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·专论与综述·

麻醉药物在肝细胞凋亡中的作用

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摘要:围术期最常用,最重要的药物是全身麻醉药(包括吸入麻醉药和静脉麻醉药),麻醉药是适应手术的需要而出现的,经过长时间的发展,它的药理作用也越来越完善。在过去几年里很多研究报道的麻醉药的药理作用与介导的细胞凋亡之间的关系主要集中在神经系统。然而,麻醉实践中大部分麻醉药物都在肝脏代谢,已有证据表明麻醉药对肝细胞也有影响。麻醉药介导的细胞凋亡作用可能与 caspase 通路,Bcl-2 家族,TRADD,FADD 等多种因素有关。但不是所有麻醉药都对肝细胞有凋亡作用,部分还具有保护作用。因此本文就现有的麻醉药对肝细胞凋亡中的作用进行了综述。

关键词:肝脏;麻醉;凋亡;药理学

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The Role of Anesthetic Drugs in Liver Apoptosis

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ABSTRACT: General anesthetics (including inhaled anesthetics and intravenous anesthetics) are the most common and important drugs during perioperative period. The advent of anesthetics is adapt to surgery. After a long period of development, its pharmacological effects have been more perfect. In the past few years, many studies have reported a relationship focused on the nervous system between anesthetic pharmacological effects and the apoptosis mechanisms. However, majority of anesthetic drugs are metabolized in the liver during the anesthesia practice. There are evidences that anesthetics also have effects on the liver cells. Anesthetics mediated apoptosis may be associated with caspase pathway, Bcl-2 family, TRADD, FADD. But not all the anesthetics cause liver cells apoptosis, even some may have protective effects. Therefore, this paper have reviewed the role of anesthetics on the hepatic apoptosis.

Key words: Liver; Anesthesia; Apoptosis; Pharmacology

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1 背景

麻醉是由威廉·莫顿在 1846 年 10 月首次在临床上推出,但早在 1844 年现代人类的发明中就提到过麻醉药一氧化二氮的临床效果[1]。麻醉药经过长时间发展,临床麻醉中已经引进了很多新世代更有效且副作用小的药物,但是这个过程还有待完善;现有的麻醉药副作用的发生率非常低,但是临床麻醉中依然可以见到其副作用导致的意外[2]。肝脏是进行药物代谢的主要器官之一,具有其独特的功能。然而,药物解毒时产生的生化副产物对肝细胞有影响,而许多药物,包括大多数麻醉药,全部或部分在肝脏中代谢。这可能就是肝细胞损伤的机制之一,对未来麻醉药的发展和引进有很大的影响。

肝细胞在代谢活动中不断产生活性氧。当肝脏有缺陷或暴露于毒素时,线粒体将产生的活性氧转化为其它形式的氧[3-5],这种氧化损伤对肝细胞结构有干扰。细胞凋亡(不是坏死)是肝脏损伤的主要机制,特别是与药物相关的,大多数麻醉药或病毒的伤害最后都会使肝细胞发生凋亡[5-10]。凋亡(程序性细胞死亡)的方式有两种:内源性途径和外源性途径[7]。虽然这两种途径导致的结果类似,但启动机制不同。内源性途径如缺乏生长介质,DNA 损伤和胞浆分离可使 Bcl-2 家族的促凋亡成员(BAX 和 BAK)在线粒体膜上蓄积[4,7,8,11,12]。这种现象可能会增加线粒体膜的通透性,使细胞色素 C 和促凋亡蛋白从线粒体转移到胞浆并激活 caspase-9 [13,14] 及其他后续 caspase 蛋白酶[5,6,15-17]。这些酶可诱导 DNA 断裂,细胞膜出泡,最终形成凋亡小体[10,15]。外源性途径可以通过细胞表面受体被触发,包括很多调亡受体尤其 FAS(CD95)和 TNF-RI[3-5,7,9,11,16-20]。调亡受体通过相关的配体激活并诱导细胞质衔接蛋白聚集, 如 TRADD(TNF 受体相关调亡结构域)和 FADD(Fas 相关凋亡结构域)。此信号转导将导致 caspase-8 活化和随后的 caspases 蛋白酶的级联反应[4,11,13,14,16-19]。这两个途径的终端都会激活 caspase-3,形成凋亡小体,所形成的凋亡小体则被吞噬细胞清除,不引起炎症反应[14]。上述的凋亡作用中残留的肝细胞包括枯否细胞,树突细胞,自然杀伤(NK)细胞,NKT 细胞,嗜中性粒细胞,肥大细胞和 T 细胞 [4,9,10,12,21-23]。细胞凋亡级联反应的最终命运由细胞结构中 Bcl-2 家族凋亡与抗凋亡蛋白之间的相互作用决定[4,7,11,16,21,24]。

2 证据采集

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近几年，大量研究已经证明大多数当前使用的麻醉药，包括静脉麻醉药（如氯胺酮，巴比妥，丙泊酚，咪达唑仑，地西泮，氯硝西泮），挥发性麻醉药（如氟烷，异氟烷，地氟烷，七氟烷），氙气等具有凋亡作用；甚至，肌松药也在动物研究中证明具有细胞凋亡特性，产生剂量依赖性的效果；同时，其他一些研究报道这些药物也可作为神经保护剂，保护脑组织免受不必要的负面影响，如“细胞凋亡，变性，炎症和能量衰竭”；然而，很重要的一点是，因为对人体进行这些研究存在困难，几乎所有的这些结果是从动物模型中得出来的[25,26]。充分的证据（特别是关于实验室证据）表明很少有神经细胞凋亡发生在脑发育过程，几乎所有的人类研究结果证明凋亡与发育之间有关联，但不存在因果关系[25,26]。

麻醉药在神经细胞凋亡中作用的研究主要集中在新生儿大脑[25]，但是，麻醉药在肝细胞凋亡中的作用还不是很清楚，以前的研究结果表明，更深层次的麻醉状态，可使神经细胞发生的凋亡更严重，例如联合应用一氧化二氮和异氟烷或氯胺酮和丙泊酚，相比任何单一用药时导致的神经细胞凋亡更严重[27]。麻醉药种类很多，但是，根据麻醉相关文献，在本文中麻醉药根据它们的功能分为四类：催眠镇静药，镇痛药，遗忘剂和肌肉松弛剂。

3 结果

3.1 催眠镇静药

与凋亡活性有关的催眠药可以分为两大类：N- 甲基 -D- 天冬氨酸（NMDA）受体拮抗剂，如氯胺酮；以及 γ- 氨基丁酸（GABA）受体激动剂，如异丙酚或硫喷妥钠[28-30]。催眠药和遗忘剂有一些重叠的临床使用，我们将在两种不同的标题里讨论他们。

(1)氯胺酮：静脉麻醉药，有许多研究讨论氯胺酮的凋亡作用，特别是对肝细胞凋亡。所有氯胺酮凋亡相关的机制中，最主要的是上调 NMDA 受体引起谷氨酸系统的高度表达和药物的代谢产物氢醌中毒[31]。氯胺酮也能抑制“磷酸化细胞外信号调节蛋白激酶”[32]和诱导“过度磷酸化 tau 样蛋白”的形成。S-(+)- 氯胺酮，氯胺酮的主要异构体之一，可致人 HepG2 细胞的凋亡，造成肝细胞和枯否细胞的损伤[15]。长期使用氯胺酮已被证明对肝细胞有损伤，甚至会导致更严重的肝纤维化[33]。研究得出结论，氯胺酮的凋亡作用在与其他麻醉药合用时更易发生，比如苯二氮卓类；长期服用氯胺酮时，氯胺酮加入到利多卡因，它以添加剂的方式增加利多卡因对细胞凋亡的影响，有些药物如可乐定具有一定的预防氯胺酮凋亡作用的特性[34-38]。

(2)硫喷妥钠：巴比妥类静脉麻醉药，他的细胞凋亡机制是通过 GABA-A 激动剂来实现[39]；还通过“CD95 无关的机制”[40]和“减毒的星形孢菌素诱导的细胞凋亡和 caspase 样活性机制”诱导淋巴细胞的调亡[40,41]。

(3)丙泊酚：最常用的静脉麻醉药之一，并且可能削弱 caspase-3 的活化；所以，丙泊酚可能减弱有些麻醉药的凋亡作用[42]，虽然存在争议[20,32]，丙泊酚具有剂量依赖性肝保护作用，减少凋亡细胞，caspase-3 和降低 PARP 在肝 L02 细胞中的裂解[43]。

(4)依托咪酯：静脉麻醉药，在体外对白血病细胞 RAW264.7 具有细胞凋亡和细胞毒性作用[44]；目前，没有动物或临床证据表明是否对肝细胞凋亡有影响。

(5)α2 肾上腺素能受体激动剂：主要用作催眠药的辅助药；两种主要的药物有可乐定和右旋美托嘧啶，两者都具有抗细胞凋亡作用，可能具有对抗氯胺酮和异氟烷凋亡作用的功能。右旋美托嘧啶可以防止异氟烷在脑和一些其他器官介导的细胞凋亡。临床上对右旋美托嘧啶可以通过剂量依赖性减弱异氟烷的细胞凋亡作用，尚存在一些争议[37,45-47]。

(6)挥发性麻醉药：这些疏水性卤化吸入药通常用于全身麻醉。作为最常见的吸入性麻醉药，具有保护作用，也有副作用：在动物大脑中对神经细胞有凋亡作用[25]，潜在的肝脏毒性[1,48]，降低血浆和红细胞中的抗氧化活性，增加 DNA 断裂和细胞调亡的作用，对肿瘤细胞具有时间依赖性细胞毒性作用[49,50]。挥发性麻醉药还具有遗传毒性，细胞毒性或致畸性等作用[51]。病毒感染可加重麻醉药物在肝细胞凋亡过程中的不良作用，从而可抑制细胞色素 450（CYP）活性并激活针对凋亡因子的肝固有免疫系统[6]。

异氟烷相关凋亡机制是 GABA-A 通路，可被右旋美托嘧啶阻止，但对用药剂量和同时使用其他麻醉药存在一些争议，如同时使用 NMDA 受体拮抗剂或 GABA 受体激动剂等麻醉药：异氟烷已被证实临床用药剂量即可造成人神经胶质瘤细胞株的凋亡；异氟烷的乳化形式通过调节丙二醛（MDA）和超氧化物歧化酶的含量发挥肝脏保护作用，提示线粒体对细胞凋亡的抑制和改善抗氧化功能是潜在的保护机制[52-54]。

氟烷可在体内外对肝脏细胞具有凋亡作用，氟烷对处理过的肿瘤细胞具有时间依赖性细胞毒性作用，虽然它不直接与 DNA 相互作用，但低剂量也对细胞基因组造成不可逆的损伤，临床剂量的氟烷在动物模型中能降低细胞的生存力，损害 DNA，并引发应激性细胞凋亡[6,51,55,56]。

(17)氙气：属于惰性气体家族，是一个真正的理想的吸入麻醉药，在临床上具有高效，满意的麻醉特点，不仅对肝脏对身体的其他主要器官，都具有独一无二的作用特点。目前还没有氙气对于肝脏不良影响的报告。它是甘氨酸高亲和力的 NMDA 受体拮抗剂，具有独特的心血管和神经保护特性。氙气的独特属性可能与多巴胺能通路的相互作用有关。它甚至可能会抑制氯胺酮，一氧化二氮和异氟烷的凋亡作用。氙气的唯一缺陷是潜在的肺动脉高压和输送到患者身边的特殊技术及成本[57]。

3.2 镇痛药

很少有研究报道有关阿片类药物在细胞凋亡中的作用；δ - 阿片类受体在肝细胞膜中很常见，在肿瘤形成，肝腺瘤病，病毒性肝炎和肝硬化的进展中起重要作用；此外，肝细胞中活化的 δ - 阿片类受体将通过专门的相互作用抑制线粒体凋亡途径，蛋白激酶 C 参与此过程；在这个过程中，阿片类药物的剂量和给药时间起重要作用：内源性阿片类药物可能通过降低肝细胞中抗氧化防御水平增加肝细胞凋亡，关于阿片类药物的研究如下[58-71]：

(1)吗啡：长期反复使用阿片类药物，尤其是吗啡，可导致阿片类受体介导的肝细胞凋亡；大剂量吗啡可在肝细胞中导致氧化应激，因此阻断阿片类受体可对抗 FAS 介导的肝炎，在动物实验反复增加吗啡剂量可能恶化宿主防御链；虽然仍存在争议，这些报道对阿片类药物在肝炎病理生理过程的研究有重要作用。

(2)脑啡肽：研究报道阿片类生长因子（即蛋氨酸（5）- 脑啡

肽)及其受体在内源途径控制细胞生长的重要作用;阿片类生长因子的浓度在癌转移阳性的病人肝组织中高于正常肝组织,肝脏中甲硫脑啡呔已被证明具有抗肿瘤活性。

(3)美沙酮:通过与 caspase 通路无关的独立的细胞凋亡机制杀死白血病细胞;美沙酮也被证明通过类似细胞凋亡的途径对小细胞肺癌起治疗作用。

(4)芬太尼:是一种合成的阿片类受体激动剂,可时间依赖性触发淋巴细胞凋亡。

(5)舒芬太尼:已被证实具有抗凋亡和调节 Bax 和 Bcl-2 表达的作用,并具有上调 p-FADD 的作用,对其它阿片类药物也具有类似的抗凋亡作用。

(6)瑞芬太尼:具有特殊药理学特性的阿片样物质化合物,主要通过血浆胆碱酯酶代谢,它的半衰期很短,因此使用的时候必需通过静脉输注。有一些研究报道瑞芬太尼在中枢神经系统和心肌具有抗凋亡作用。在一个动物研究模型中,瑞芬太尼的抗炎和抗凋亡作用对肝脏有保护作用,这项研究表明用瑞芬太尼预处理可以在体内外减轻肝损伤; 这种保护作用是通过 NOS 产生的但与阿片类受体无关,由活性氧维持作用;所以瑞芬太尼具有一些特殊的功能,其特殊作用途径和代谢途径(即与其他麻醉药不同)也可能改善其他阿片类药物对肝细胞的作用。

3.3 遗忘剂

遗忘剂中苯二氮卓类是围手术期中最常使用的药物,苯二氮卓类无论是在体内或体外都具有介导细胞凋亡的潜力;苯二氮卓类药物凋亡效应在与其他药物联合应用时更大(尤其对肝脏),比如与氯胺酮或其他的苯二氮卓类药物合用;苯二氮卓类药物的凋亡作用可被维生素 C 抑制, 这可能与维生素 C 还原细胞内谷胱甘肽水平有关。咪唑安定是这类麻醉药物的代表,咪唑安定呈剂量依赖性细胞凋亡作用,他与 GABA 受体无关,随血浆浓度的增加导致细胞坏死 [7,14,38,39,72,73]。

3.4 肌松药

肌松药是在手术过程中用于防止肢体运动的麻醉药物(用于术中制动或 ICU 内改善辅助通气),其对肝细胞凋亡的影响尚未清楚[74-77]:

(1)泮库溴铵:一个古老的非去极化长效肌松药,被证明在临床使用浓度时对外周血淋巴细胞具有凋亡作用。

(2)顺阿曲库铵:中等强效的肌松药,其代谢过程中产生的丙烯酸酯诱导的氧化应激反应在人细胞系中是一个非常有效的细胞凋亡的触发因素。

(3)新斯的明:肌松药的拮抗剂,它并没有被报道具有凋亡活性。

4 小结与展望

本文就世界范围内临床中常用的麻醉药对肝细胞的影响,尤其是对肝细胞凋亡作用和一些副作用小的麻醉药进行了讨论。综上所述,麻醉药物对肝细胞凋亡的机制尚未清楚,可能与 caspase 通路,Bcl-2 家族,TRADD,FADD 等多种因素相互作用有关。由于麻醉药种类很多,临床上实施麻醉的时候也经常联合使用多种麻醉药物,药物之间不同组合,产生的效果也很复杂,对研究的进行产生了困难。已有的研究均采用体内或体外模型,单一药物或两种药物进行对比研究,对多种全麻药联合应用所产生的效果欠缺报道。所以实施麻醉时应考虑多角度综合性的麻醉,采用低基础风险的策略。减少麻醉时间,术中尽量使用对细胞凋亡影响小的麻醉药(如丙泊酚,瑞芬太尼),联合应用减轻麻醉药凋亡作用的辅助药 (如右旋美托嘧啶, 美沙酮),以期减少术中或术后麻醉药对肝细胞凋亡的影响。麻醉药对细胞凋亡作用的研究任重而道远,需多学科合作攻关,需要长时间努力。希望未来更多的研究报道联合用药时药物之间不同组合所产生的相互作用与药物代谢动力学变化对全身各个器官的影响,以期更准确地指导临床用药,提高临床麻醉的安全性。

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