How do general anesthetics work?

氯胺酮的临床作用与机制研究进展

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摘要 氯胺酮是常用的静脉麻醉剂之一, 临床应用已超过50年. 近年来, 针对氯胺酮的药理作用研究取得了多方面的进展. 本文从氯胺酮的麻醉作用、镇痛作用、快速抗抑郁作用和副作用等方面简要介绍其临床作用与机制研究的进展. 这些进展将从剂量依赖性和靶点广泛性的角度提示一般麻醉剂发挥作用的复杂性.

关键词 氯胺酮, 麻醉剂, 镇痛, 抗抑郁, 副作用

一般麻醉剂是如何发挥作用的? 这是Science提出的125个科学前沿问题之一. 氯胺酮(ketamine)是临床常用的苯环己哌啶类静脉麻醉药物的代表, 是近年来临床与基础研究发展较快的麻醉剂之一. 在临床实践中, 因为其具有诱导迅速、作用时间较短、苏醒较快、对呼吸和循环系统影响较轻等特点, 常用于满足儿科、产科、围手术期及特殊疾病患者的麻醉需求^[1].

近10年来, 尤其是2010年以后, 针对氯胺酮神经药理作用的研究论文数量呈爆发式增长, 主要围绕氯胺酮的快速抗抑郁作用展开, 另有研究关注其麻醉机制、镇痛作用和副作用等内容^[2]. 这些研究显示, 氯胺酮在不同剂量下亲和多种受体(如阿片受体)与离子通道(如钠离子通道与钾离子通道), 可能对不同脑区多种关键分子、多种基本神经活动的功能存在广泛影响, 从而在个体水平上产生多样的药理作用, 体现了一般麻醉剂发挥作用的复杂性. 这些研究也提示可以从氯胺酮的多重临床作用出发, 重新理解抑郁症、麻醉和疼痛等过程的神经机制.

1 氯胺酮的麻醉作用及其机制研究进展

氯胺酮是离子型谷氨酸受体亚型N-甲基-D-天冬氨酸受体(N-methyl-D-aspartic acid receptor, NMDAR)的药理学阻断剂, 可以与蛋白质数据库(protein data bank, PDB)中编码为4TLM的NMDAR三级结构单位结合, 占据离子通道位点, 广泛地抑制谷氨酸能突触的正常生理功能^[3]. 一般认为, 氯胺酮作为麻醉药物的药理基础是选择性地阻断皮层联络系统和丘脑-皮层系统, 临床出现痛觉消失而意识可能部分存在的分离麻醉(dissociative anesthesia)状态. 这一猜想已被部分证实. Schroeder等人^[4]的研究指出, 在氯胺酮麻醉下, 恒河猴(*Macaca mulatta*)的皮层之间联络减弱, 与其他针对GABA能(GABAergic, GABA为 γ -aminobutyric acid, 即 γ -氨基丁酸)系统设计的麻醉剂获得相近的结果, 提示不同麻醉剂诱导的无意识状态可能由同样的神经网络状态导致. Lee等人^[5]的研究证实氯胺酮对患者额叶-颞叶联络的干扰作用.

近年来, 对氯胺酮麻醉作用的机制研究不仅局限于NMDAR. 超极化激活环核苷酸门控通道

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(hyperpolarization-activated cyclic nucleotide-gated channels, HCN通道)可以调控神经元膜电位稳定性,参与形成丘脑-新皮层系统同步化脑电活动^[6]. Chen等人^[7]于2009年提出氯胺酮可以通过结合HCN1抑制h电流(hyperpolarization-activated cation currents, I_h),从而诱导皮层锥体神经元超极化,增强突触传递,可能是实现镇静作用的基础. 进一步的研究使用了新皮层和海马脑区特异性的HCN1基因敲除小鼠(*Mus musculus*),发现在HCN1条件性敲除小鼠中氯胺酮失去了对h电流和突触功能的调控,确定了前脑的HCN1是氯胺酮诱导的浅全麻状态(遗忘和意识丧失)的靶点,而保留对外界伤害性刺激的反应^[8,9]. 此外,PI3K-AKT-mTOR通路激活可以加快氯胺酮麻醉的苏醒,并改善学习记忆状态^[10]. 上述研究结果符合氯胺酮作为麻醉剂的临床药理特点,提示其发挥麻醉作用存在新机制.

2 氯胺酮的镇痛作用及其机制研究进展

临床研究中早已确定氯胺酮具有镇痛作用^[11],而且是少有的用于治疗复杂性区域疼痛综合征(complex regional pain syndrome, CRPS)的有效药物之一^[12]. 氯胺酮治疗慢性痛可获得优于其他NMDAR阻断剂以及安慰剂的良好镇痛效果^[13],并可以缓解其慢性痛相关的负性情绪^[14]. 为避免高剂量氯胺酮的副作用,采用多次皮下注射低剂量氯胺酮,仍能在关节炎模型大鼠(*Rattus norvegicus*)中观察到明显的镇痛作用,而未观察到明显副作用,与临床实际相符,提示合理控制氯胺酮剂量可以实现镇痛效果,并避免副作用^[15]. 此外,针对急诊患者进行的研究也显示,使用低于麻醉剂量的氯胺酮获得的急性镇痛效果与静脉注射吗啡接近^[16,17],拓展了氯胺酮作为镇痛药物的使用范围.

氯胺酮的镇痛机制至少包括以下两方面:一方面,作为NMDAR阻断剂,氯胺酮干预慢性痛中枢敏化过程. NMDAR是形成突触可塑性的关键分子,参与慢性痛中枢敏化的形成^[18]. 一般认为,氯胺酮通过对脊髓和更高级的中枢神经系统NMDAR的药理阻断实现其镇痛功能^[19]. 此外, Sawynok^[20]总结了既往的临床研究与基础研究,针对慢性痛的外周敏化机制,提出在局部使用低剂量氯胺酮以控制神经病理痛的设想. 另一方面,氯胺酮与阿片受体存在相互作用^[20]. 临床研究显示,吗啡联用低剂量氯胺酮可

以获得更优的镇痛效果^[21,22],可能与氯胺酮可以逆转吗啡耐受有关^[23]. 另有研究显示,氯胺酮可以阻断背根神经节(dorsal ganglion root, DRG)和脊髓背角(dorsal horn of spinal cord)的钠通道和钾通道^[24,25],提示足够剂量的氯胺酮可能参与镇痛.

然而,在癌症痛患者中,氯胺酮的镇痛作用存在争议: Hardy等人^[26]的随机化安慰剂对照的双盲研究结果显示,皮下注射氯胺酮作为阿片类药物的佐剂或单独用药并未能表现出优于安慰剂组的效果. 这一研究的流程和结论遭到了 Leppert^[19]和 Jackson等人^[27]的质疑,他们认为Hardy等人在病例选择、不良事件控制、用药时程与剂量等方面考虑不周,以致出现假阴性结果. 另外,临床观察到氯胺酮停药后反而出现痛敏现象, Olofsen等人^[28]指出可能原因是其代谢产物去甲氯胺酮产生与氯胺酮相反的神经作用,并非氯胺酮本身的作用结果.

3 氯胺酮的抗抑郁作用及其机制研究进展

基于对脑内谷氨酸能系统参与形成抑郁症等情绪障碍的基础研究进展, Berman等人^[29]在2000年进行了安慰剂对照的双盲临床研究,单次静脉注射氯胺酮治疗抑郁症患者,获得了快速的抗抑郁效果,随后这一效果被证明可以长期持续^[30,31]. 此后,大量的临床对照试验和荟萃分析结果都证实了低于麻醉剂量的氯胺酮经静脉或口服给药可以快速改善抑郁症患者的抑郁心情和自杀倾向^[2,32-36]. 在此期间,氯胺酮的抗抑郁机制得到广泛而深入的研究,这也促进了对于抑郁症发病机制的探讨.

针对氯胺酮抗抑郁机制的既往研究主要关注前额叶皮层(prefrontal cortex, PFC)这一抑郁症的病因脑区,其机制可能包含以下不同研究层次的药理作用.

(i) 分子与突触水平. NMDAR是抑郁症的研究靶点之一^[37,38]. 研究表明, NMDA GluN2A亚基的点突变对氯胺酮的药理作用无影响^[39],而GluN2B亚基对于氯胺酮发挥抗抑郁作用至关重要^[40]. 氯胺酮可以通过阻断抑制性GABA能神经元的NMDAR,实现谷氨酸能神经元的去抑制,产生谷氨酸爆发,激活其下级神经元AMPA (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor)和mTOR (the mechanistic target of rapamycin)信号通路,最终促进突触蛋白合成与BDNF释放(图1)^[41]. 这些分子是脑内维持和调控突触功能的关键蛋白, NMDAR与

图 1 低剂量氯胺酮发挥快速抗抑郁作用的分子机制. 在前额叶皮层, 氯胺酮通过阻断NMDA受体, 抑制GABA能中间神经元功能, 引起谷氨酸能神经元释放谷氨酸增加, 激活AMPA受体与L型VDCC钙通道, 最终导致BDNF的合成与释放增加. 上述过程通过Akt与ERK信号通路激活mTOR信号通路, 与EF2 通路共同增加突触蛋白合成. BDNF与突触蛋白合成促进突触的形成与成熟, 改变突触可塑性, 实现了快速的抗抑郁作用

Figure 1 The molecular mechanism of the rapid anti-depressive effects of low-dose ketamine. In prefrontal cortex, ketamine leads to glutamate bursts by blocking NMDAR of presynaptic GABAergic interneurons, which disinhibits the activity of the glutamatergic neurons. The rapid rising excitatory neurotransmitter glutamate, activates AMPAR and L-VDCC calcium channels, contributing to the synthesis and release of BDNF. Also, the activation of AMPAR and L-VDCC initiates the mTOR pathway by Akt/ERK signaling only to increase the synthesis of synaptic proteins together with EF2 pathways. BDNF and synaptic proteins play key roles in the formation and maturation of synapses, and thus reconstruct synaptic plasticity, which make ketamine a rapid antidepressant

AMPA是突触可塑性的分子基础, mTOR通路调控多种突触蛋白(如PSD95, Synapsin I 与Arc等)的转运与功能, 脑源性神经营养因子(brain derived neurotrophic factor, BDNF)对突触的形成和成熟具有调控作用. 因此, 新突触形成被认为是氯胺酮发挥快速抗抑郁作用的本质^[42]. 但有研究对这种观点提出质疑, Yang等人^[43]利用在体双光子成像技术观察到, 使用氯胺酮-甲苯噻嗪联合麻醉引起的树突丝状伪足(dendritic filopodia)数量瞬时轻微增加不如丰富环境造成的影响, 且联合麻醉不影响树突棘的数目, 然而这一研究并未否认突触功能增强这一结论, 也无法排除甲苯噻嗪的影响.

值得注意的是, 氯胺酮的快速抗抑郁效果并非所有NMDAR阻断剂的共性, 而是其独有的^[3]. 例如, 同为NMDAR阻断剂的二甲金刚胺(memantine)并不具有氯胺酮的快速抗抑郁作用. 基础研究表明, 两者结构上的差异使二甲金刚胺在生理浓度镁离子环境中结合NMDAR的能力与氯胺酮不同, 最终下游分子信号通路的激活(eukaryotic elongation factor 2 kinase, eEF2K)与BDNF存在差异^[3,44].

(ii) 脑区与环路水平. 在动物光遗传学实验中, 光激活PFC脑区可以产生类似于氯胺酮的抗抑郁

效果^[45], 抑制PFC亚区下边缘皮层(infralimbic cortex, IL)功能阻断氯胺酮的抗抑郁效果^[46], 提示PFC对抑郁样行为存在调控作用. 氯胺酮所诱导的PFC的脑区功能改变也调控了环路功能. Lv等人^[47]利用功能性磁共振成像技术, 在灵长类动物中发现氯胺酮造成的局部的突触可塑性改变可以引起皮层-边缘系统-纹状体环路广泛的网络重构, 为氯胺酮的作用机制提供了新的探索角度. 在人类被试中, 氯胺酮减弱了NMDAR和AMPA介导的额叶-顶叶联系, 改善多脑区协同活动的动态模式, 可能是形成快速抗抑郁效果的原因^[48].

在近期的动物研究中, 调控大脑环路功能的GABA能中间神经元也受到广泛关注. PV神经元(parvalbumin interneurons)是中间神经元的一种. 氯胺酮可以通过NADPH氧化酶的作用引起PV神经元表型丢失(loss of phenotype)^[49], 表现为小白蛋白(parvalbumin)和GABA合成酶67 (glutamic acid decarboxylase 67, GAD67)表达水平下降. 这种表型丢失可能与Neuregulin 1-ErbB4信号通路功能下调有关, 是氯胺酮发挥抗抑郁作用的机制之一^[50,51].

上述实验结果体现了从动物向人类、从单一脑区向脑网络的研究趋势, 提示氯胺酮作为NMDAR阻断剂在脑内发挥作用的广泛性与复杂性.

4 氯胺酮的管控现状与神经精神副作用研究进展

氯胺酮因存在精神错乱的严重副作用以及潜在的滥用风险,至今尚未被美国食品药品监督管理局(Food and Drug Administration, FDA)认证为抗抑郁药物,并被列入1971年精神药品公约的第I类药物加以严格管控^[32]. 近期研究显示,其精神错乱副作用的产生原因可能是GABA能神经元的表型丢失引起的皮层—皮层下网络高频振荡失稳,这一机制与精神分裂症存在共性^[49,50,52].

近年来也有其他研究提示,氯胺酮可以使新生

啮齿类动物和灵长类动物神经发育期神经元出现神经凋亡(neuroapoptosis)^[53,54],孕期暴露也能导致子代长久的脑损伤^[55],引起运动学习能力的下降^[56]. 基于上述动物实验结果,已有研究人员计划开展临床试验明确其在儿童麻醉中是否存在潜在危险性^[57]. 已有研究显示,多巴胺、AMPA激活和伤害性刺激可以减缓这一损伤^[53,58,59].

综上所述,由于氯胺酮发挥药理学效应具有剂量依赖性与靶点广泛性,在临床实践中应谨慎使用. 出于氯胺酮的用药风险考虑,筛选机制相似但安全性更强的拟氯胺酮类药物已经成为快速抗抑郁药物的研究热点^[60].

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Research progress in the mechanisms of the clinical effects of ketamine

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Ketamine is primarily known as an effective NMDAR (*N*-methyl-*D*-aspartic acid receptor) blocker. As one of the intravenous anesthetics, ketamine has been widely used in clinical practice for more than 50 years, exhibiting several different outcomes besides the original anesthetic effects. Recent studies provide insights into the mechanisms of the following neuropharmacological effects of ketamine: (i) Anesthesia. The anesthetic effects of ketamine are mainly due to its ability to decrease the inter-cortical communications to generate dissociative anesthesia. Besides the well-known NMDAR, another target for ketamine to show anesthetic effects has been reported to be hyperpolarization-activated cyclic nucleotide-gated channels (HCN channels). (ii) Analgesia. Ketamine not only exhibits blockade on NMDAR in the central nervous system, but also reverses opioid tolerance when combined with morphine at a low dose. The affinity with sodium and potassium channels makes ketamine possible for analgesia at high doses. However, the clinical analgesic effect is currently controversial, and the allodynic cases after the discontinuation of ketamine are probably caused by its metabolic product norketamine. (iii) Anti-depression. Ketamine is recently regarded as a rapid antidepressant drug for its contribution to neurogenesis through several molecular processes, such as the glutamate burst by activating presynaptic NMDAR and AMPAR (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor), the synaptic protein synthesis and transportation by activating mTOR (mechanistic target of rapamycin), and the synaptic maturation by releasing BDNF (brain derived neurotrophic factor). At the circuit level, ketamine widely reconstructs circuits by dual regulation on NMDAR and AMPAR, and causes loss of phenotype of the PV GABAergic neurons (parvalbumin-positive interneurons). (iv) Side effects. Ketamine is strictly constrained for its psychiatric side effects resulted from the potent disruption on neural network stability, which shares similar neuro-circuit etiology with schizophrenia. Also, the potential ketamine-induced neuroapoptosis might generate risks for anesthesia during pregnancy and childhood, which is under deep investigation. Due to the potential risks of ketamine, more attention should be paid to the development of novel anesthetics keeping the anesthetic, analgesic and antidepressant effects of ketamine, however, without the potential psychiatric side effects. Thus, exceeding novel knowledge, makes ketamine a representative example for the complexity of anesthetics due to its global targets and dose-dependent properties, which provides a breakthrough point both for the mechanism researches for the working models of general anesthetics and for exploring the state of consciousness of human beings.

ketamine, anesthetics, analgesia, antidepressant, side effect

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