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◇综 述◇

δ阿片受体激动剂在疾病治疗中的新进展

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摘要 阿片类药物是临床上常用药物,主要作用于分布在中枢、外周神经元等处的不同亚型的阿片受体,是治疗急性疼痛或癌痛的首选药物。δ阿片受体(DOR)激动剂是一种以δ受体为目标受体的阿片类药物,近年来因其对心脏、脑、肝脏等多器官的缺血/再灌注损伤改善作用及治疗精神和神经类疾病的潜力,得到广泛关注。该文就DOR激动剂在多种疾病治疗中的机制研究进行综述,并对其临床应用前景进行展望,发现DOR激动剂对器官抗缺血/再灌注损伤的作用可能通过减少凋亡和线粒体损伤,激活多种信号通路来实现;此类药物亦表现出抗炎、抗抑郁和治疗神经退行性疾病的作用,为DOR激动剂应用于相关疾病治疗提供新的视角。

关键词 DOR激动剂;缺血/再灌注损伤;心肌梗死;脓毒症;帕金森病;抑郁症

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阿片类药物已可以安全有效地应用于急性疼痛和癌痛的治疗[1],目前许多研究正显示出它在其他疾病治疗中的潜力[2]。阿片类药物分为天然阿片类药物、半合成和合成阿片类药物[3]。阿片类药物主要作用于三种阿片受体亚型,即μ、κ和δ阿片受体,它们广泛分布于中枢和外周神经元[4]。广为人知的μ阿片受体激动剂,如吗啡及其衍生物、芬太尼等已在临床用于镇痛[5]。而近期的大量研究[6]显示,δ阿片受体(delta opioid receptor,DOR)激动剂在抗缺血/再灌注(ischemia/reperfusion,I/R)损伤和改善负面情绪方面有良好作用,这引起了学者们的广泛关注。I/R损伤发生在急性心肌梗死和缺血性脑卒中等严重疾病的发生发展过程中,导致氧化应激、炎症等多种损害[7]。寻找缓解I/R损伤的治疗药物是当务之急。近年来,已有研究[8]报道人工合成的δ阿片肽(D-丙2,D-亮5)-脑啡肽([D-Ala2,D-Leu5]-enkephalin,DADLE)具有抗I/R损伤的组织保护作用。另外,研究[9-11]报道SNC80、KNT-

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close phylogenetic affinities with Brucella melitensis. Moreover, the phylogenetic tree analysis indicated that these strains coalesced within the same branch, the findings were in alignment with the results obtained from BCSP31-PCR and AMOS-PCR assays. ***Conclusion*** Brucella melitensis assumes a predominant position in the transmission dynamics within this area, identifying individuals involved in sheep breeding, slaughtering, vending, and related occupations as high-risk groups. The outcomes of this study offer molecular biological substantiation for the distribution of brucellosis patients in this region, contribute to genotyping endeavors and tracing studies associated with the pathogen, and concurrently verify the efficacy of 16S rRNA molecular tracing.

Key words brucellosis; pathogen surveillance; BCSP31-PCR; AMOS-PCR; 16S rRNA; brucella melitensis

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127、ARM390 等其他 DOR 激动剂也有对 I/R 损伤的潜在疗效。该文就 DOR 激动剂在各种疾病治疗中的研究进展进行综述并展望其未来应用前景。

1 DOR 激动剂在 I/R 中的作用

1.1 心肌 I/R 损伤 在中国,急性心肌梗死(acute myocardial infarction,AMI)的病死率一直保持较高的增长速度[12],疾病防控形势日益严峻。除药物溶栓治疗外,部分新型药物如螺内酯、秋水仙碱等仍处于动物实验阶段[13],因而继续开发新的药物以提升 AMI 的治疗效果具有长远意义。目前已发现多种 DOR 激动剂对心肌缺血/再灌注损伤(myocardial ischemia/reperfusion injury,MIRI)具有改善作用(表 1)。有关研究[14-15]表明,DOR 激动剂可通过直接或间接途径发挥对缺血后心脏的保护作用,如减少心肌细胞凋亡及减轻心肌细胞线粒体损伤等。吗啡可在激活 DOR 后,使表皮生长因子受体(epidermal growth factor receptor,EGFR)激活,从而激活 PI3K/Akt、MAPK 和 JAK/STAT-3 通路,减轻 MIRI 损伤[16];Okubo et al[17]采用家兔心肌 I/R 模型发现吗啡可通过激活 DOR,从而减少心肌细胞凋亡和心脏的梗死面积,发挥抗 MIRI 作用。值得关注的是,近期多项研究[18]显示 DADLE 在 MIRI 中有重要的心脏保护作用。在 MIRI 小鼠中应用 DADLE 处理后,C57BL/6J 小鼠心肌细胞的 TCF4、Wnt3a 和 β-Catenin 表达水平明显下降,提示 DADLE 可通过抑制 Wnt/β-Catenin 信号通路发挥抗 MIRI 作用[19]。Wang et al[20]发现 DOR 激动剂 SNC-121 可诱导小窝蛋白转运至线粒体,在心肌缺血时减轻心肌细胞线粒体损伤,进而发挥对心肌的保护作用。此外,MIRI 还会带来组织炎症和心律失常等一系列后果[14]。Maslov et al[21]发现 Delt-Dvar 和 Delt-E 对 MIRI 后的心律失常有显著的预防作用;这两种激动剂作用于 δ_2 阿片受体,它存在于脑和脊髓等组织细胞中,外周使用其激动剂可产生镇痛、抗心肌损伤和体温调节等生物学效应[22]。其他 DOR 激动剂,如 BW373U86 和 p-Cl-Phe DPDPE[23],也表现出对缺血心肌的保护作用。以上研究揭示了 DOR 激动剂能通过激活多种分子信号通路,减轻线粒体损伤和细胞凋亡,从而有效减轻 MIRI 所引起的炎症和功能障碍,减少梗死面积,为推进其临床应用奠定了理论基础。

1.2 脑 I/R 损伤 缺血性脑卒中(ischemic stroke,IS)是一种常见的脑血管疾病,致死率高。其病因是脑供血血管异常狭窄或堵塞,致使脑组织缺血坏死,引起脑 I/R 损伤(cerebral ischemia/reperfusion injury,CIRI)[24]。目前有针对急性 IS 的诊断和治疗措施[25],但患者预后不良、病死率高等问题仍然存在[26],需要进行机制研究和开发更多药物。已有研究[27]表明,在 IS 引发 CIRI 时,DADLE 具有一定的神经保护作用。Chen et al[28]构建大脑中动脉闭塞/再灌注(middle cerebral artery occlusion/reperfusion,MCAO/R)模型,进行侧脑室埋管注射 DADLE 后发现,DADLE 能够明显减少脑梗死的面积,并可能通过基质金属蛋白酶(matrix metalloproteinase,MMP)介导释放肝素结合生长因子(HB-EGF),进而转激活 EGFR 来减轻 CIRI。亦有研究[29]表明 DADLE 可能提高 DOR 表达,并以 AMPK/mTOR/ULK1 信号通路依赖的方式增强神经元细胞自噬,发挥神经保护作用。淀粉样前体蛋白(amyloid precursor protein,APP)是一种神经保护因子,与急性神经元损伤中的神经保护密切相关[30]。Min et al[31]以 MCAO/R 模型小鼠为研究对象,发现一种非肽类 DOR 激动剂 Tan-67 可能通过上调 APP 的表达实现在 IS 发生时的神经保护作用。Zhang et al[32]发现,DADLE 可能通过降低裂解天冬氨酸特异性的半胱氨酸蛋白水解酶 9(Caspase-9)含量及降低 Bax 与 Bcl-2 蛋白水平的比值来减少脑微血管内皮细胞(brain microvascular endothelial cells,BMECs)的凋亡,进而减轻 CIRI。BMECs 也是新近发现的有内源性 DOR 表达的细胞类型,可能作为 DOR 激动剂靶点进行深入研究,以期在 CIRI 中加强对血管内皮的保护,改善血脑屏障

表 1 发挥抗 MIRI 作用的 DOR 激动剂及其机制

Tab.1 The anti-MIRI effects and mechanisms of DOR agonists

Name	Mechanism	References
Morphine	Activating PI3K/AKT, MAPK, and JAK/STAT3 pathway	[16-17]
DADLE	Inhibiting Wnt/β-catenin signaling pathway	[19]
SCN-121	Inducing the transfer of caveolin to mitochondria and reducing the damage of myocardial mitochondria	[20]
Delt-Dva, Delt-E	Effectively reducing the incidence of arrhythmia after I/R	[21]
BW373U86, p-Cl-Phe DPDPE	Significantly reducing myocardial infarction area in animal experiments	[23]

的功能。Deng et al[33]研究显示,DADLE 作用在建立氧糖剥夺/复氧复糖(oxygen-glucose deprivation/reoxygenation,OGD/R)模型的 BMECs 上,可上调瞬时受体电位香草醛受体 4(TRPV4)的表达,并且可能通过增加其介导的钙离子内流,提升细胞线粒体自噬水平,从而改善线粒体功能。除 DADLE 外,有报道[34]称 DOR 激动剂 BW373U86 可能通过血脑屏障,发挥抗 CIRI 的作用。以上研究成果均提示 DOR 激动剂具有抗 CIRI 能力,显示出其用于治疗 IS 的转化潜力。

1.3 肝、肺和脊髓 I/R 损伤 I/R 对其他器官,如肝、肺和脊髓等的组织亦会造成不同程度损伤。关于肺脏,有学者研究显示 OGD/R 过程中,DADLE 可能在上调 MAPK 通路的酪氨酸激酶磷酸化程度的同时,下调 P38 的磷酸化,使二者动态平衡,从而减轻 I/R 对肺部造成的损伤[35];DADLE 还可以激活核因子 E2 相关因子 2/血红素加氧酶-1(Nrf2/HO-1)通路,以减轻小鼠肝脏所受 I/R 损伤[36]。此外,章建平 等[37]建立兔脊髓 I/R 损伤模型,测定其脊髓组织中的 DOR mRNA 表达水平的变化,发现其表达水平持续下降,提示了 DOR 可能参与该过程;Fu et al[38]报道,DADLE 能有效减少兔的脊髓 I/R 损伤所致死亡的神经元数目。综上所述,DOR 激动剂对 I/R 损伤的肺、肝和脊髓等多器官均表现出保护能力,值得进一步探索。

2 DOR 激动剂在脓毒症及其并发症中的作用

脓毒症常见于感染、创伤和手术后,是一种多器官障碍综合征,是导致患者术后或严重损伤后死亡的主要原因[39]。目前脓毒症及其并发症尚欠缺有效治疗手段[40],迫切需要探索更多的药物靶点和机制。有研究[41-42]表明,DADLE 可有效降低脓毒症病死率。Tang et al[41]的报道中指出 DADLE 可能通过减少高迁移率族蛋白 B1(HMGB1)的分泌并使其维持在较低水平,从而减少感染脓毒症的雄性大鼠的病死率。柴振中 等[43]建立脓毒症模型,测得给予 DADLE 的大鼠脑组织中 α7 烟碱型乙酰胆碱受体(α7 nicotinic acetylcholine receptor,α7nAChR)含量显著升高,证明 DADLE 可能通过激活 α7nAChR 来减轻炎症反应,以此降低脓毒症损伤。以上研究成果均体现 DOR 激动剂可应用于脓毒症及其并发症的治疗。

3 DOR 激动剂在精神、神经类疾病中的作用

3.1 抑郁症 抑郁症是一种常见的精神障碍,抑郁症患者往往伴随严重的行为和心理障碍,如社交障碍、自残等,甚至最终走向自杀[44]。患抑郁症的人群中,有近 10% ~20% 存在治疗效果差、治疗抵抗的现象[45]。解决这些问题的现实需求十分迫切,但同时也对研发抗抑郁症的药物提出了更多的挑战。DOR 激动剂的一些最新研究进展或许将为抑郁症的治疗注入新鲜活力。Chen et al[46]报道在以中枢给药的方式给予 DOR 激动剂 SNC80 治疗炎性疼痛小鼠的过程中,出现了强迫游泳试验(forced swim test,FST)中不动时间占比下降,即说明 SNC80 表现出显著的抗抑郁样作用。Wu et al[9]发现慢性束缚应激模型小鼠在注射 SNC80 后,在悬尾试验和 FST 中的不动时间均明显减少;进一步使用原肌球蛋白激酶受体 B(TrkB)抑制剂 ANA-12 可以消除 SNC80 的上述抗抑郁作用,提示 SNC80 可能通过 BDNF-TrkB 信号通路介导抗抑郁作用。此外,一种从菠菜叶片中提取的天然阿片肽 Rubiscolin-6 也表现出了对抑郁症的治疗潜力[47],其高安全性和口服活性为药物的研发带来了新的希望。上述研究均表明 DOR 激动剂在抗抑郁方面有重要研究意义,有望为未来抑郁症的治疗提供新的思路。

3.2 帕金森病(Parkinson's disease,PD) PD 是世界第二大神经退行性疾病,患者常出现行动迟缓、肌肉僵硬、震颤,还常伴有睡眠障碍、认知障碍等多种精神疾病[48]。目前针对 PD 的治疗多为对症治疗,尚无根治 PD 的特效药出现[49]。因而,开发新的特效药、攻克 PD 无疑是 21 世纪全球卫生健康的重要议题。研究[50]发现,DOR 可能是治疗 PD 的一个有效靶点,DOR 激动剂也因此成为 PD 潜在治疗药物。有学者报道[50],经 DOR 激动剂 UFP-512 作用后,PTEN 诱导假定激酶 1(PINK1)表达上调且切割型 Caspase 3 下调,从而使细胞免受缺氧和神经毒素的影响。神经毒素 1-甲基-4-苯基吡啶离子(1-methyl-4-phenyl-pyridinium ion,MPP^+)可通过破坏黑质多巴胺能神经元而模拟 PD 疾病过程[51]。Shivling et al[52]指出,DADLE 可能通过 Nrf2/HO-1 信号通路介导神经保护作用。此外,SNC-80 也被指出会抑制未折叠蛋白反应(unfolded protein response,UPR)应激传感器,进而减轻氧化应激损伤和发挥抗炎作用,从而对 PD 模型引发的神经元损伤表现出缓解作用[53]。综上所述,多种 DOR 激动剂在 PD 治疗方面表现出较好的潜力,这对未来 PD 药物研发具有启发作用。

4 展望

先前对阿片类药物的关注主要集中镇痛作用上,应用于传统的术后镇痛和抑制癌痛。而近年来,阿片类药物的其他作用在不断被发现。目前,DOR激动剂在心脏、脑、肝、肺和脊髓等多个器官的抗 I/R 损伤治疗中的效果显著,受到越来越多的关注,甚至在神经及精神类疾病(如抑郁症、帕金森病等)的治疗中也展现出潜力(图 1)。随着研究深入,DOR激动剂有望成为多种疾病防治药物的候选者。

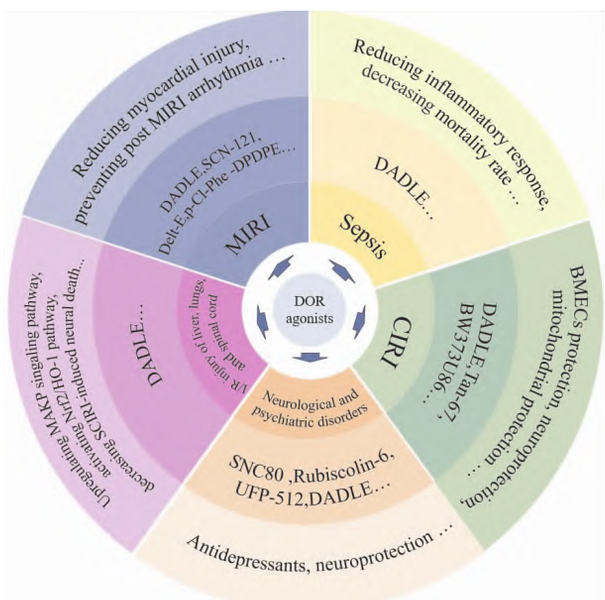

图 1 DOR 激动剂在疾病治疗中作用

Fig. 1 Role of DOR agonists in disease treatment

参考文献

[1] Ballantyne J C. Opioid analgesia: perspectives on right use and utility[J]. Pain Physician, 2007, 10(3): 479 – 91.

[2] Nagase H, Saitoh A. Research and development of κ opioid receptor agonists and δ opioid receptor agonists[J]. Pharmacol Ther, 2020, 205: 107427. doi: 10.1016/j.pharmthera.2019.107427.

[3] Nafziger A N, Barkin R L. Opioid therapy in acute and chronic pain[J]. J Clin Pharmacol, 2018, 58(9): 1111 – 22. doi: 10.1002/jcph.1276.

[4] Stein C. Opioid receptors[J]. Annu Rev Med, 2016, 67: 433 – 51. doi: 10.1146/annurev – med – 062613 – 093100.

[5] Phil S. The opioid epidemic: crisis and solutions[J]. Annu Rev Pharmacol Toxicol, 2018, 58: 143 – 59. doi: 10.1146/annurev – pharmtox – 010617 – 052534.

[6] Subedi K, Wang H. δ-Opioid receptor as a potential therapeutic target for ischemic stroke[J]. Neural Regen Res, 2020, 15(1): 20 – 4. doi: 10.4103/1673 – 5374.264443.

[7] Wu Q, Xu R, Zhang K, et al. Characterization of early myocardial inflammation in ischemia-reperfusion injury[J]. Front Immunol, 2023, 13: 1081719. doi: 10.3389/fimmu.2022.1081719.

[8] Fu D, Liu H, Zhu J, et al. [D-Ala2, D-Leu5]enkephalin inhibits TLR4/NF- κB signaling pathway and protects rat brains against focal ischemia-reperfusion injury[J]. Mediators Inflamm, 2021, 2021: 6661620. doi: 10.1155/2021/6661620.

[9] Wu S, Ning K, Wang Y, et al. Up-regulation of BDNF/TrkB signaling by δ opioid receptor agonist SNC80 modulates depressive-like behaviors in chronic restraint-stressed mice[J]. Eur J Pharmacol, 2023, 942: 175532. doi: 10.1016/j.ejphar.2023.175532.

[10] Fujii H, Uchida Y, Shibasaki M, et al. Discovery of δ opioid receptor full agonists lacking a basic nitrogen atom and their antidepressant-like effects[J]. Bioorg Med Chem Lett, 2020, 30(12): 127176. doi: 10.1016/j.bmcl.2020.127176.

[11] DiCello J J, Saito A, Rajasekhar P, et al. Agonist-dependent development of delta opioid receptor tolerance in the colon[J]. Cell Mol Life Sci, 2019, 76(15): 3033 – 50. doi: 10.1007/s00018 – 019 – 03077 – 6.

[12] Center For Cardiovascular Diseases The Writing Committee Of The Report On Cardiovascular Health And Diseases In China N. Report on cardiovascular health and diseases in China 2023: an updated summary[J]. Biomed Environ Sci, 2024, 37(9): 949 – 92. doi: 10.3967/bes2024.162.

[13] Tardif J C, Kouz S. Efficacy and safety of colchicine and spironolactone after myocardial infarction: the CLEAR-SYNERGY trial in perspective[J]. Eur Heart J Acute Cardiovasc Care, 2024, 13(12): 843 – 4. doi: 10.1093/ehjacc/zuae135.

[14] See Hoe L, Patel H H, Peart J N. Delta opioid receptors and cardioprotection[J]. Handb Exp Pharmacol, 2018, 247: 301 – 34. doi: 10.1007/164_2017_6.

[15] Glattard E, Welters I D, Lavaux T, et al. Endogenous morphine levels are increased in sepsis: a partial implication of neutrophils[J]. PLoS One, 2010, 5(1): e8791. doi: 10.1371/journal.pone.0008791.

[16] Xu J, Bian X, Zhao H, et al. Morphine prevents ischemia/reperfusion-induced myocardial mitochondrial damage by activating δ-opioid receptor/EGFR/ROS pathway[J]. Cardiovasc Drugs Ther, 2022, 36(5): 841 – 57. doi: 10.1007/s10557 – 021 – 07215 – w.

[17] Okubo S, Tanabe Y, Takeda K, et al. Ischemic preconditioning and morphine attenuate myocardial apoptosis and infarction after ischemia-reperfusion in rabbits: role of delta-opioid receptor[J]. Am J Physiol Heart Circ Physiol, 2004, 287(4): H1786 – 91. doi: 10.1152/ajpheart.01143.2003.

[18] Headrick J P, See Hoe L E, Du Toit E F, et al. Opioid receptors and cardioprotection – 'opioidergic conditioning' of the heart[J]. Br J Pharmacol, 2015, 172(8): 2026 – 50. doi: 10.1111/bph.13042.

[19] Liu L, Sun Y, Wang Y, et al. D-Ala2, D-Leu5]-enkephalin (DADLE) provides protection against myocardial ischemia reper-

fusion injury by inhibiting Wnt/β-Catenin pathway[J]. BMC Cardiovasc Disord, 2024, 24(1): 115. doi: 10.1186/s12872-024-03790-6.

[20] Wang J W, Xue Z Y, Wu A S. Mechanistic insights into δ-opioid-induced cardioprotection: involvement of caveolin translocation to the mitochondria[J]. Life Sci, 2020, 247: 116942. doi: 10.1016/j.lfs.2019.116942.

[21] Maslov L N, Oeltgen P R, Lishmanov Y B, et al. Activation of peripheral delta opioid receptors increases cardiac tolerance to arrhythmogenic effect of ischemia/reperfusion[J]. Acad Emerg Med, 2014, 21(1): 31-9. doi: 10.1111/acem.12286.

[22] Dietis N, Rowbotham D J, Lambert D G. Opioid receptor subtypes: fact or artifact?[J]. Br J Anaesth, 2011, 107(1): 8-18. doi: 10.1093/bja/aer115.

[23] Mukhomedzyanov A V, Popov S V, Gorbunov A S, et al. Comparative analysis of infarct-limiting activity of peptide and non-peptide δ- and κ-opioid receptor agonists during heart reperfusion *in vivo*[J]. Bull Exp Biol Med, 2024, 176(3): 338-41. doi: 10.1007/s10517-024-06020-3.

[24] Rabinstein A A. Treatment of acute ischemic stroke[J]. Continuum (Minneap Minn), 2017, 23(1, Cerebrovascular Disease): 62-81. doi: 10.1212/CON.0000000000000420.

[25] Mendelson S J, Prabhakaran S. Diagnosis and management of transient ischemic attack and acute ischemic stroke: a review[J]. JAMA, 2021, 325(11): 1088-98. doi: 10.1001/jama.2020.26867.

[26] 翟华筝, 陈露露, 汪 凯, 等. 真实世界急性缺血性卒中血管内治疗预后分析[J]. 安徽医科大学学报, 2023, 58(2): 292-6. doi: 10.19405/j.cnki.issn1000-1492.2023.02.021.

[26] Zhai H Z, Chen L L, Wang K, et al. Analysis of the factors of acute ischemic stroke patients after endovascular treatment in the real world[J]. Acta Univ Med Anhui, 2023, 58(2): 292-6. doi: 10.19405/j.cnki.issn1000-1492.2023.02.021.

[27] Wang S, Duan Y, Su D, et al. Delta opioid peptide [d-Ala2, d-Leu5]enkephalin (DADLE) triggers postconditioning against transient forebrain ischemia[J]. Eur J Pharmacol, 2011, 658(2-3): 140-4. doi: 10.1016/j.ejphar.2011.02.006.

[28] Chen M, Wu S, Shen B, et al. Activation of the δ opioid receptor relieves cerebral ischemic injury in rats *via* EGFR transactivation [J]. Life Sci, 2021, 273: 119292. doi: 10.1016/j.lfs.2021.119292.

[29] Lai Z, Gu L, Yu L, et al. Delta opioid peptide [d-Ala2, d-Leu5]enkephalin confers neuroprotection by activating delta opioid receptor-AMPK-autophagy axis against global ischemia[J]. Cell Biosci, 2020, 10: 79. doi: 10.1186/s13578-020-00441-z.

[30] Hefter D, Ludewig S, Draguhn A, et al. Amyloid, APP, and electrical activity of the brain[J]. Neuroscientist, 2020, 26(3): 231-51. doi: 10.1177/1073858419882619.

[31] Min J W, Liu Y, Wang D, et al. The non-peptidic δ-opioid receptor agonist Tan-67 mediates neuroprotection post-ischemically and is associated with altered amyloid precursor protein expression, maturation and processing in mice[J]. J Neurochem, 2018, 144(3): 336-47. doi: 10.1111/jnc.14265.

[32] Zhang R, Chen M, Deng Z, et al. Delta opioid peptide targets brain microvascular endothelial cells reducing apoptosis to relieve hypoxia-ischemic/reperfusion injury[J]. Pharmaceutics, 2022, 15(1): 46. doi: 10.3390/pharmaceutics15010046.

[33] Deng Z, Chen X, Zhang R, et al. Delta opioid peptide [D-ala2, D-leu5]-Enkephalin's ability to enhance mitophagy *via* TRPV4 to relieve ischemia/reperfusion injury in brain microvascular endothelial cells[J]. Stroke Vasc Neurol, 2025, 10(1): 32-44. doi: 10.1136/svn-2023-003080.

[34] Yang L, Zhao X, Sun M, et al. Delta opioid receptor agonist BW373U86 attenuates post-resuscitation brain injury in a rat model of asphyxial cardiac arrest[J]. Resuscitation, 2014, 85(2): 299-305. doi: 10.1016/j.resuscitation.2013.10.022.

[35] 黄伟青, 刘升明, 武 钊, 等. DADLE 对大鼠急性全脑缺血再灌注继发肺损伤的作用[J]. 中国病理生理杂志, 2014, 30(9): 1689-93. doi: 10.3969/j.issn.1000-4718.2014.09.025.

[35] Huang W Q, Liu S M, Wu Z, et al. Effect of DADLE on lung injury in rats with acute global cerebral ischemia-reperfusion[J]. Chin J Pathophysiol, 2014, 30(9): 1689-93. doi: 10.3969/j.issn.1000-4718.2014.09.025.

[36] Zhou Y, Zhang J, Lei B, et al. DADLE improves hepatic ischemia/reperfusion injury in mice *via* activation of the Nrf2/HO-1 pathway[J]. Mol Med Rep, 2017, 16(5): 6214-21. doi: 10.3892/mmr.2017.7393.

[37] 章建平, 方 华, 张竞超, 等. 脊髓缺血再灌注损伤中δ阿片受体的表达变化[J]. 中国医学工程, 2015, 23(2): 3-4.

[37] Zhang J P, Fang H, Zhang J C, et al. Change of δ opioid receptor expression during spinal cord ischemia reperfusion injury[J]. China Med Eng, 2015, 23(2): 3-4.

[38] Fu D, Liu H, Liu H, et al. Effects of D-Ala2, D-Leu5-Enkephalin pre-and post-conditioning in a rabbit model of spinal cord ischemia and reperfusion injury[J]. Mol Med Rep, 2019, 20(6): 4811-20. doi: 10.3892/mmr.2019.10729.

[39] Rudd K E, Johnson S C, Agesa K M, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study[J]. Lancet, 2020, 395(10219): 200-11. doi: 10.1016/S0140-6736(19)32989-7.

[40] Lo A H, Kee A C, Li A, et al. Controversies in sepsis management-what is the way forward?[J]. Ann Acad Med Singap, 2020, 49(9): 661-8.

[41] Tang C W, Feng W M, Du H M, et al. Delayed administration of D-Ala2-D-Leu5-enkephalin, a delta-opioid receptor agonist, improves survival in a rat model of sepsis[J]. Tohoku J Exp Med, 2011, 224(1): 69-76. doi: 10.1620/tjem.224.69.

[42] Zhao P, Kuai J, Gao J, et al. Delta opioid receptor agonist attenuates lipopolysaccharide-induced myocardial injury by regulating autophagy[J]. Biochem Biophys Res Commun, 2017, 492(1): 140-6. doi: 10.1016/j.bbrc.2017.06.029.

[43] 柴振中, 姚丽琴, 王建娥, 等. δ阿片受体激动剂 DADLE 对

脓毒症大鼠神经内分泌免疫网络的影响[J]. 浙江创伤外科, 2019, 24(4): 656-9. doi: 10.3969/j.issn.1009-7147.2019.04.002.

[43] Chai Z Z, Yao L Q, Wang J E, et al. Effect of DADLE on the changes of neuroendocrine-immune system in rats with sepsis[J]. Zhejiang J Trauma Surg, 2019, 24(4): 656-9. doi: 10.3969/j.issn.1009-7147.2019.04.002.

[44] Zetterqvist M. The DSM-5 diagnosis of nonsuicidal self-injury disorder: a review of the empirical literature[J]. Child Adolesc Psychiatry Ment Health, 2015, 9: 31. doi: 10.1186/s13034-015-0062-7.

[45] Zhdanava M, Pilon D, Ghelerter I, et al. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States[J]. J Clin Psychiatry, 2021, 82(2): 20m13699. doi: 10.4088/JCP.20m13699.

[46] Chen C M, Ding H, Mabry K M, et al. Enhanced antidepressant-like effects of a delta opioid receptor agonist, SNC80, in rats under inflammatory pain[J]. Pharmacol Biochem Behav, 2022, 214: 173341. doi: 10.1016/j.pbb.2022.173341.

[47] Mitsumoto Y, Sato R, Tagawa N, et al. Rubiscolin-6, a δ-opioid peptide from spinach RuBisCO, exerts antidepressant-like effect in restraint-stressed mice[J]. J Nutr Sci Vitaminol (Tokyo), 2019, 65(2): 202-4. doi: 10.3177/jnsv.65.202.

[48] Tysnes O B, Storstein A. Epidemiology of Parkinson's disease[J]. J Neural Transm (Vienna), 2017, 124(8): 901-5. doi: 10.1007/s00702-017-1686-y.

[49] Reich S G, Savitt J M. Parkinson's disease[J]. Med Clin N Am, 2019, 103(2): 337-50. doi: 10.1016/j.mcna.2018.10.014.

[50] Xu Y, Zhi F, Shao N, et al. Cytoprotection against hypoxic and/or MPP^+ injury: effect of δ-opioid receptor activation on caspase 3[J]. Int J Mol Sci, 2016, 17(8): 1179. doi: 10.3390/ijms17081179.

[51] Pifl C, Hornykiewicz O, Blesa J, et al. Reduced noradrenaline, but not dopamine and serotonin in motor thalamus of the MPTP primate: relation to severity of Parkinsonism[J]. J Neurochem, 2013, 125(5): 657-62. doi: 10.1111/jnc.12162.

[52] Shivling Mali A, Honc O, Hejnova L, et al. Opioids alleviate oxidative stress *via* the Nrf2/HO-1 pathway in LPS-stimulated microglia[J]. Int J Mol Sci, 2023, 24(13): 11089. doi: 10.3390/ijms241311089.

[53] Begum M E T, Sen D. DOR agonist (SNC-80) exhibits anti-parkinsonian effect *via* downregulating UPR/oxidative stress signals and inflammatory response *in vivo*[J]. Neurosci Lett, 2018, 678: 29-36. doi: 10.1016/j.neulet.2018.04.055.

Progress in the role of delta opioid receptor agonists in disease treatment

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Abstract Opioids are commonly used drugs in the clinic, mainly targeting different subtypes of opioid receptors distributed in central and peripheral neurons. They are the preferred drugs for treating acute pain or cancer pain. Delta opioid receptor (DOR) agonists are opioid drugs that target the delta opioid receptor. In recent years, they have received widespread attention due to their ability to improve ischemia/reperfusion injury in multiple organs such as the heart, brain, and liver, as well as their potential for treating mental and neurological disorders. This review summarizes the mechanism research of DOR agonists in treating a variety of diseases, prospects their clinical application prospects, and finds that DOR agonists may exert anti-ischemia/reperfusion injury effects on organs by reducing apoptosis and mitochondrial damage, and activating various signaling pathways; they also exhibit anti-inflammatory, antidepressant, and therapeutic effects on neurodegenerative diseases, providing a new perspective for the application of DOR agonists in treating related diseases.

Key words DOR agonists; ischemia/reperfusion injury; myocardial infarction; sepsis; Parkinson's disease; depression

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