•综述•

烟碱 $\alpha4\beta2$ 型受体与相关疾病及药物研究进展

孔德文, 于子茹, 周启蒙, 杜冠华*

(中国医学科学院、北京协和医学院药物研究所, 北京 100050)

摘要: $\alpha4\beta2$ 型烟碱受体 (nAChR) 是一种配体门控离子通道, 在整个神经系统几乎都有分布, 参与乙酰胆碱、多巴胺、γ-氨基丁酸、去甲肾上腺素等神经递质的调节和释放, 在机体的学习、记忆、认知、注意力、炎症以及疼痛中发挥重要作用。大量研究表明, $\alpha4\beta2$ 型 nAChR 是阿尔茨海默症、帕金森病、癫痫、抑郁症、尼古丁依赖、疼痛等神经系统性疾病的重要治疗靶点, 对以老年痴呆为主的神经退行性疾病早期诊断和疗效检测具有重要意义。本文总结了 $\alpha4\beta2$ 型 nAChR 在神经系统性疾病治疗中的作用、机制以及相关药物研究进展, 为筛选和开发更合适的 $\alpha4\beta2$ 型 nAChR 相关化合物提供理论依据。

关键词: 烟碱型乙酰胆碱受体; $\alpha4\beta2$; 神经系统疾病; 药物

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$\alpha4\beta2$-Nicotine acetylcholine receptor: advances in relevant diseases and drugs

KONG De-wen, YU Zi-ru, ZHOU Qi-meng, DU Guan-hua*

(*Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*)

Abstract: The $\alpha4\beta2$-nicotinic acetylcholine receptor (nAChR) is a ligand-gated ion channel that is distributed throughout the nervous system. It is involved in the regulation of various neurotransmitters including acetylcholine, dopamine, γ-aminobutyric acid, and norepinephrine. $\alpha4\beta2$-nAChR plays an important role in learning, memory, cognition, attention, inflammation, and pain. A large number of studies have shown that $\alpha4\beta2$-nAChR is an important therapeutic target for neurological diseases such as Alzheimer's disease, Parkinson's disease, epilepsy, depression, nicotine dependence, pain, etc. It is an important target in the early diagnosis and curative effect detection of neurodegenerative diseases including Alzheimer's disease. This review summarizes the role, mechanisms and related drug research advances on $\alpha4\beta2$-nAChR ligand drugs in neurological diseases, as well as providing a theoretical basis for identifying and developing more suitable $\alpha4\beta2$-nAChR-related compounds.

Key words: nicotine acetylcholine receptor; $\alpha4\beta2$; nervous system disease; drug

烟碱型乙酰胆碱受体 (nicotinic acetylcholine receptors, nAChRs) 属于 cys-loop 受体超家族, 是一种配体门控离子通道蛋白, 分为 N1 和 N2 两种主要亚型。N2 受体也叫肌肉型烟碱受体, 主要分布于神经−骨骼肌接头的终板膜上[1], 而 N1 型受体则主要分布在自主神经节突触后膜和中枢神经系统, 因此也叫神经型烟碱受体。哺乳动物的烟碱受体由不同的亚单位组成, 已经确认的亚单位有多种, 现已证明, 亚单位 $\alpha1$、$\beta1$、δ、ε 和 γ 组成 N1 受体, 其余亚单位 $\alpha2$～10、$\beta2$～4 均存在于神经型烟碱受体[2]。

中枢神经系统中的 nAChRs 是由不同亚单位组成的多功能的同源或异源五聚受体[3,4], 即由 5 种不同的亚单位聚合而成一个具有特定功能的受体, 分布在大脑的不同区域。中枢神经系统中含量最丰富的是烟碱 $\alpha4\beta2$ 型和烟碱 $\alpha7$ 型两种受体亚型, 其中, $\alpha7$ 型 nAChR

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*通讯作者 Tel: 86-10-63165184, E-mail: dugh@imm.ac.cn

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只在大脑皮层、下丘脑和海马及一些脑干核团中出现, 而 $\alpha4\beta2$ 型 nAChR 几乎分布在整个神经系统[5], 参与机体的认知注意、学习记忆、发育衰老以及疼痛等多种生理过程。受体的缺失、过度激活、抑制或脱敏都会引起人类的疾病, 科学家围绕 nAChR 合成了大量相关化合物用于调节机体胆碱神经功能, 并对其药理作用进行了大量的研究。本文综合介绍了 $\alpha4\beta2$ 型烟碱受体在哺乳动物大脑中的结构、分布和功能, 总结了受体在神经系统性疾病发生和治疗中的重要作用、机制研究以及相关药物研究进展。

1 烟碱 $\alpha4\beta2$ 型受体

1.1 烟碱 $\alpha4\beta2$ 型受体结构与分布 烟碱 $\alpha4\beta2$ 型受体是由 $\alpha4$ 和 $\beta2$ 两种亚单位按照 2 ($\alpha4$)∶3 ($\beta2$) 和 3 ($\alpha4$)∶2 ($\beta2$) 两种比例组成的乙酰胆碱受体 5 聚体亚型, 前者对 $\alpha4\beta2$ 型 nAChR 配体表现出相对较高的敏感性。$\alpha4\beta2$ 型 nAChR 广泛分布于丘脑、海马、纹状体、杏仁核、腹侧被盖区 (VTA)、蓝斑和中缝背核等大脑区域, 与多种中枢神经功能和疾病相关。$\alpha4\beta2$ 型 nAChR 的 α 亚基是受体的结合亚基, 其配体结合位点在胞外结构域的两个相邻亚基之间, 而 β 亚基为结构亚基, 用于维持受体结构的稳定性。每个亚单位都有一个大的氨基末端胞外结构域 (ECD) 和 4 个跨膜 α-螺旋链段 (M1～M4), 其中 M4 与 M3 之间有一个细胞内环状结构域, 另一端则是一个较短的延伸至胞外的羧基[6]。2016 年 Morales-Perez 等[7]解析出了人源 $\alpha4\beta2$ 型 nAChR 的 X-ray 晶体结构, 明确了每个氨基酸的空间分布和每个亚单位的二级结构, 发现配体结合位点位于 $\alpha4$ 亚基的 A-loop、B-loop、C-loop 和相邻 $\beta2$ 亚基上的 β-sheet 所形成的结合口袋中, 因此利用虚拟分子对接模拟程序, 设计并合成了一系列配体药物, 也为 $\alpha4\beta2$ 型 nAChR 与配体相互作用的深度研究提供了有用的参考。

1.2 烟碱 $\alpha4\beta2$ 型受体的功能 大多数 $\alpha4\beta2$ 型 nAChR 位于突触前, 通过调节乙酰胆碱 (ACh)、多巴胺 (DA)、去甲肾上腺素 (NE)、5-羟色胺 (5-HT)、γ-氨基丁酸 (GABA) 和谷氨酸 (Glu) 等各种神经递质的释放而发挥作用, 位于突触后膜的受体则介导快速兴奋性突触的传递[2]。烟碱受体被激活后, 结构发生改变, 通道开放, 使 Na^+ 和 Ca^{2+} 通过, 并在 Ca^{2+} 浓度的控制下影响细胞内的一系列复杂的信使级联反应[6], 但长期暴露于 ACh 或烟碱受体激动剂下, 这种离子反应速率会逐渐下降, 即受体处于脱敏状态。这种与配体结合后出现的通道开放、关闭及脱敏使 nAChR 发生构效状态的转换, 也使得烟碱受体功能更加复杂。研究表明, $\alpha4\beta2$ 型 nAChR 参与神经元生存、神经保护以及突触可塑性等多项功能, 并在记忆、学习、认知以及镇痛等方面发挥重要作用[8]。

2 烟碱 $\alpha4\beta2$ 型受体与神经系统疾病

2.1 烟碱 $\alpha4\beta2$ 型受体与阿尔茨海默症 阿尔茨海默症 (Alzheimer's disease, AD) 是一种以渐进性记忆认知功能障碍为主要表现的神经退行性疾病。AD 的病理特征之一是前脑基底部胆碱能神经元变性[9], 而乙酰胆碱与人的学习、记忆及认知密切相关[10], 因此 Bartus 等[11]提出了胆碱能假说作为其关键的病理生理学机制。目前, 临床上治疗 AD 最主要的方式是抑制 ACh 分解, 他克林、多奈哌齐、加兰他明和利斯的明是仅有的被 FDA 批准上市的 4 种乙酰胆碱酯酶抑制剂, 但由于其有限的治疗效果、不良反应及耐受性, AD 治疗仍然是一个亟待解决的难题。

许多研究报道, AD 患者大脑中的 $\alpha4\beta2$ 型 nAChR 含量显著下降, 其密度的降低也反映了 AD 患者认知功能状态, 可作为一种成像生物标志物[12]。临床研究表明, 尼古丁、ABT-418 (人工合成激动剂)[13]等受体激动剂能明显改善 AD 患者记忆力和学习能力。β-淀粉样蛋白 (Aβ) 异常沉积是 AD 的发病机制之一, 而尼古丁可以通过活化的激酶 C 受体 1 (RACK1) 依赖性激活蛋白激酶 C (PKC), 促进 Aβ 前体蛋白非淀粉样加工[14,15], 降低 Aβ 聚集产生的毒性。研究表明, 共同激活 $\alpha7$ 和 $\alpha4\beta2$ nAChR 可以逆转 Aβ42 诱导的钙过度兴奋[16], 并且 Samra 等[17]研制的具有 Aβ 斑块/$\alpha4\beta2$ nAChR 双亲和力的药物能够靶向清除受体附近的 Aβ 斑块, 有望成为治疗 AD 的新方法。

2.2 烟碱 $\alpha4\beta2$ 型受体与帕金森病 帕金森病 (Parkinson's disease, PD) 是一种发病率仅次于 AD 的神经退行性疾病, 主要临床特征为静止性震颤、肌强直、动作迟缓和姿势步态, 其病理机制是黑质−纹状体的多巴胺神经元死亡。目前针对 PD 运动症状应用的左旋多巴制剂等替代治疗能够缓解症状, 但不能阻止病情发展, 并且还会出现疗效减退、症状波动和精神障碍等不良反应。

研究发现, 在 PD 患者和模型动物的脑干和额叶皮层中, nAChR 的 $\beta2$ 亚单位均表达降低[18]。Domino 等[19]在猴实验中证实, 合用尼古丁、ABT-089、ABT-894[20]等 $\alpha4\beta2$ 型 nAChR 激动剂对左旋多巴改善帕金森症状具有协同作用, 并且可以减少治疗过程中出现的运动障碍和开关现象等不良反应, 单独使用 $\alpha4\beta2$ 型 nAChR 激动剂也能够明显改善 6-羟基多巴胺 (6-OHDA) 诱导大鼠黑质单侧病变引起的运动功能障碍[21], 而当合用受体拮抗剂[22]或者敲除 $\alpha4$ nAChR 基因[23]时, 保护作用显著性下降, 说明 $\alpha4\beta2$ 型 nAChR 是 PD 治疗的一个重要靶点。激动剂与 $\alpha4\beta2$ 型 nAChR 结合后, 诱导黑质纹状体区域多巴胺释放, 并且长期使用能够

抑制氧化应激, 诱导神经营养因子表达, 从而降低大鼠半侧中前脑横断所引起的黑质纹状体变性。α-突触核蛋白的积累和聚集也是PD的重要发病机制之一, 最新的研究发现, 较大的聚集性α-突触核蛋白呈剂量依赖性、非竞争性、非使用依赖性地部分抑制α4β2型nAChR, 导致基底神经节胆碱能功能减退以及神经元变性[18,24], 而尼古丁可以通过激活D3R-nAChR异构体, 防止α-突触核蛋白聚集[25], 提示改善特定聚集α-突触核蛋白诱导α4β2型nAChR功能缺失可能是PD治疗的新策略。

2.3 烟碱α4β2型受体与抑郁症 抑郁症是一种常见的慢性精神疾病, 表现为悲伤、失去兴趣和快感、负罪感或自卑感及注意力不集中等, 影响到全球约3亿人[26]。目前, 抗抑郁药主要针对调节DA、5-HT和NE再摄取的单胺转运体[27], 但近三分之二抑郁症患者未获得有效治疗[28], 而临床试验发现, 烟碱乙酰胆碱能化合物可以缓解常规药物治疗耐药的患者的症状[29, 30], 并且临床抗抑郁药安非他酮在α4、α6或β2 nAChR基因敲除的小鼠中表现出更好的药效[31], 提示α4β2型nAChR在抑郁症发生和治疗中起着重要的作用。

胆碱能假说提出, 体内胆碱能活性超过肾上腺素时会引起抑郁[32], 敲除β2基因后, 小鼠在强迫游泳实验中不动时间减少, 攀爬时间增加[33], 表明体内缺乏β2 nAChR介导的信号可以表现出类抗抑郁表型。研究表明, 乙酰胆碱受体拮抗剂和部分激动剂均能改善动物的抑郁样症状[34-36], 其中激动剂被认为是通过干扰乙酰胆碱信号转导活性发挥作用。烟碱受体能够强化多巴胺神经传递作用、调节促肾上腺皮质激素释放因子 (CRF) 和下丘脑−垂体−肾上腺素 (HPA) 轴功能亢进以及海马细胞质和视交叉上核的昼夜节律[37-39], 从而发挥情绪调控作用。另外, α4β2型nAChR还可以通过PI3K/AKT/mTOR信号通路上调海马和杏仁核中的脑源性神经营养因子 (BDNF) 和5HTA1受体水平[40], 并且能降低基底外侧杏仁核区域c-fos活性[34], 从而改善慢性应激小鼠的抑郁样行为。

2.4 烟碱α4β2型受体与癫痫 癫痫是神经系统常见疾病, 常染色体显性遗传夜额叶癫痫 (autosomal dominant nocturnal frontal lobe epilepsy, ADNFLE) 是第一个明确为常染色体变性遗传的部分性癫痫[41], 表现为夜间成串的运动症状, 大约12%的ADNFLE家族携带编码异源α4β2型神经元烟碱样受体亚基的突变基因[36,42], 提示这些受体的改变可能是癫痫神经网络紊乱的根源。

Picard等[43]推测, 突变α4β2型nAChR不能使丘脑同步化脑电活动及时停止, 导致皮质和丘脑觉醒状态失衡, 引起丘脑额叶神经环路异常活动, 从而导致ADNFLE。研究表明,瓜蟾卵母细胞α4β2型nAChR突变后[44-46], 受体敏感性可能发生改变[47], 细胞Ca^{2+}通透性和依赖性降低[48,49], 突变受体功能受到抑制。Aracri等[50]也证明, α4β2型nAChR能调节GABA在快速放电 (FS) 神经元上的释放, 并持续调节小鼠额叶区2 (Fr2) 的FS层V神经元的抑制性突触后电流 (IPSC)。

研究发现, 突触前烟碱受体兴奋可以直接或间接促进谷氨酸释放, 进而兴奋谷氨酸*N*-甲基-*D*-天冬氨酸 (NMDA) 受体, 引起一系列级联反应导致癫痫发作, 例如α4β2型nAChR部分激动剂CYT能够抑制拉考沙胺、左乙拉西坦、普瑞巴林等抗癫痫药物对6 Hz电刺激的保护作用[51], 而PPARα激动剂非诺贝特能负性调节β2 nAChR功能, 降低对传统疗法无反应患者的癫痫发作频率[52]。同时也有研究者发现, 特发性全身性癫痫 (IGE) 患者前扣带回皮层 (ACC) 中α4β2型nAChR配体F-A-85280结合电位比率指数 (BPRI) 显著增加, 说明α4β2烟碱样受体也能调节其他遗传性癫痫, 并且可以作为其诊断生物标记[53]。

2.5 烟碱α4β2型受体与疼痛 研究发现, α4β2型nAChR的激动剂、部分激动剂和阳性变构调节剂 (PAMs) 在许多动物模型中能够有效缓解神经性和炎性疼痛, 并且这种作用在α4β2型nAChR基因敲除[54]或者联用α4β2型nAChR拮抗剂后明显降低, 进一步证明α4β2型nAChR是镇痛治疗的重要靶点。α4β2型nAChR大量存在的大核 (NRM)、中缝背核 (DR) 和篮斑 (LC) 是单胺能抑制性疼痛途径的主要作用区域, α4β2型nAChR能够通过调节ACh、DA、GABA和NE等多种神经递质, 在疼痛信号中发挥重要作用[55,56], 并且可以通过JAK2-STAT3等通路抑制炎症因子白细胞介素1β (IL-1β) 和白细胞介素6 (IL-6) 的表达, 从而抑制炎性疼痛[57]。

很多激动剂由于其严重的不良反应而不能被开发为药物, 比如地棘蛙素、ABT-594[58]等都在临床试验中出现运动或肠胃不适, 但进一步研究发现, α4β2型nAChR激动剂与PAMs联用能够提高效能[59,60], 但不增加催吐阈值, 从而降低不良反应。整体而言, 与现有的镇痛药相比, α4β2型nAChR配体有更好的疗效和更小的不良反应, 目前面临的挑战是继续将临床前功效转化为临床使用。

2.6 α4β2型nAChR与戒烟 吸烟引起的疾病已经成为严重的公共卫生及社会问题之一, 烟草中的尼古丁被吸入后, 与中脑腹侧被盖区的nAChR结合, 促使大量的DA被释放到伏隔核 (NAcc), 产生愉悦感, 也因此产生依赖性[61]。研究发现, 敲除α4 nAChR或β2 nAChR基因, 尼古丁活性下降[62,63]。而在中脑腹侧被盖区敲除β2 nAChR基因后再恢复表达, 小鼠也会再次出现寻找

尼古丁的行为, 并且DA释放也随之增加[64], 这些结果进一步表明了 $\alpha4\beta2$ 型nAChR与尼古丁成瘾性密切相关。目前, 针对尼古丁依赖的治疗药物除尼古丁替代疗法(NRT) 和抗抑郁药物安非他酮外, 具有 $\alpha4\beta2$ 型nAChR选择性的部分激动剂伐尼克兰已经应用于戒烟。

伐尼克兰作为部分激动剂, 一方面作为激动剂能够与受体结合, 导致DA释放, 缓解对尼古丁的渴望和戒断症状, 另一方面它同时占据了尼古丁结合位点, 从而起到拮抗尼古丁的作用[65]。有研究人员发现, 伐尼克林相对于NRT[66]和安非他酮[67], 能够更显著地降低戒烟者对烟草的渴求, 并且具有更好的服用依从性。

目前, 有越来越多的 $\alpha4\beta2$ 型nAChR选择性激动剂或部分激动剂用于尼古丁成瘾性研究, 例如Sazetidine-A也是一种 $\alpha4\beta2$ 型nAChR部分激动剂, 能够有效地减少尼古丁[68]、酒精[69]以及可卡因[69]等化合物的成瘾性, 并且长期服用不会上调 $\alpha4\beta2$ 型nAChR受体水平。$\alpha4\beta2$ 型nAChR是尼古丁的直接作用靶点, 因此选择性针对该受体进行药物治疗可以从源头上减少戒断症状和对尼古丁的依赖性。

2.7 烟碱 $\alpha4\beta2$ 型 nAChR 与其他疾病 缺血性疾病是血管性认知障碍 (VIC) 最常见的原因, 研究发现尼古丁可以通过上调 $\alpha4\beta2$ 型nAChR抑制肿瘤坏死因子 α (TNF-α)、IL-1β、IL-6等炎症因子的释放, 从而改善缺血大鼠的缺血性认知障碍, 发挥神经保护作用[70]; 另一方面, 尼古丁还能够改善多柔比星和环磷酰胺治疗癌症时引起的认知障碍, 并且这种作用能够被 $\alpha7$ 型nAChR拮抗剂和 $\alpha4\beta2$ 型nAChR拮抗剂所阻断, 但其作用机制需进一步研究[71]。

$\alpha4\beta2$ 型nAChR还与注意缺陷多动障碍 (ADHD) 密切相关, ADHD是儿童期常见的神经行为发育障碍性疾病, 特征是缺乏注意力、过度活跃和冲动, 并一直持续到成年期。ABT-418[72]、ABT-089、AZD3480[73]等 $\alpha4\beta2$ 型nAChR激动剂能够显著改善成人ADHD患者的症状, 可以增加前额皮质、海马和纹状体区域内 $\alpha4$ 和 $\beta2$ 受体蛋白的表达, 但对其mRNA表达没有影响, 提示这种受体数量的增加可能是通过转录后的某种机制介导的。

3 基于受体的药物研究

目前, 许多烟碱受体相关化合物已经用于神经系统相关疾病的治疗, 用于治疗的 $\alpha4\beta2$ 型nAChR相关化合物主要包括激动剂、部分激动剂、拮抗剂以及变构调节剂, 其中既有从动植物中提取的天然化合物, 例如地棘毒素、金雀花碱等, 也有根据天然配体结构设计合成的化合物, 以及根据 $\alpha4\beta2$ 型nAChR的X-ray结构分子对接虚拟筛选后进行药效验证得到的候选药物, 其中, 脂肪胺和含氮芳香杂环的拼合体是化合物对 $\alpha4\beta2$ 型nAChR高亲和力的共同结构特征[74]。

大量的化合物对 $\alpha4\beta2$ 型nAChR具有很高的亲和力, 在临床前研究中表现出良好药效和耐受性, 但能通过临床研究上市的药物少之又少, 这可能与化合物的受体亚型选择性、亲和力以及药代动力学等因素有关。表1[13,73,75-97]总结了部分目前已经进入临床研究的 $\alpha4\beta2$ 型nAChR相关配体化合物的研究阶段和临床主要治疗症状等信息, 其中部分候选药物在临床试验过程中由于其疗效不足或者严重的不良反应而被停止研究, 例如TC-1734在AD临床IIB期试验中未能表现出比安慰剂更好的药效, ABT-594在II期临床疼痛治疗过程中出现的恶心、呕吐等不良反应, 但是由于 $\alpha4\beta2$ 型nAChR与多种神经系统疾病密切相关, 部分候选药物在前期研究基础上继续在其他疾病治疗方面进行探究, 或者合用受体变构调节剂以减少不良反应, 从而期待获得较好的临床效果。

4 总结与展望

目前, 研究者围绕 $\alpha4\beta2$ 型nAChR及其配体已经做了大量的研究。在中枢神经系统中, $\alpha4\beta2$ 烟碱受体亚型占与烟碱有高亲和力的nAChR总量的90%, 分布极为广泛, 一般通过调节多巴胺等神经递质的释放发挥神经保护作用, 但是 $\alpha4\beta2$ 型nAChR在不同的神经系统疾病患者脑内含量变化不同, 因此需要针对性使用激动剂或拮抗剂改善不同的病理损伤, 例如 $\alpha4\beta2$ 型nAChR激动剂能够降低AD患者脑内的Aβ聚集, 改善PD患者 α-突触核蛋白积累导致的神经元损伤。而在抑郁症患者体内, $\alpha4\beta2$ 型nAChR部分激动剂或拮抗剂则可以通过拮抗胆碱能活性进一步影响HPA轴功能、BDNF等与抑郁症相关的通路和细胞因子发挥作用。$\alpha4\beta2$ 型nAChR分布极广, 其发挥作用的基础与疾病本身的病理损伤和其位置密切相关, 例如 $\alpha4\beta2$ 型nAChR的突变会导致ADNFLE等遗传性癫痫的发生, 烟草中的尼古丁持续性刺激中脑腹侧被盖区的 $\alpha4\beta2$ 型nAChR导致大量DA的释放产生依赖作用。但是, 也正是由于 $\alpha4\beta2$ 型nAChR分布广, 功能复杂, 即使 $\alpha4\beta2$ 型nAChR高选择性药物也可能具有复杂的作用甚至产生不良反应, 尤其是全身给药后分布到大脑的所有部位时。另一方面, $\alpha4\beta2$ 型nAChR调控生命活动的机制研究仍然有限, 并且缺乏特异性、全面性的受体与药物分子相互作用机制的深入研究。

$\alpha4\beta2$ 型nAChR相关化合物在许多神经系统疾病中表现出的治疗效果启示其良好的发展前景, 目前针对该受体开发了很多激动剂、部分激动剂、拮抗剂和变构调节剂, 但是化合物药效不一, 存在很高的临床试验

Table 1 Advances on neurological diseases of main compound with $\alpha4\beta2$ nicotinic acetylcholine receptors (nAChR) activity. AD: Alzheimer's disease; ADHD: Attention-deficit/hyperactivity disorder. *Clinical research discontinued

Compound	Ligand type	Highest phase	Active indication	Reference
A-366833	Agonist	Phase I	Pain	[75]
ABT-894	Agonist	Phase II*; Phase II	Pain; ADHD	[76,77]
ABT-594	Agonist	Phase II*	Pain	[78-81]
ABT-418	Agonist	Phase II*	AD; ADHD	[13,72,82]
TC-1734	Agonist	Phase II*; Phase II	AD; ADHD	[73,83,84]
TC-6683	Agonist	Phase I*, Phase II*	AD; ADHD	[85,86]
TC-2696	Agonist	Phase II*	Pain	[82]
S-38232	Agonist	Phase I*	AD	[87]
Varenicline	Partial agonist	Marketed; Phase II	Smoking cessation; depression	[88]
SSR591813	Partial agonist	Phase II*	Smoking cessation	[89]
Lobeline	Partial agonist	Phase III*; Phase II	Smoking cassation; ADHD	[90]
ABT-089	Partial agonist	Phase II	ADHD	[91]
TC-1734	Agonist	Phase II*	AD	[92]
TC-5214	Antagonist	Phase III	Depression	[93,94]
TC-2216	Antagonist	Phase I	Depression, anxiety disorders	[95]
Bupropion	Antagonist	Marketed	Depression, smoking cessation	[96,97]
TC-6499	Positive allosteric modulator	Phase I*	Pain	

淘汰率, 因此需要更准确地理解化合物作用于$\alpha4\beta2$型nAChR的细微差别, 以及与疾病之间的关系, 这有助于开发新的、药效好、不良反应小的药物。

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利益冲突: 不存在利益冲突关系。

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