSON E. Antagonism by antimuscarinic and neuroleptic compounds at the five cloned human muscarinic cholinergic receptors expressed in Chinese hamster ovary cells[J]. J Pharmacol Exp Ther, 1992, 260(2): 576-580

[2] KLINKENBERG I, BLOKLAND A. The validity of scopolamine as a pharmacological model for cognitive impairment: a review of animal behavioral studies[J]. Neurosci Biobehav Rev, 2010, 34(8): 1307-1350

[3] KOCH A, CASCORBI I, WESTHOFEN M, et al. The neurophysiology and treatment of motion sickness[J]. Dtsch Arztebl Int, 2018, 115(41): 687-696

[4] MINEUR Y S, CAHUZAC E L, MOSE T N, et al. Interaction between noradrenergic and cholinergic signaling in amygdala regulates anxiety- and depression-related behaviors in mice[J]. Neuropsychopharmacology, 2018, 43(10): 2118-2125

[5] WOHLEB E S, GERHARD D, THOMAS A, et al. Molecular and cellular mechanisms of rapid-acting antidepressants ketamine and scopolamine[J]. Curr Neuropharmacol, 2017, 15(1): 11-20

[6] LE RAY D, BERTRAND S S, DUBUC R. Cholinergic modulation of locomotor circuits in vertebrates[J]. Int J Mol Sci, 2022, 23(18): 10738

[7] LOHANI S, MOBERLY A H, BENISTY H, et al. Spatiotemporally heterogeneous coordination of cholinergic and neocortical activity[J]. Nat Neurosci, 2022, 25(12): 1706-1713

[8] HARDY T K, WAKELY D. The amnesic properties of hyoscine and atropine in pre-anaesthetic medication[J]. Anaesthesia, 1962, 17: 331-336

[9] CROW T J, GROVE-WHITE I G. An analysis of the learning deficit following hyoscine administration to man[J]. Br J Pharmacol, 1973, 49(2): 322-327

[10] LIN C H, LUNG H L, LI S T, et al. Delirium after transdermal scopolamine patch in two children[J]. J Neuropsychiatry Clin Neurosci, 2014, 26(2): E01-E02

[11] VAN SASSENBROECK D K, HEMELSOET D M, VANWALLEGHEM P, et al. Three cases of substitution errors leading to hyoscine hydrobromide overdose[J]. Clin Toxicol(Phila), 2005, 43(7): 861-865

[12] GOLDBERG J A, REYNOLDS J N J. Spontaneous firing and evoked pauses in the tonically active cholinergic interneurons of the striatum[J]. Neuroscience, 2011, 198: 27-43

[13] HERRERO J L, ROBERTS M J, DELICATO L S, et al. Acetylcholine contributes through muscarinic receptors to attentional modulation in V1[J]. Nature, 2008, 454(7208): 1110-1114

[14] KWAKYE G F, JIMéNEZ J, JIMéNEZ J A, et al. Atropa belladonna neurotoxicity: implications to neurological disorders[J]. Food Chem Toxicol, 2018, 116(Pt B): 346-353

[15] DA COSTA RODRIGUES K, LEIVAS DE OLIVEIRA R, DA SILVA CHAVES J, et al. A new arylsulfanyl-benzo-2, 1, 3-thiadiazoles derivative produces an anti-amnesic effect in mice by modulating acetylcholinesterase activity[J]. Chem Biol Interact, 2022, 351: 109736

[16] AYKAC A, OZBEYLI D, UNCU M, et al. Evaluation of the protective effect of *Myrtus communis* in scopolamine-induced Alzheimer model through cholinergic receptors[J]. Gene, 2019, 689: 194-201

[17] BHUVANENDRAN S, KUMARI Y, OTHMAN I, et al. Amelioration of cognitive deficit by embelin in a scopolamine-induced Alzheimer's disease-like condition in a rat model[J]. Front Pharmacol, 2018, 9: 665

[18] KOHNEN-JOHANNSEN K L, KAYSER O. Tropane alkaloids: chemistry, pharmacology, biosynthesis and production[J]. Molecules, 2019, 24(4): 796

[19] BLEY. Deutsches Apothekerbuch[J]. Archiv Der Pharmazie, 1847, 99(1): 78-80

[20] GRYNKIEWICZ G, GADZIKOWSKA M. Tropane alkaloids as medicinally useful natural products and their synthetic derivatives as new drugs[J]. Pharmacol Rep, 2008, 60(4): 439-463

[21] WHO. WHO model list of essential medicines - 22nd list,

2021[R]. 2021
[22] GOLDMANN A, MILAT M L, DUCROT P H, et al. Tropane derivatives from calystegia sepium[J]. Phytochemistry, 1990, 29(7): 2125-2127
[23] AFEWERKI S, WANG J X, LIAO W W, et al. The chemical synthesis and applications of tropane alkaloids[J]. Alkaloids Chem Biol, 2019, 81: 151-233
[24] BOLAND D M. Disposition of toxic drugs and chemicals in man, 12th edition[J]. J Anal Toxicol, 2020, 44(9): e13-e13
[25] PICCIOTTO M R, HIGLEY M J, MINEUR Y S. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior[J]. Neuron, 2012, 76(1): 116-129
[26] ANANTH M R, RAJEBHOSALE P, KIM R, et al. Basal forebrain cholinergic signalling: development, connectivity and roles in cognition[J]. Nat Rev Neurosci, 2023, 24(4): 233-251
[27] GOTTI C, ZOLI M, CLEMENTI F. Brain nicotinic acetylcholine receptors: native subtypes and their relevance[J]. Trends Pharmacol Sci, 2006, 27(9): 482-491
[28] THIELE A. Muscarinic signaling in the brain[J]. Annu Rev Neurosci, 2013, 36: 271-294
[29] HA A, KIM S J, SHIM S R, et al. Efficacy and safety of 8 atropine concentrations for myopia control in children: a network meta-analysis [J]. Ophthalmology, 2022, 129(3): 322-333
[30] YAM J C, JIANG Y, TANG S M, et al. Low-concentration atropine for myopia progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control [J]. Ophthalmology, 2019, 126(1): 113-124
[31] GONG Q, JANOWSKI M, LUO M, et al. Efficacy and adverse effects of atropine in childhood myopia: a meta-analysis[J]. JAMA Ophthalmol, 2017, 135(6): 624-630
[32] AL JERAISY M, ALFURAIH M, ALSAIF R, et al. Efficacy of scopolamine transdermal patch in children with sialorrhea in a pediatric tertiary care hospital[J]. BMC Pediatr, 2020, 20(1): 437
[33] LEUNG A K, HON K L. Motion sickness: an overview[J]. Drugs Context, 2019, 8: 2019-9-4
[34] VAN ESCH H J, VAN ZUYLEN L, GEIJTEMAN E C T, et al. Effect of prophylactic subcutaneous scopolamine butylbromide on death rattle in patients at the end of life: the SILENCE randomized clinical trial[J]. JAMA, 2021, 326(13): 1268-1276
[35] HAMPEL H, MESULAM M M, CUELLO A C, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease[J]. Brain, 2018, 141(7): 1917-1933
[36] RENNER U D, OERTEL R, KIRCH W. Pharmacokinetics and pharmacodynamics in clinical use of scopolamine[J]. Therapeutic Drug Monitoring, 2005, 27(5): 655-665
[37] KARCZMAR A G. Exploring the vertebrate central cholinergic nervous system[M]. New York: Springer, 2006: 1-698
[38] HAWRYLYCZ M J, LEIN E S, GUILLOZET-BONGAARTS A L, et al. An anatomically comprehensive atlas of the adult human brain transcriptome[J]. Nature, 2012, 489(7416): 391-399
[39] LEVEY A I, KITT C A, SIMONDS W F, et al. Identification and localization of muscarinic acetylcholine receptor proteins in brain with subtype-specific antibodies[J]. J Neurosci, 1991, 11(10): 3218-3226
[40] MARINO M J, ROUSE S T, LEVEY A I, et al. Activation of the genetically defined m1 muscarinic receptor potentiates N-methyl-D-aspartate (NMDA) receptor currents in hippocampal pyramidal cells[J]. Proc Natl Acad Sci U S A, 1998, 95(19): 11465-11470
[41] 左 杰. 东莨菪碱分子印迹聚合物的制备与固相萃取研究[D]. 合肥: 中国科学技术大学, 2019
[42] KESHAVARZ B, GOLDING J F. Motion sickness: current concepts and management[J]. Curr Opin Neurol, 2022, 35(1): 107-112
[43] ZHANG L L, LIU H Q, YU X H, et al. The combination of scopolamine and psychostimulants for the prevention of severe motion sickness[J]. CNS Neurosci Ther, 2016, 22(8): 715-722
[44] GOLDING J F, GRESTY M A. Pathophysiology and treatment of motion sickness[J]. Curr Opin Neurol, 2015, 28(1): 83-88
[45] SMITH P F. Recent developments in the understanding of the interactions between the vestibular system, memory, the hippocampus, and the striatum [J]. Front Neurol, 2022, 13: 986302
[46] KOHL R L, HOMICK J L. Motion sickness: a modulatory role for the central cholinergic nervous system[J]. Neurosci Biobehav Rev, 1983, 7(1): 73-85
[47] EISENMAN L M. Motion sickness may be caused by a neurohumoral action of acetylcholine[J]. Med Hypotheses, 2009, 73(5): 790-793
[48] SAKATA E, OHTSU K, SAKATA H. Motion sickness: its pathophysiology and treatment[J]. Int Tinnitus J, 2004, 10(2): 132-136
[49] NAPADOW V, SHEEHAN J D, KIM J, et al. The brain circuitry underlying the temporal evolution of nausea in humans[J]. Cereb Cortex, 2013, 23(4): 806-813
[50] QI R, SU Y, PAN L, et al. Anti-cholinergics mecamylamine and scopolamine alleviate motion sickness-induced gastrointestinal symptoms through both peripheral and

central actions[J]. Neuropharmacology, 2019, 146: 252-263

[51] 刘振明,蒋谋珅,丁 蒙. 东莨菪碱-新斯的明-吗啡联合用于硬膜外下肢骨科术后镇痛的疗效观察[J]. 临床合理用药杂志,2015,8(5):68-69

[52] 洪庚辛,李建华,金国章. 东莨菪碱镇痛作用的研究[J]. 生理学报,1984,58(2):149-156

[53] CULLHED S, LOFSTROM B. Obstetric analgesia with pethidine and scopolamine[J]. Lancet, 1961, 1(7168): 75-77

[54] 杨 锋. 阿托品联合东莨菪治疗急性有机磷中毒疗效观察[J]. 求医问药(下半月),2012,10(8):70

[55] 何仁辉. 东莨菪碱抢救急性重度杀虫双中毒30例疗效观察[J]. 中国职业医学,2012,39(3):226-228

[56] MCCARRON R M, SHAPIRO B, RAWLES J, et al. Depression[J]. Ann Intern Med, 2021, 174(5): ITC65-ITC80

[57] BORROTO-ESCUELA D O, AMBROGINI P, CHRUŚCICKA B, et al. The role of central serotonin neurons and 5-HT heteroreceptor complexes in the pathophysiology of depression: a historical perspective and future prospects[J]. Int J Mol Sci, 2021, 22(4): 1927

[58] CHEN B H, AHN J H, PARK J H, et al. Effects of scopolamine and melatonin cotreatment on cognition, neuronal damage, and neurogenesis in the mouse dentate gyrus[J]. Neurochem Res, 2018, 43(3): 600-608

[59] PRICE R B, DUMAN R. Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model[J]. Mol Psychiatry, 2020, 25(3): 530-543

[60] CARHART-HARRIS R L, NUTT D J. Serotonin and brain function: a tale of two receptors[J]. J Psychopharmacol, 2017, 31(9): 1091-1120

[61] BERRIDGE M J. Vitamin D and depression: cellular and regulatory mechanisms[J]. Pharmacol Rev, 2017, 69(2): 80-92

[62] VOLETI B, NAVARRIA A, LIU R J, et al. Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses[J]. Biol Psychiatry, 2013, 74(10): 742-749

[63] FOGAçA M V, WU M, LI C, et al. Inhibition of GABA interneurons in the mPFC is sufficient and necessary for rapid antidepressant responses[J]. Mol Psychiatry, 2021, 26(7): 3277-3291

[64] NAVARRIA A, WOHLEB E S, VOLETI B, et al. Rapid antidepressant actions of scopolamine: role of medial prefrontal cortex and M1-subtype muscarinic acetylcholine receptors[J]. Neurobiol Dis, 2015, 82: 254-261

[65] FUREY M L, DREVETS W C. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial[J]. Arch Gen Psychiatry, 2006, 63(10): 1121-1129

[66] PARK L, FUREY M, NUGENT A C, et al. Neurophysiological changes associated with antidepressant response to ketamine not observed in a negative trial of scopolamine in major depressive disorder[J]. Int J Neuropsychopharmacol, 2019, 22(1): 10-18

[67] CHEN J C C, SUMNER R L, NAGA V K, et al. A randomized controlled trial of intravenous scopolamine versus active-placebo glycopyrrolate in patients with major depressive disorder[J]. J Clin Psychiatry, 2022, 83(5): 21m14310

[68] DREVETS W C, FUREY M L. Replication of scopolamine's antidepressant efficacy in major depressive disorder: a randomized, placebo-controlled clinical trial[J]. Biological psychiatry, 2010, 67(5): 432-438

[69] WANG S, GUO P, FENG M, et al. The efficacy of scopolamine for patients with Parkinson's disease and depression: two case reports[J]. Asian J Psychiatr, 2020, 52: 102107

[70] BITTENCOURT S, FERRAZOLI E, VALENTE M F, et al. Modification of the natural progression of epileptogenesis by means of biperiden in the pilocarpine model of epilepsy[J]. Epilepsy Research, 2017, 138: 88-97

[71] MELLER S, KÄUFER C, GAILUS B, et al. Scopolamine prevents aberrant mossy fiber sprouting and facilitates remission of epilepsy after brain injury[J]. Neurobiol Dis, 2021, 158: 105446

[72] KIM Y H, LEE Y, KIM D, et al. Scopolamine-induced learning impairment reversed by physostigmine in zebrafish[J]. Neurosci Res, 2010, 67(2): 156-161

[73] YOUSUF H, GIRARDI E M, CROUSE R B, et al. Muscarinic antagonists impair multiple aspects of operant discrimination learning and performance[J]. Neurosci Lett, 2023, 794: 137025

[74] SALVATIERRA A T, BERRY S D. Scopolamine disruption of septo-hippocampal activity and classical conditioning[J]. Behav Neurosci, 1989, 103(4): 715-721

[75] ANTONOVA E, PARSLOW D, BRAMMER M, et al. Scopolamine disrupts hippocampal activity during allocentric spatial memory in humans: an fMRI study using a virtual reality analogue of the Morris water maze[J]. J Psychopharmacol, 2011, 25(9): 1256-1265

[76] RASHID H, AHMED T. Muscarinic activity in hippocampus and entorhinal cortex is crucial for spatial and fear memory retrieval[J]. Pharmacol Rep, 2019, 71(3): 449-456

[77] PARK J H, CHOI H Y, CHO J H, et al. Effects of chronic scopolamine treatment on cognitive impairments and myelin basic protein expression in the mouse hippocampus

[J]. J Mol Neurosci, 2016, 59(4): 579-589
[78] LEE J C, PARK J H, AHN J H, et al. Effects of chronic scopolamine treatment on cognitive impairment and neurofilament expression in the mouse hippocampus[J]. Mol Med Rep, 2018, 17(1): 1625-1632
[79] NAVARRO N M, KRAWCZYK M C, BOCCIA M M, et al. Extinction and recovery of an avoidance memory impaired by scopolamine[J]. Physiol Behav, 2017, 171: 192-198
[80] MELAMED J L, DE JESUS F M, MAIOR R S, et al. Scopolamine induces deficits in spontaneous object-location recognition and fear-learning in marmoset monkeys[J]. Front Pharmacol, 2017, 8: 395
[81] 何 雷. 东莨菪碱对小鼠边界细胞空间信息编码的影响[J]. 南京医科大学学报(自然科学版), 2022, 42(9): 1230-1234
[82] LUYTEN L, NUYTS S, BECKERS T. Low-dose systemic scopolamine disrupts context conditioning in rats[J]. J Psychopharmacol, 2017, 31(6): 667-673
[83] ZOLOTOV N N, SCHEPETKIN I A, VORONINA T A, et al. Therapeutic effect of novel cyanopyrrolidine-based prolyl oligopeptidase inhibitors in rat models of amnesia[J]. Front Chem, 2021, 9: 780958
[84] BRINZA I, ABD-ALKHALEK A M, EL-RAEY M A, et al. Ameliorative effects of rhoifolin in scopolamine-induced amnesic zebrafish (danio rerio) model[J]. Antioxidants (Basel), 2020, 9(7): 580
[85] LANGER K G. The history of amnesia-a review[J]. Curr Neurol Neurosci Rep, 2021, 21(8): 40
[86] BEJAR C, WANG R H, WEINSTOCK M. Effect of rivastigmine on scopolamine-induced memory impairment in rats[J]. Eur J Pharmacol, 1999, 383(3): 231-240
[87] QU Z, ZHANG J, YANG H, et al. *Prunella vulgaris* L., an edible and medicinal plant, attenuates scopolamine-induced memory impairment in rats[J]. J Agric Food Chem, 2017, 65(2): 291-300
[88] ZHAO J, LI K, WANG Y, et al. Enhanced anti-amnestic effect of donepezil by Ginkgo biloba extract (EGb 761) via further improvement in pro-cholinergic and antioxidative activities[J]. J Ethnopharmacol, 2021, 269: 113711
[89] OBOH G, ADEDAYO B C, ADETOLA M B, et al. Characterization and neuroprotective properties of alkaloid extract of *Vernonia amygdalina* Delile in experimental models of Alzheimer's disease[J]. Drug Chem Toxicol, 2022, 45(2): 731-740
[90] AYKAC A, TERALI K, ÖZBEYLI D, et al. A multi-parameter evaluation of the neuroprotective and cognitive-enhancing effects of *Origanum onites* L. (Turkish Oregano) essential oil on scopolamine-induced amnestic rats[J]. Metab Brain Dis, 2022, 37(4): 1041-1055
[91] ZHAO T, ZHONG S, XU J, et al. PAYCS alleviates scopolamine-induced memory deficits in mice by reducing oxidative and inflammatory stress and modulation of gut microbiota-fecal metabolites-brain neurotransmitter axis[J]. J Agric Food Chem, 2022, 70(9): 2864-2875
[92] ZHOU J, YANG W S, SUO D Q, et al. Moringa oleifera seed extract alleviates scopolamine-induced learning and memory impairment in mice[J]. Front Pharmacol, 2018, 9: 389
[93] BRINZA I, AYOUB I M, ELDAHSHAN O A, et al. Baicalein 5, 6-dimethyl ether prevents memory deficits in the scopolamine zebrafish model by regulating cholinergic and antioxidant systems[J]. Plants (Basel), 2021, 10(6): 1245
[94] DUMITRU G, EL-NASHAR H A S, MOSTAFA N M, et al. Agathisflavone isolated from *Schinus polygamus* (Cav.) cabrera leaves prevents scopolamine-induced memory impairment and brain oxidative stress in zebrafish (Danio rerio)[J]. Phytomedicine, 2019, 58: 152889
[95] BRINZA I, ABD-ALKHALEK A M, EL-RAEY M A, et al. Ameliorative effects of rhoifolin in scopolamine-induced amnesic zebrafish (danio rerio) model[J]. Antioxidants (Basel), 2020, 9(7): 580
[96] DETURE M A, DICKSON D W. The neuropathological diagnosis of Alzheimer's disease[J]. Mol Neurodegener, 2019, 14(1): 32
[97] FERREIRA-VIEIRA T H, GUIMARAES I M, SILVA F R, et al. Alzheimer's disease: targeting the cholinergic system[J]. Curr Neuropharmacol, 2016, 14(1): 101-115
[98] ARAFA N M S, ALI E H A, HASSAN M K. Canagliflozin prevents scopolamine-induced memory impairment in rats: comparison with galantamine hydrobromide action[J]. Chem Biol Interact, 2017, 277: 195-203
[99] CHEN W N, YEONG K Y. Scopolamine, a toxin-induced experimental model, used for research in Alzheimer's disease[J]. CNS Neurol Disord Drug Targets, 2020, 19(2): 85-93
[100] HERNÁNDEZ-RODRÍGUEZ M, ARCINIEGA-MARTÍNEZ I M, GARCÍA-MARÍN I D, et al. Chronic administration of scopolamine increased GSK3βP9, beta secretase, amyloid beta, and oxidative stress in the hippocampus of wistar rats[J]. Mol Neurobiol, 2020, 57(9): 3979-3988
[101] DAS T K, JANA P, CHAKRABARTI S K, et al. Curcumin downregulates GSK3 and Cdk5 in scopolamine-induced Alzheimer's disease rats abrogating Aβ (40/42) and tau hyperphosphorylation[J]. J Alzheimers Dis Rep, 2019, 3(1): 257-267
[102] JOSEPH E, VILLALOBOS-ACOSTA D, TORRES-RAMOS M A, et al. Neuroprotective effects of apocynin and galantamine during the chronic administration of scopol-

amine in an Alzheimer's disease model[J]. J Mol Neurosci,2020,70(2):180-193

[103]HUANG J M,HUANG F I,YANG C R. Moscatilin ameliorates tau phosphorylation and cognitive deficits in Alzheimer's disease models[J]. J Nat Prod,2019,82(7):1979-1988

[104]YAMAMOTO S,NISHIYAMA S,KAWAMATA M,et al. Muscarinic receptor occupancy and cognitive impairment:a PET study with[11C](+)3-MPB and scopolamine in conscious monkeys[J]. Neuropsychopharmacology,2011,36(7):1455-1465

[105]SARTER M,GIVENS B,BRUNO J P. The cognitive neuroscience of sustained attention:where top-down meets bottom-up[J]. Brain Research Reviews,2001,35(2):146-160

[106]DUNNE M P,HARTLEY L R. Scopolamine and the control of attention in humans[J]. Psychopharmacology(Berl),1986,89(1):94-97

[107]LEVIN E D,BUSHNELL P J,REZVANI A H. Attention-modulating effects of cognitive enhancers[J]. Pharmacol Biochem Behav,2011,99(2):146-154

[108]VOLGIN A D,YAKOVLEV O A,DEMIN K A,et al. Understanding central nervous system effects of deliriant hallucinogenic drugs through experimental animal models[J]. ACS Chem Neurosci,2019,10(1):143-154

[109]SANZ C,ZAMBERLAN F,EROWID E,et al. The experience elicited by hallucinogens presents the highest similarity to dreaming within a large database of psychoactive substance reports[J]. Front Neurosci,2018,12:7

[110]LAGEJU N,NEUPANE D,JAISWAL L S,et al. Hyoscine butylbromide induced psychosis:a case report[J]. Clin Case Rep,2022,10(5):e05807

[111]BULUT N S,ARPACıOĞLU Z B. Acute onset psychosis with complex neurobehavioural symptomatology following the intramuscular injection of hyoscine butylbromide:a case report with an overview of the literature[J]. Eur J Hosp Pharm,2022,29(5):294-297

[112]XUEREB G,CALLEJA T,BORG J,et al. Unintentional overdose of hyoscine hydrobromide in a young child[J]. BMJ Case Rep,2020,13(2):e234029

[113]MUELLER K,PEEL J L. Scopolamine produces locomotor stereotypy in an open field but apomorphine does not[J]. Pharmacol Biochem Behav,1990,36(3):613-617

[114]SIPOS M L,BURCHNELL V,GALBICKA G. Effects of selected anticholinergics on acoustic startle response in rats[J]. J Appl Toxicol,2001,21(Suppl 1):S95-S101

[115]WILSON J E,MART M F,CUNNINGHAM C,et al. Delirium[J]. Nat Rev Dis Primers,2020,6(1):90

[116]QIU Y,CHEN D,HUANG X,et al. Neuroprotective effects of HTR1A antagonist WAY-100635 on scopolamine-induced delirium in rats and underlying molecular mechanisms[J]. BMC Neurosci,2016,17(1):66

[117]QIU Y,HUANG X,HUANG L,et al. 5-HT(1A)receptor antagonist improves behavior performance of delirium rats through inhibiting PI3K/Akt/mTOR activation-induced NLRP3 activity[J]. IUBMB Life,2016,68(4):311-319

[118]CHEON S Y,KOO B N,KIM S Y,et al. Scopolamine promotes neuroinflammation and delirium-like neuropsychiatric disorder in mice[J]. Sci Rep,2021,11(1):8376

[119]VOLGIN A D,YAKOVLEV O A,DEMIN K A,et al. Acute behavioral effects of deliriant hallucinogens atropine and scopolamine in adult zebrafish[J]. Behav Brain Res,2019,359:274-280

[120]LAKSTYGAL A M,KOLESNIKOVA T O,KHATSKO S L,et al. DARK classics in chemical neuroscience:atropine,scopolamine,and other anticholinergic deliriant hallucinogens[J]. ACS Chem Neurosci,2019,10(5):2144-2159

[121]ABDEL-HAFEZ A A,MESELHY M R,NAKAMURA N,et al. Effects of paeoniflorin derivatives on scopolamine-induced amnesia using a passive avoidance task in mice;structure-activity relationship[J]. Biol Pharm Bull,1998,21(11):1174-1179

[122]LEONARD M,ADAMIS D,SAUNDERS J,et al. A longitudinal study of delirium phenomenology indicates widespread neural dysfunction[J]. Palliat Support Care,2015,13(2):187-196

[123]THOMAS C,HESTERMANN U,KOPITZ J,et al. Serum anticholinergic activity and cerebral cholinergic dysfunction:an EEG study in frail elderly with and without delirium[J]. BMC Neurosci,2008,9:86

[124]SHAH D,BLOCKX I,KELIRIS G A,et al. Cholinergic and serotonergic modulations differentially affect large-scale functional networks in the mouse brain[J]. Brain Struct Funct,2016,221(6):3067-3079

[125]American Psychiatric Association The diagnostic and statistical manual of mental disorders[M]. 5th edition. Washington,DC,2013:256-268

[126]PEZZE M A,MARSHALL H J,CASSADAY H J. Scopolamine impairs appetitive but not aversive trace conditioning:role of the medial prefrontal cortex[J]. J Neurosci,2017,37(26):6289-6298

[127]TRZEPACZ P T. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine[J]. Semin Clin Neuropsychiatry,2000,5(2):132-148

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