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瑞马唑仑的药理学特性和器官保护机制研究进展

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摘　要

目的：瑞马唑仑是一种新型超短效苯二氮䓬类药物，通过高选择性结合γ-氨基丁酸A型受体(GABA$_A$受体)发挥快速、可控的镇静作用，其羧酸酯酶依赖代谢途径避免了肝药酶介导的药物相互作用。药代动力学显示其分布快、清除率高，且不受年龄或轻中度肝肾功能影响。瑞马唑仑展现出多器官保护潜力，包括通过抑制炎症反应、激活抗氧化通路和调节凋亡/焦亡减轻脑、心、肺、肝肾损伤，并通过脊髓GABA能突触调控缓解神经痛。总之，瑞马唑仑兼具理想麻醉药物特性和多靶点器官保护功能，在围术期器官保护、危重症镇静等领域具有重要应用前景。未来研究需进一步验证其临床转化价值。

关键词

瑞马唑仑，CNS7056，药理学，器官保护，作用机制

Research Progress on the Pharmacological Characteristics and Organ Protective Mechanisms of Remimazolam

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Abstract

Objective: Remimazolam is a novel ultra-short-acting benzodiazepine that exerts rapid and

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controllable sedative effects through highly selective binding to γ-aminobutyric acid type A receptors ($GABA_A$ receptors). Its carboxylesterase-dependent metabolic pathway avoids drug-drug interactions mediated by hepatic enzymes. Pharmacokinetic studies demonstrate rapid distribution, high clearance rate, and unaffected metabolism by age or mild-to-moderate hepatic/renal impairment. Remimazolam exhibits multi-organ protective potential, including mitigating brain, heart, lung, liver, and kidney injuries by suppressing inflammatory responses, activating antioxidant pathways, and regulating apoptosis/pyroptosis, as well as alleviating neuropathic pain via spinal GABAergic synaptic modulation. In summary, remimazolam combines ideal anesthetic properties with multi-target organ protection, showing significant application prospects in perioperative organ protection and critical care sedation. Future research should further validate its clinical translation value.

Keywords

Remimazolam, CNS7056, Pharmacology, Organ Protection, Mechanism of Action

1. 引言

瑞马唑仑作为一种新型超短效苯二氮䓬类药物，凭借其快速起效、代谢稳定及可控性强的特点，近年来在镇静麻醉领域备受关注。与传统苯二氮䓬类药物相比，瑞马唑仑通过高选择性结合 γ-氨基丁酸 A 型受体(γ-aminobutyric acid type A receptor，$GABA_A$ 受体)亚型，实现精准的中枢抑制作用，同时其独特的羧酸酯酶依赖代谢途径避免了肝药酶介导的药物相互作用风险。更引人注目的是，新近研究发现瑞马唑仑不仅具有卓越的镇静效能，还展现出多器官保护潜力，涉及抗炎、抗氧化、抗凋亡及神经突触可塑性调控等多重机制。因此，本文综述瑞马唑仑的药理学特性、器官保护作用机制的最新研究进展，为其进一步临床应用和分子机制研究提供理论依据。

2. 药理学特性

瑞马唑仑有两种不同的盐形式(苯磺酸盐和甲苯磺酸盐)，两者药理学特性基本类似，都是通过高选择性结合 $GABA_A$ 受体发挥中枢抑制作用。瑞马唑仑对 $GABA_A$ 受体 α1、α2、α3 及 α5 亚型均表现出显著的正变构调节效应，通过增强 γ-氨基丁酸介导的氯离子(Cl^-)通道开放，诱导神经细胞内 Cl^-浓度升高及膜超极化，从而抑制神经元兴奋性，实现镇静、催眠与抗焦虑作用[1] [2]。得益于对受体亚型的高选择性，瑞马唑仑在临床中可精准调控中枢镇静深度，但由于 $GABA_A$ 受体在大脑广泛分布，其可能显著影响脑血流动力学[3]，需加强麻醉期间循环功能监测。尽管近期病例报道提示瑞马唑仑与咪达唑仑等苯二氮䓬类药物存在潜在交叉过敏风险[4]，但现有证据仍明确支持 $GABA_A$ 受体作为核心靶点，且临床中尚未发现显著的非选择效应[5] [6]，其亚型特异性结合模式及耐药性机制仍需进一步阐明。

2.1. 药代动力学

瑞马唑仑的药代动力学符合三室模型[7] [8]，与咪达唑仑相比，单次静脉推注后清除率高 3 倍，平均停留时间缩短 1/7，且呈线性药代动力学特征(剂量与体重无关) [9]。瑞马唑仑具有中央室分布容积小(0.11 L/kg)、稳态分布容积适中(35.4 L)、高清除率(1.15 L/min)及短终末半衰期(67~70 min)等特点。这些特性使

其快速分布、高效清除，展现出卓越的超短效镇静效应[7]。瑞马唑仑口服生物利用度低，加上苦味特性，滥用可能性低[10]；鼻内粉末剂型绝对生物利用度达 50%，但严重鼻腔疼痛限制了其临床应用[11]。因此，目前临床用药仍以静脉为主。

瑞马唑仑在体内通过羧酸酯酶 1 (CES-1)介导水解生成无活性代谢物 CNS7054 和甲醇，CNS7054 对 $GABA_A$ 受体亲和力仅为瑞马唑仑的 1/320~1/400 [5]，对靶点外受体亦无显著结合活性，避免了药物蓄积风险。瑞马唑仑整个代谢过程不依赖细胞色素 P450 酶系(Cytochrome P450 enzyme system, CYP450)，与瑞芬太尼、艾司洛尔等麻醉药物无显著相互作用，但氨苯砜与鲁非酰胺可能抑制其代谢[12]。一项 5 天持续输注试验显示瑞马唑仑在人肝细胞代谢稳定，对肝细胞无有害影响，提示长期应用安全性[13]。

瑞马唑仑主要通过尿液排出，静脉给药 4 小时后尿液 CNS 7054 的占比达 98.63% [14]。研究显示，瑞马唑仑在终末期肾衰竭者、轻–中度肝功能损害者和正常人代谢参数相似，但重度肝功能损害(Child-Pugh C 级)者伴随消除延迟，用药需谨慎[15]。关于年龄因素方面，研究表明老年(年龄中位数 66 岁)与青年(21 岁)间无显著药代参数差异[14]；儿童群体清除率与成人相近，但半衰期更短(约 39 分钟) [8]。尽管个体差异存在，大多数患者使用瑞马唑仑时不需要进行明显的剂量调整[16]。

2.2. 药效学

瑞马唑仑起效迅速，静脉注射 0.05 mg/kg 开始产生镇静作用，镇静深度呈剂量依赖性[9]，静脉注射 ≥0.075 mg/kg 能在 1~2 分钟内发挥峰值镇静作用，且表现出比咪达唑仑更深的镇静和更快的恢复[9] [17]。Chae 等研究表明，导致意识丧失和呼吸抑制相关的 50%有效剂量(ED50)和 95%有效剂量(ED95)分别为 0.11~0.19 和 0.14~0.27 mg/kg，随着患者年龄增加，瑞马唑仑有效镇静剂量降低，建议 40 岁以内、60~80 岁和 80 岁以上的患者最佳剂量分别为 0.25~0.33、0.19~0.25 和 0.14~0.19 mg/kg [18]。瑞马唑仑的作用可被苯二氮䓬受体拮抗剂氟马西尼快速逆转，但需注意，若药物剂量过高或存在蓄积，氟马西尼的短半衰期可能导致镇静作用再次出现[19]。

瑞马唑仑的镇静效应与血药浓度高度相关，常以脑电双频指数(Bispectral Index, BIS)和改良的观察者警觉性/镇静评估(Modified Observer's Assessment of Alertness/Sedation, MOAA/S)评估[20]。最近研究显示 BIS 和患者状态指数(Patient State Index, PSI)与效应室浓度和 MOAA/S 评分相关性最强(预测概率 Pk = 0.76~0.81)，可作为瑞马唑仑镇静的可靠指标[21]。效应室浓度 ≥1000 ng/mL 时瑞马唑仑需辅助通气比例达 48.6%~50%，潮气量下降 41%~48%，安全性与疗效需结合呼吸支持策略进行平衡[22]。前期研究发现瑞马唑仑耐受性较好，长期输注镇静作用也不会累积[23] [24]。最近 Vellinga 等报道瑞马唑仑代谢物 CNS7054 可能导致急性耐受，但通过靶控输注(target-controlled infusion, TCI)精准滴定，可最小化其临床影响，维持有效镇静深度[25]。

3. 器官保护作用

3.1. 脑保护作用

瑞马唑仑具有多效性神经保护机制。早期 Xu 等人(2021)的抗神经胶质瘤研究表明，瑞马唑仑衍生物(RFMSP)通过抑制核因子 κB p65 (Nuclear factor kappa-light-chain-enhancer of activated B cells p65, NF-κB p65)核转位、靶向抑制生存素及 X 连锁凋亡抑制蛋白水平、并激活半胱氨酸天冬氨酸蛋白酶(Caspase)级联反应发挥治疗作用，该研究为胶质瘤治疗提供了新思路，也提示瑞马唑仑对神经功能具有潜在影响[26]。随后的研究证实瑞马唑仑通过抑制核苷酸结合寡聚化结构域样受体含 pyrin 结构域蛋白 3 (nucleotide-binding oligomerization domain-like receptors pyrin domain containing 3, NLRP3)炎性小体依赖性细胞焦亡，促进小胶质细胞向抗炎表型(M2)极化，减轻脑缺血再灌注损伤和神经炎症[27] [28]。瑞马唑仑还能激活蛋白激

酶 B (Protein kinase B, AKT)/糖原合成酶激酶-3β (Glycogen synthase kinase-3β, GSK-3β)/核因子 E2 相关因子 2 (Nuclear factor erythroid 2-related factor 2, NRF2)通路，抑制氧化应激和细胞凋亡(活性氧和丙二醛降低，超氧化物歧化酶和谷胱甘肽过氧化物酶活性升高) [29]。在小鼠脓毒血症模型中，瑞马唑仑通过激活海马组织沉默信息调节因子 1 (Silent information regulator 1, Sirt1)/叉头框蛋白 O1 (Forkhead box protein O1, FoxO1)通路抑制 NF-κB 活化，维持血脑屏障完整性，抑制白细胞介素-6 (Interleukin-6, IL-6)、肿瘤坏死因子-α (Tumor necrosis factor-α, TNF-α)、白细胞介素-1β (Interleukin-1β, IL-1β)、丙二醛等炎症介质和氧化应激产物释放，减少神经元凋亡，减轻脓毒症引起的脑损伤[30]。

瑞马唑仑对术后认知功能障碍具有改善作用。在脂多糖(Lipopolysaccharide, LPS)诱导的大鼠脓毒症脑功能障碍模型中，瑞马唑仑通过激活膈下迷走神经-α7 烟碱型乙酰胆碱受体(α7 nicotinic acetylcholine receptor, α7nAChR)介导的 NRF2/血红素加氧酶-1 (Heme oxygenase-1, HO-1)信号通路，抑制全身及海马炎症反应，并上调脑源性神经营养因子(Brain-derived neurotrophic factor, BDNF)、突触后密度蛋白 95 Postsynaptic density protein 95, PSD95)等认知相关蛋白，发挥抗炎和神经保护作用[31]。Zhou 等(2025)在 LPS 诱导的小鼠神经炎症模型，研究发现瑞马唑仑通过调节转位蛋白(Translocator protein, TSPO)抑制小胶质细胞活化，并促进其向抗炎表型(M2)极化，降低促炎因子(IL-6、IL-1β、TNF-α)水平，从而改善海马神经元损伤和认知功能[32]。在深低温停循环模型中，瑞马唑仑通过抑制高迁移率族蛋白 B1 (High mobility group box 1 protein, HMGB1)-Toll 样受体 4 (Toll-like receptor 4, TLR4)-NF-κB 通路，减少海马神经元凋亡及小胶质细胞活化，改善认知功能[33]。在猪心脏骤停模型中观察到瑞马唑仑后处理可减轻复苏后脑组织炎症、氧化应激及细胞凋亡/坏死性凋亡，但其观察时间仅 24 小时，缺乏长期神经功能评估[34]。Chen 等(2025)进一步发现，瑞马唑仑联合穿心莲内酯可协同激活腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)/沉默信息调节因子 1 (Silent information regulator 1, SIRT1)通路，显著抑制海马组织炎症因子(TNF-α、IL-1β、IL-6)分泌及细胞凋亡，显著增强对体外循环术后认知障碍的改善效果，为联合用药策略提供依据[35]。

瑞马唑仑在不同年龄段对认知功能的影响及其机制的研究逐渐分化。Zhou 等人(2022)在小鼠模型中揭示了瑞马唑仑的潜在神经毒性：重复给药可通过谷氨酸兴奋性毒性诱导神经元凋亡、Tau 蛋白异常磷酸化及 Aβ 斑块沉积，并激活星形胶质细胞与小胶质细胞，最终导致认知行为障碍[36]。而 Liu 等(2022)发现瑞马唑仑短期暴露虽短暂增加老龄小鼠 Tau 蛋白磷酸化，但长期观察显示其延缓脑代谢衰退并改善记忆功能，提示其在老年麻醉中的潜在安全性优势[37]。Shi 等人(2024)对比了瑞马唑仑与咪达唑仑对幼年小鼠的短期认知影响，研究发现，两者重复暴露均导致短期记忆损伤(Y 迷宫测试)，但瑞马唑仑的损伤程度更轻，且伴随 Caspase-3 上调、更少的神经元凋亡(CA1/CA3 区)、更轻的长时程增强抑制及 BDNF/PSD95 表达下降，提示其在儿科麻醉中的相对优势[38]。Tang 等发现新生小鼠暴露于瑞马唑仑可导致成年期突触蛋白(如海马胆碱乙酰转移酶)表达减少、树突棘密度降低及小胶质细胞增生，表现出认知缺陷及抑郁样行为，提示其发育期神经毒性风险[39]。Zhao 等(2024)在胫骨骨折模型中证实术后认知损伤主要源于手术本身而非麻醉，手术组小鼠海马区磷酸化 Tau 蛋白(Phosphorylated Tau protein, p-Tau)水平升高、小胶质细胞活化及炎症因子 IL-6 增加，而瑞马唑仑组未显示类似神经病理变化，该研究支持瑞马唑仑作为安全麻醉药物的潜力[40]。

此外，多项研究揭示瑞马唑仑抗焦虑作用的复杂性。Yang 等在中风后焦虑模型中揭示，瑞马唑仑通过同源结构域相互作用蛋白激酶 2 (Homeodomain-interacting protein kinase 2, HIPK2)-组蛋白去乙酰化酶 3 (Histone deacetylase 3, HDAC3)轴抑制线粒体碎片化，减少小胶质细胞对突触的过度吞噬，从而改善焦虑行为，突显其在病理条件下的治疗潜力[41]。Fan 等人(2025)聚焦于慢性睡眠剥夺引发的焦虑样行为，揭示了瑞马唑仑通过抑制干扰素基因刺激蛋白(Stimulator of interferon genes, STING)通路的激活，改善海马

CA1 区神经元钙活动缺陷，从而缓解焦虑的分子机制，证实了瑞马唑仑的抗焦虑潜力[42]。此外，Cheng 等人(2023)通过改良多平台水迷宫构建睡眠剥夺大鼠模型，研究发现睡眠剥夺导致海马 CA1 区神经元排列紊乱、尼氏小体减少、逃避潜伏期延长及磷酸化 Tau 蛋白(Phosphorylated Tau protein, p-Tau)表达升高，而瑞马唑仑干预可减少 Tau 蛋白病理损伤，显著改善上述病理变化，并提升脑源性神经营养因子及神经递质水平[43]。然而，Cheung 等通过大鼠模型发现，瑞马唑仑通过增强外侧隔核(LS)至丘脑室旁核(RE)的长程 GABA 能抑制投射，干扰海马–隔核环路介导的恐惧消退，可能削弱基于暴露疗法的焦虑治疗效果，提示其治疗情境依赖性，为抗焦虑药物与暴露疗法联用困境提供了机制层面的解释[44]。

总的来说，瑞马唑仑兼具多重脑保护作用及潜在神经双向效应[45]。瑞马唑仑通过调控炎症小体(NLRP3、HMGB1)、氧化应激(NRF2)、突触可塑性(PSD95)及神经环路(GABA 能抑制)等多途径发挥神经调控作用，但其效应具有显著的情境依赖性。未来需要深度解析各种通路的交互作用；进一步明确瑞马唑仑发育期暴露的安全阈值、对老年患者的长期影响，以及联合用药的协同机制，以平衡其临床风险与获益。

3.2. 心脏保护作用

多项研究提示瑞马唑仑对心脏具有多通路协同保护机制，Xu 等人(2024)通过小鼠心肌缺血再灌注模型及体外巨噬细胞实验，揭示瑞马唑仑通过抑制 NF-κB 通路(靶向 p50/p65 亚基磷酸化位点)减少巨噬细胞向 M1 型极化，从而降低炎症，改善心脏功能(射血分数提升、梗死面积减少) [46]；Liu 等人(2024)则在小鼠心肌缺血再灌注模型中证实其通过抑制 NLRP3/IL-1β 通路缓解线粒体氧化应激及炎症因子(IL-6、TNF-α)释放，从而减轻心肌损伤[47]。Shen 等人(2024)进一步在猪心脏骤停–复苏模型中观察到瑞马唑仑的跨器官保护效应，通过调控 GABAA 受体减轻脑损伤(降低 IL-6、丙二醛及细胞凋亡水平)，但具体分子机制未明[34]；Yoshikawa 等人(2024)通过临床随机试验及离体心脏实验，发现瑞马唑仑对心脏收缩力的抑制显著弱于丙泊酚，其机制与心脏缺乏 $GABA_A$ 受体 γ 亚基相关，为其临床心脏安全性提供分子依据[48]。

3.3. 肺保护作用

Yang 等人(2024)在支气管肺炎模型中揭示，瑞马唑仑通过促进 3-磷酸肌醇依赖性蛋白激酶 1 (3-phosphoinositide-dependent protein kinase 1, PDPK1)泛素化，减少其降解，激活 AKT 磷酸化并抑制 NLRP3 炎症小体活性，显著降低 IL-6、TNF-α 等炎症因子水平，且 PDPK1 抑制剂(PHT-427)可逆转此效应[49]；Zhang 等人(2024)进一步在呼吸机诱导的肺损伤模型中证实，瑞马唑仑通过激活 TSPO 抑制巨噬细胞焦亡，下调焦亡相关蛋白(NLRP3、caspase-1、GSDMD)，减少 IL-1β、IL-18 释放，并改善肺组织病理，同时 TSPO 过表达可逆转机械牵张对巨噬细胞活力的抑制，缓解呼吸机相关肺损伤[50]。Li 等人(2025)在 LPS 诱导的急性肺损伤模型中证实，瑞马唑仑通过激活 TSPO 依赖的磷脂酰肌醇 3-激酶(Phosphoinositide 3-kinase, PI3K)/AKT 通路，调控 B 细胞淋巴瘤-2 (B-cell lymphoma-2, Bcl-2)/Bcl-2 相关 X 蛋白(Bcl-2-associated X protein, Bax)、剪切型 Caspase-3/7 及细胞色素 C，从而抑制内皮细胞凋亡，其保护作用可被 PI3K 抑制剂(LY294002)或 TSPO 拮抗剂(PK-11195)阻断，凸显多靶点协同抗炎机制[51]。

3.4. 肝肾保护作用

瑞马唑仑通过靶向不同外周受体及信号通路展现跨器官保护效应。Song 等人(2024)在叶酸诱导的急性肾损伤–慢性肾脏病(Acute kidney injury to chronic kidney disease transition, AKI-CKD)转化模型中证实，瑞马唑仑通过外周苯二氮䓬受体通路抑制炎症细胞浸润、减少胶原沉积及细胞外基质积累，并阻断骨髓

源性成纤维细胞活化与巨噬细胞向肌成纤维细胞转化，且该保护作用可被 PK-11195 部分逆转[52]；Fang 等人(2021)在脓毒症相关急性肝损伤研究中进一步揭示，瑞马唑仑通过激活外周苯二氮䓬受体并抑制巨噬细胞 p38 磷酸化，显著降低转氨酶水平及 IL-6、TNF-α 等促炎因子释放，其受体依赖性机制经 PK-11195 拮抗验证[53]；Shi 等人(2024)在肝脏缺血再灌注损伤模型中则发现，瑞马唑仑通过抑制丝裂原活化蛋白激酶(Mitogen-activated protein kinase, MAPK)/细胞外信号调节激酶(Extracellular signal-regulated kinase, ERK)通路(降低 p38 和 ERK1/2 磷酸化)减少肝细胞凋亡及 TNF-α、IL-6 释放，其效应可被 MAPK/ERK 激动剂逆转[54]；此外，Yin 等人(2024)在脓毒症免疫调控研究中提出新机制，瑞马唑仑通过 $GABA_A$ 受体介导的 Cl^-内流纠正赖氨酸激酶 1 (With-no-lysine kinase 1, WNK1)缺陷引起的巨噬细胞过度炎症反应(IL-1β/IL-6/TNF-α↓)，为免疫稳态调节提供新靶点[55]。

3.5. 减轻神经病理性疼痛

多项研究揭示了瑞马唑仑在不同疼痛模型中的作用机制：Xie 等人(2021)在神经病理性疼痛模型中证实，该药物通过抑制缓激肽受体 B1 (Bradykinin receptor B1, BDKRB1)受体介导的 NF-κB 核转位及自噬溶酶体形成，减少促炎因子释放，其效应可被 BDKRB1 激动剂 R838 逆转[56]；Peng 团队(2024)基于骨癌疼痛小鼠模型发现，瑞马唑仑通过激活脊髓星形胶质细胞的 TSPO 受体，抑制 ERK 信号通路及炎症因子释放，产生剂量依赖性镇痛效果，且该作用可被 TSPO 拮抗剂 PK-11195 阻断[57]；Hoshino 研究(2024)在炎症性疼痛模型中则观察到，瑞马唑仑特异性增强脊髓背角 GABA 能突触传递(表现为微小抑制性突触后电流频率增加和衰减时间延长)，同时降低磷酸化 ERK 活性，但对兴奋性突触无显著影响，显示其对脊髓 GABA 受体的选择性调控作用[58]。

4. 结论

瑞马唑仑作为兼具快速镇静与多器官保护潜力的新型药物，其药理特性与临床价值已得到广泛验证。在药理学层面，其短效代谢特性、非 CYP450 依赖的清除途径及精准的 $GABA_A$ 受体调控为其临床安全性奠定了基础。在器官保护方面，瑞马唑仑通过抑制炎症小体(如 NLRP3、HMGB1)、激活抗氧化通路(NRF2/HO-1)及调节细胞凋亡/焦亡相关信号(如 caspase 级联、Bcl-2/Bax)，在脑、心、肺、肝肾等多器官中表现出保护效应，同时通过脊髓 GABA 能突触调控缓解神经病理性疼痛。然而，其神经保护作用存在争议：短期应用可能改善老年认知功能，但发育期暴露或诱导突触发育异常；脓毒症模型中可减轻脑损伤，却可能干扰恐惧消退相关的心理治疗。未来研究需聚焦于以下方向：1) 建立年龄分层剂量模型，明确儿童及老年患者的神经安全性阈值；2) 解析代谢物 CNS7054 的急性耐受机制及靶控输注优化策略；3) 探索联合用药的协同保护机制；4) 验证跨器官保护通路的临床转化效能。瑞马唑仑的多效性为其在危重症麻醉、围术期器官保护及慢性炎症性疾病治疗中的应用提供了新思路，但其风险与获益的平衡仍需更多高质量等级临床随机对照试验验证。

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