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综 述

婴幼儿发育期全身麻醉药暴露对认知功能的影响及机制

赵 欣[1,2]，郝利军[1,2,3]，张雨彤[1,2]，张 宇[1,2]，张 策[1,2,*]

山西医科大学[1]生理学系；[2]细胞生理学教育部重点实验室，太原 030001；[3]山西省人民医院麻醉科，太原 030012

摘 要：随着医疗技术的进步，各类先进设备、检测手段不断增加，通过手术或其他有创方式救治的疾病谱不断增加。越来越多的婴幼儿需要接受全身麻醉药(全麻药)麻醉进行临床检查或治疗，而全麻药是否对仍处在发育期的婴幼儿脑结构和功能(如认知)产生影响是一个重要、复杂而又有争议的问题，因而受到神经生物学、麻醉学和儿科学等领域学者的高度关注。人群调查结果证实，发育期短期单次全麻药暴露对认知功能的影响较弱，多次全麻药暴露则会对认知功能造成损伤。基于动物的研究进一步揭示了发育期全麻药暴露的损伤机制。全麻药暴露的时间点较麻醉时长更关键，突触形成高峰期最易受全麻药损伤；在突触形成高峰期，全麻药暴露可诱导胞内钙超载、线粒体损伤、能量代谢失衡，损伤细胞功能；启动细胞凋亡，诱导过度自噬，导致细胞丢失；抑制突触相关蛋白的表达，突触形成受损，干扰突触传递过程及可塑性，影响神经环路和脑区功能活动。因此，细胞损伤、细胞丢失和神经环路功能受损构成发育期全麻药暴露损伤认知功能的重要机制。此外，有研究应用高通量组学技术对全麻药暴露引起的差异表达基因进行了初步筛选，为深入研究全麻药损伤的基因表达及调控机制提供了新思路。本文从整体行为学、神经元网络、细胞损伤、基因表达及调控和脑功能代谢等方面对发育期全麻药暴露影响认知功能及相关机制的研究进展进行综述，希望能为临床婴幼儿全麻方案的制定提供理论依据。

关键词：全身麻醉药；脑发育；认知；影响；机制
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Influence of general anesthetic exposure in developing brain on cognition and the underlying mechanisms

ZHAO Xin[1,2], HAO Li-Jun[1,2,3], ZHANG Yu-Tong[1,2], ZHANG Yu[1,2], ZHANG Ce[1,2,*]

[1]*Department of Physiology;* [2]*Key Laboratory for Cellular Physiology of Ministry of Education, Shanxi Medical University, Taiyuan 030001, China;* [3]*Department of Anesthesiology, Shanxi Provincial People's Hospital, Taiyuan 030012, China*

Abstract: With the evolution of medical techniques and technology, an increasing number of infants, neonates, and fetuses are exposed to general anesthesia for clinical diagnostic and therapeutic process. The neurotoxic effects of general anesthetics on developing brain have been a subject of concern and considerable research interest. Population-based study confirmed that single short-term general anesthetic exposure does not affect nervous system function, but multiple exposures to general anesthesia could damage cognitive function. Animal studies further discovered the underlying mechanisms. Nervous system is most susceptible to general anesthetics during the brain growth spurt. The time-point is more critical than the duration of exposure to general anesthetics. General anesthetics can induce intracellular calcium overload, disturb energy metabolism, promote cell apoptosis and lead to cell loss. General anesthetics can damage synaptic structure, transmission and plasticity, and impair brain function. High throughput omics technologies have been used to screen the differentially expressed genes induced by general anesthetics, which provide further understanding of the mechanism of general anesthetics affecting cognitive function. This review provides an update on the pathophysiologic mechanisms underlying the anesthesia-neurotoxicity, which will be helpful to provide instructions for the clinical use of general anesthesia in children.

Key words: general anesthetic; developing brain; cognitive; influence; mechanism

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*Corresponding author. Tel: +86-351-4135631; E-mail: cezh2002@yahoo.com

目前婴幼儿发育期全身麻醉药 (全麻药) 暴露对神经系统发育及认知功能的影响已经成为全社会和相关专业领域学者关心的焦点科学问题。全麻药主要通过影响中枢神经系统发挥麻醉作用，婴幼儿患者全麻药的应用为临床各项检查和治疗的顺利进行提供重要保障。据统计，在美国每年有约 150~200 万 3 岁以下患者接受全身麻醉手术 [1]。人类大脑快速发育期从胚胎晚期持续到生后 2~3 年，这一时期大脑对内外环境的改变异常敏感，在此阶段使用全麻药对大脑发育产生的影响及其机制是神经科学领域以及儿科和麻醉领域亟待解决的重要科学问题。本综述旨在促进对全麻药影响脑发育及认知功能机制的理解，以期为婴幼儿发育期全麻药的应用提供有价值的参考。

1 脑的发育

神经系统由神经元和胶质细胞共同构成，是一个复杂的功能系统 [2]。神经系统的发育跨越了出生前到出生后的几年时间。神经系统发育早期，胚胎中的前体多能干细胞增殖分化为神经元和神经胶质细胞，神经元在胶质细胞的引导下迁移形成分层组织，经过树突分叉、树突棘形成、轴突定向等过程在神经元之间建立突触联系，之后神经元通过凋亡控制神经元和突触的整体数量 [3]，最终建立起一个高度有效的功能网络，既保证信息数据的快速处理，又保证最低的能量消耗 [4]。在神经系统整个发育过程中，突触形成高峰期是最脆弱的时期 [5]，人类的突触形成高峰期大约在妊娠 6 个月至出生后 3 年之间 [3, 6]，在此期间，任何可能影响神经系统发育的物质或事件都可能会危害神经系统成熟之后的功能。

2 婴幼儿发育期全麻药暴露影响认知功能的人群研究结果

全麻药主要包括吸入麻醉药和静脉麻醉药，作用于中枢神经系统，能可逆性地引起意识丧失、感觉 (特别是痛觉) 及反射消失、骨骼肌松弛等，但仍保持延髓生命中枢的功能。

在全球范围内，目前主要有三个人群项目研究发育期全麻药暴露对认知功能的影响，分别是：(1) 由美国食品药品监督管理局与国际麻醉研究学会共同发起的 PANDA (pediatric anesthesia and neurodevelopment assessment) 项目；(2) 由澳大利亚皇家儿童医院主持进行的 GAS (general anesthesia and apoptosis study) 项目；(3) 由美国梅奥医学中心和美国国家毒理研究中心合作开展的 MASK (Mayo anesthesia safety in kids study) 项目。

PANDA 项目和 GAS 项目报告显示，单次短时全麻药暴露不会影响认知功能。MASK 项目报告显示，单次麻醉药暴露不影响认知功能，但多次重复麻醉药暴露会降低认知功能。PANDA 项目选取的是 3 岁之前单次全麻行腹股沟斜疝手术的患者，其全麻药暴露的平均时间为 80 min，在患者 10 岁左右时进行检测，结果显示，患者在学习记忆、运动速度、视觉空间功能、注意力、执行功能、语言和行为等方面与对照相比均无差别 [7]。GAS 项目选取采用全麻行腹股沟斜疝手术的婴幼儿患者，这些患者全麻手术时年龄均小于 60 周，全麻药暴露时间均短于 1 h，2 岁时采用第三版贝利婴幼儿发展量表评价患者神经发育情况，结果显示其神经发育未受影响 [8]。MASK 项目选取 3 岁之前无麻醉药暴露、单一麻醉药暴露以及多次重复麻醉药暴露的患者，在其 8~12 岁和 15~20 岁时，采用美国国家毒理研究中心的操作性测试和神经心理评估对神经发育情况进行评估。评估报告显示三组患者的记忆相关功能没有显著差异；但多次重复暴露的患者在基于学习及智力的神经功能方面存在显著差别，表现为运算速度和静息运动能力下降 [9]。除上述三项研究之外，其他人群研究也发现早期全麻药暴露和手术与后期的行为学习和神经发育之间存在关联。加拿大的 2 项队列研究发现麻醉和手术会增加儿童发育不良的风险 [10, 11]。瑞士的一项研究发现 4 岁之前接受麻醉和手术的孩子与对照组相比，16 岁左右时的学习成绩有轻微降低 [12]。

综合这些人群研究结果，单次短期应用全麻药可以被认定是安全的，而多次重复麻醉会对认知功能产生较为长久的影响。但是基于人群的研究结果来分析评价全麻药对认知功能产生的影响较为复杂，其中存在有较多混杂因素，例如患者基础疾病、患者基础疾病治疗过程中应用的其他药物等，这些混杂因素使得确定全麻药暴露和后果的因果关系变得很困难，因此即使有大规模人群观察所得到的大数据也依然很难确定全麻药暴露本身是否可以影响神经发育并导致认知功能受损。因此，在动物水平严格控制实验条件进行了一系列相关的研究，旨在寻找证据明确发育期全麻药暴露对认知功能的影响及其生物学机制。

3 发育期全麻药暴露影响认知功能的机制研究

目前有大量动物实验观察全麻药暴露对认知功能的影响及可能的机制，这些动物包括啮齿类动物和非人灵长类动物。啮齿类动物突触形成高峰期大概在出生后 7 天左右，非人灵长类动物突触形成高峰期约在出生后一个月内。

3.1 动物认知功能受损

在动物突触形成高峰期给予全麻药暴露，其认知功能发育会晚于未暴露的动物，并且在成年后两者认知功能出现差距。在非人灵长类动物发现单次长时程或多次全麻药暴露会使得动物的认知功能受损。6 日龄恒河猴 24 h 氯胺酮暴露后，从 10 月龄开始并在随后的 2~3 年里表现出认知发育的迟滞，包括学习能力、颜色及位置辨别能力、任务完成的准确度、任务完成的速度、完成任务的动机等均弱于正常对照 [13]。Baxter 等将恒河猴出生后一个月内 3 次 (7、14 和 28 日龄) 暴露于七氟烷 4 h，6 月龄时采用人类入侵范式 (human intruder paradigm) 进行测试，结果显示，与正常对照相比，这些恒河猴更容易表现出焦虑相关行为 [14]。1 月龄恒河猴接受 5 h 异氟烷单次或 3 次暴露，3 次暴露组的动物暴露后很快表现出运动反射受损，在 12 月龄时对新的社交环境呈现出较高程度的焦虑，更多地表现出从属或妥协行为，而单次暴露的动物与正常对照相比无差别 [15]。啮齿类动物实验也发现单次长时间 [16–18] 或多次短期接触全麻药会导致显著的神经认知发育受损 [19, 20]。单次七氟醚麻醉 7 日龄小鼠 6 h，引起其 80 日龄时恐惧学习记忆受损 [21]。6~7 日龄大鼠七氟醚麻醉 2 h，连续 3 d，45 日龄时自发活动增强、部分工作记忆受损 [22]。全麻药还可轻易穿过胎盘屏障损伤胎儿，异氟醚麻醉孕鼠 1 h，幼鼠出生后 28 日龄时空间学习记忆能力受损 [23]。

3.2 神经元网络功能受损

全麻药暴露影响突触结构。7 日龄大鼠丙泊酚暴露 (2 h、4 h 和 6 h) 后立即取材，发现全脑组织中突触相关蛋白，包括突触前的神经生长相关蛋白 43 (growth associated protein-43, GAP-43)、synaptophysin、α-synuclein，跨突触的 N-cadherin，突触后的 drebrin、MAP-2 等蛋白的表达均发生改变，其中 synaptophysin、α-synuclein、N-cadherin 和 drebrin 表达减少，GAP-43 和 MAP-2 表达增加 [24]。异氟烷暴露 6 h 导致 7 日龄大鼠皮层和丘脑组织内突触蛋白 synaptophysin、synaptobrevin、amphiphysin、SNAP-25 和 CaMKII 表达降低 [25]。突触相关蛋白表达的改变提示突触的结构及功能受到全麻药破坏，研究也证实全麻药暴露改变了突触结构。7 日龄小鼠异氟烷暴露 4 h 后，21 日龄时海马神经元上长细形态的树突棘减少，但树突密度无改变 [26]；7 日龄大鼠七氟烷暴露 30 min 后内侧前额叶和躯体感觉皮层树突棘密度降低 [27]。另外，GAP-43 和 MAP-2 表达增加可能是神经组织启动了维持轴突和树突结构完整性及稳定性的补偿机制。

全麻药暴露影响突触传递及可塑性。体外培养的 7 日龄大鼠海马脑片异氟烷直接暴露 6 h 后，微抑制性突触后电流 (miniature inhibitory postsynaptic potential, mIPSC) 的频率增加 [28]。7 日龄大鼠七氟烷暴露 30 min，90 日龄时内侧前额叶和躯体感觉皮层的场兴奋性突触后电位 (field excitatory postsynaptic potential, fEPSP) 双脉冲易化增强 [27]。7 日龄大鼠异氟烷暴露 6 h，14 日龄时丘脑网状核脑片抑制性突触传递减弱，表现为诱发抑制性突触后电流 (evoked inhibitory postsynaptic current, eIPSC) 幅度减小、衰减加快、双脉冲比值减小 [29, 30]，mIPSC 无变化；兴奋性突触传递增强，表现为诱发兴奋性突触后电流 (evoked excitatory postsynaptic current, eEPSC) 的 AMPA 成分增高而 NMDA 成份无改变，mEPSC 幅度也显著增加 [30]；21~28 日龄时海马脑片下托区 eIPSC 衰减加快、双脉冲比值增加 [31]。这些结果提示全麻药影响突触传递及短时程可塑性包括了突触前和突触后的机制。全麻药暴露影响突触的长时程可塑性，单次长时全麻药暴露会抑制突触的长时程增强 (long-term potentiation, LTP)。7 日龄大鼠七氟烷暴露 30 min，90 日龄时内侧前额叶和躯体感觉皮层 LTP 无变化 [27]，而 7 日龄大鼠异氟烷暴露 6 h 后，21[26]、30[16] 日龄时海马 LTP 均减弱，提示全麻药可使得与学习和记忆形成密切相关的海马脑区的神经元环路发生长时程破坏。

全麻药暴露会导致脑区活动减弱。Aksenov 等采用眨眼条件反射 (eyeblink classical conditioning, ECC) 评价发育期全麻药暴露的兔子成年后的学习和记忆功能，并且在行为检测的同时进行清醒状态血氧水平依赖的 (blood oxygenation level dependent, BOLD) 功能性磁共振成像 (functional magnetic resonance imaging, fMRI) 的检测，即任务态的 fMRI 观察。兔子在 8、11、14 日龄时共接受 3 次异氟烷暴露 (2 h)，3 月龄时手术植入头部固定装置，之后进

行 ECC 训练。在训练前及训练 10 天后进行 fMRI 检测，比较训练学习前后脑功能的差异。行为结果显示，发育期全麻药暴露会减慢成年后 ECC 的建立；fMRI 结果显示行为训练主要启动胡须体觉皮层脑区的活动，在未暴露的动物，皮层全层均发生活化，并且在学习前后脑区活化的体积及活化脑区的活动强度没有改变，而在暴露组动物，皮层活化范围减小，主要局限在表层，学习后脑区活化的体积较学习前降低约 54%，但活化脑区的活动强度无改变，fMRI 成像的结果提示全麻药会使得相关脑区活动减退 [32]。

3.3 神经元及胶质细胞丢失

发育期全麻药暴露会导致脑组织内神经元及胶质细胞的丢失。脑发育三个不同阶段 (分别为孕 122 天、5 日龄和 35 日龄) 的恒河猴氯胺酮暴露 24 h 后立即取材，结果显示孕 122 天的胎猴、5 日龄的小猴皮层组织出现显著的神经细胞凋亡和坏死，而 35 日龄恒河猴没有相同的表现 [33]，提示脑发育的早期阶段 (孕 122 天和生后 5 天) 较晚期阶段 (生后 35 天) 对氯胺酮导致的神经细胞死亡更敏感。另外，即使较短时间 (5 h) 的氯胺酮暴露，孕 120 天的胎儿及 6 日龄的恒河猴与对照相比，也呈现出显著的神经细胞凋亡 [34]，并且，胎儿神经细胞凋亡水平是婴儿脑的 2.2 倍，提示胎儿脑组织更易受损。这些结果提示全麻药暴露的时间点较持续时间更能影响损伤的后果 [35, 36]。此外，即使在麻醉过程中严密检测动物的生命体征并维持其平稳也无法减少细胞丢失，5~7 日龄恒河猴分别暴露于异氟烷、氯胺酮或丙泊酚 5 h，麻醉过程中维持正常生命体征，仍发现神经元发生凋亡 [37, 38]。全麻药诱导凋亡的细胞并不仅限于神经元，短时 3 h 的异氟烷暴露使得 7 日龄恒河猴脑组织神经元和少突胶质细胞均发生凋亡 [39]。6 日龄恒河猴异氟烷暴露 5 h 引起的凋亡细胞中，52% 是少突胶质细胞，48% 为神经元 [40]，20 日龄恒河猴 5 h 异氟烷暴露引起的细胞凋亡中 66% 为少突胶质细胞，而 34% 为神经元 [41]。与神经元相比较，少突胶质细胞对全麻药更为敏感，并且神经元对全麻药的易感性随着年龄增长而逐渐减弱，而少突胶质细胞的易感性并未随之减弱。基于少突胶质细胞在神经元髓鞘形成中的重要作用，发育早期全麻药暴露可能会损伤正常的髓鞘发生。啮齿类动物的实验也证实全麻药暴露可引起广泛脑区出现显著的神经细胞凋亡 [16, 42]。全麻药可轻易地穿过胎盘屏障，宫内或者生后早期全麻药暴露均引起广泛的细胞丢失 [5, 43–49]。

全麻药可诱导细胞自噬。体外培养细胞，丙泊酚暴露会浓度和时间依赖性地诱导细胞自噬，低浓度短时间暴露增加保护性自噬，高浓度长时间暴露则使得自噬失调，诱导细胞凋亡 [50]。在离体培养的海马神经元，过表达自噬时线粒体功能失调的关键调控分子 Pink-1 (PTEN-induced kinase 1) 可显著缓解丙泊酚诱导的凋亡和氧化损伤 [51, 52]。这些基于细胞水平的实验结果提示自噬可能参与发育期全麻药暴露所致的细胞丢失。

3.4 神经细胞损伤机制

发育期全麻药暴露引起的细胞损伤最初开始于线粒体或者粗面内质网。线粒体是维持能量平衡参与凋亡的重要细胞器，是麻醉药相关毒性的亚细胞靶点 [53]。全麻药可启动线粒体依赖的凋亡途径，引起 Bcl-2 下调，线粒体膜通透性增加、细胞色素 C 增加和一系列 caspase 的激活 [36, 42]。全麻药可影响线粒体的分裂和融合 [31]，在正常情况下，线粒体分裂和融合保证了线粒体的正常重建和再生 [54]，分裂障碍会导致线粒体肥大，融合障碍会导致线粒体破碎。全麻药可使得线粒体融合和分裂失衡 [31]，导致过量氧自由基生成，造成新生突触的能量代谢障碍，最终损害树突棘以及突触的形成、稳定和功能 [55–58]。突触形成关键期线粒体功能障碍会导致发育中神经元的凋亡。粗面内质网是神经元胞内重要的钙离子来源和调控者，胞内钙离子调控神经元发育的多个方面，包括突触形成和功能、细胞膜兴奋性、蛋白合成、神经元凋亡和自噬等 [59–61]。内质网被认为是麻醉药导致发育神经毒性的重要的初级环节和一系列导致线粒体功能障碍事件的启动者。异氟烷可以激活 IP_3 受体诱导内质网钙释放，线粒体 Bcl-xL 蛋白表达减少，促进发育中脑组织内神经元的凋亡和死亡 [62, 63]。丙泊酚、地氟烷、七氟烷也可以通过调控 IP_3 受体，引起胞浆内钙超载，增加线粒体膜通透性，最终导致线粒体肿胀、失控以及大量促凋亡因子的释放 [64]。

3.5 基因表达及调控机制

5~6 日龄非人灵长类动物 2.5% 七氟烷暴露 9 h，取额叶组织进行 DNA 芯片检测，筛选出差异表达基因，其中大部分基因与神经系统发育及功能相关，另有一些基因与脂质代谢密切相关；进一步采用脂质组学分析发现关键脂质成分 (磷脂酰乙醇胺、磷

脂酰丝氨酸和磷脂酰甘油) 下调；蛋白芯片分析发现细胞因子表达异常 [65]。高通量组学技术将为深入研究全麻药暴露影响认知功能的基因表达及调控机制提供新思路。

3.6 对脑代谢功能的影响

氢质子磁共振波谱 (proton magnetic resonance spectroscopy, ^{1}HMRS) 是一种无创性测定活体组织代谢与生化指标的磁共振技术，可在体检测脑组织中的代谢物。Zvi 等选取 59 例 (2~7 岁) 需全麻后行核磁共振成像 (magnetic resonance imaging, MRI) 检查的儿童，随机给予七氟烷或丙泊酚麻醉，在进行 MRI 结构成像的同时检测顶叶皮层内代谢物水平，结果显示，与丙泊酚相比，七氟烷麻醉后顶叶皮层内乳酸和葡萄糖浓度及患者术后谵妄指数均较高，且乳酸和葡萄糖浓度与术后谵妄发生指数呈正相关 [66]。通常乳酸和葡萄糖的浓度升高表明神经活动增强，谵妄的发生和乳酸之间的联系提示全麻药增强了无意识状态下的皮层活动，可能会干扰麻醉结束后脑功能连接状态的快速恢复。

3.7 不同类型全麻药暴露对认知功能影响及机制的比较

全麻药包括静脉全麻药和吸入全麻药。儿科常用静脉全麻药有丙泊酚、氯胺酮等，吸入麻醉药有七氟烷、异氟烷等。表 1 对不同类型全麻药发育期暴露对认知功能、细胞丢失、突触结构和功能的影响进行了文献总结。不同种类全麻药均可导致动物认知功能减退，氯胺酮使得恒河猴任务完成的精确度及反应速度降低、动机受损 [13]，小鼠自发运动能力、空间学习记忆能力下降 [17, 18]；七氟烷可导致恒河猴更易出现焦虑等负性情绪 [14]，大鼠自发活动增多 [22]、空间学习记忆能力下降 [19]，小鼠恐惧学习记忆受损 [21]；异氟烷暴露后恒河猴更易出现焦虑等负性情绪 [15]，大鼠空间学习记忆受损 [16]。不同种类全麻药均可导致脑组织细胞丢失 [16, 20, 23, 33, 34, 36]，累及神经元和少突胶质细胞，细胞丢失的主要方式是凋亡；不同种类全麻药均可影响突触结构和功能，丙泊酚 [24] 和异氟烷 [25] 均可导致突触关键蛋白表达降低；七氟烷可短暂降低树突棘密度 [27]，使得海马 mEPSC 频率增加，mIPSC 幅度降低、频率升高 [67]，但不影响 LTP [27]。异氟烷可导致长细形状树突棘减少 [26]、eEPSC 和 mEPSC 幅度增加 [30]，mIPSC 频率增加 [28]，eIPSC 双脉冲易化增强、衰减加快 [31]；海马 LTP 减弱 [26]。总之，由于不同实验采用不同的麻醉药、选取不同的动物，检测指标和检测的方法手段也有所不同。总体来说，各类型全麻药暴露均会导致动物不同方面的认知功能减退，包括自发活动、学习记忆功能、精神情绪等；导致脑组织细胞丢失；影响突触的结构、密度、传递过程及可塑性，主要表现为突触密度降低、兴奋性突触传递增强、抑制性突触传递减弱、LTP 减弱等。

4 总结

使用全麻药麻醉是对婴幼儿患者进行疾病临床检查和治疗的重要辅助手段。全麻药对婴幼儿患者神经系统发育和认知功能的影响是全麻药应用的重要理论依据。科学家们针对婴幼儿发育期全麻药暴露对认知功能的影响进行了人群观察和动物实验，证实突触形成高峰期多次重复或单次长时全麻药应用会对个体成年后的认知功能产生损伤。全麻药可损伤线粒体和粗面内质网，诱导神经元和少突胶质细胞凋亡；减少突触数目，干扰突触传递及可塑性，破坏脑区神经环路信息传递，最终导致认知行为发生改变 (图 1)。全麻药还可影响葡萄糖代谢，可能通过其代谢产物干扰麻醉结束后脑功能连接状态的快速恢复。高通量的组学技术证实全麻药暴露使得基因表达发生改变，包括 mRNA、microRNA 等，未来可深入挖掘这些组学数据，从基因表达调控的角度补充完善全麻药暴露影响认知功能的机制。尽管基因的表达及其调控机制极其复杂，但我们相信一定能够从中筛选出关键基因及关键通路。总之，婴幼儿发育期全麻药暴露对脑高级认知功能的神经生物学机制亟待明晰，其结果将对临床麻醉医师制定最合理的婴幼儿临床全麻方案提供理论依据，并且为麻醉辅助药物的选择和研发提供新的思路。

* * *

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表1. 发育期不同类型全麻药暴露对认知功能影响的比较

Table 1. Effects of early exposure to different types of general anesthetics on cognitive function

General anesthetics	Animal	Age	Exposure duration	Observation time point	Results	Reference
Propofol	Rhesus monkey	PND 7	5 h	9 h after exposure	Neuron apoptosis	[37]
	Rat	PND 7	2–6 h	0–24 h after exposure	Influenced expression of crucial synaptic proteins	[24]
Ketamine	Rhesus monkey	Pregnant animal at G120	5 h, 24 h	Fetus	Cell apoptosis	[33, 34]
		PND 5–7	5 h, 24 h	After exposure	Cell apoptosis	[33, 34, 37]
		PND 7	24 h	3 years old	Long-lasting cognitive deficits Deficits in learning and color and position discrimination tasks Deficits in accuracy of task performance and response speed	[13]
	Rat	PND 7	20 mg/kg 6 times	6 h after the last injection	Neuronal cell apoptosis	[20]
	Mouse	PND 10	25 mg/kg	24 h after exposure	Cell apoptosis	[17]
		PND 10	25 mg/kg	PND 55–70	Deficits of the spontaneous motor activity test; Deficits of learning and retention memory	[17, 18]
Sevoflurane	Rhesus monkey	PND 7	4 h, 3 times	6 months old	Significantly higher frequency of anxiety-related behaviors	[14]
	Rat	PND 7	30 min	6 h after exposure	Decreased spine densities	[27]
		PND 7	30 min	PND 90	Larger paired-pulse facilitation; No changes in the long-term potentiation, short- and long-term memory	[27]
		PND 6	2 h, 3 times	PND 21–35	Hyper-locomotion; Impairment of working memory	[22]
		PND 7	2 h, 3 times	PND 45–50	Spatial memory dysfunction	[19]
	Mouse	PND 7	6 h	After exposure	Cell apoptosis	[21]
		PND 7	6 h	PND 82	Impaired long-term memory in fear tests	[21]
Isoflurane	Rhesus monkey	PND 7	5 h	3 h after exposure	Cell apoptosis	[37, 38]
		PND 6	3 h, 5 h	3 h after exposure	Cell apoptosis (Neuron, 48%; Oligodendrocyte, 52%)	[39, 40]
		PND 20 PND 40	5 h	3 h after exposure	Cell apoptosis (Neuron, 34%; Oligodendrocyte, 66%)	[41]

To be continued

Continued

General anesthetics	Animal	Age	Exposure duration	Observation time point	Results	Reference
		PND 5	5 h, 3 times	PND28	Motor reflex deficits	[15]
		PND 5	5 h, 3 times	12 months old	Increased anxiety and affiliative/appeasement behavior responded to new social environment	[15]
	Rat	Pregnant rats at G 14	1 h	PND 28	Cell apoptosis	[23]
		Pregnant rats at G 14	1 h	PND 28	Spatial memory and learning impairments	[23]
		PND 7	6 h	After exposure	Cell apoptosis	[16, 42]
		PND 7	6 h	0–42 h after exposure	Transiently modulated synaptic proteins	[25]
		PND 7	6 h	P10–P18	Lasting reduction in the amplitude of eIPSCs; Faster decays of eIPSCs; Decreased paired-pulse ratio of eIPSCs; Increased AMPA component of eEPSCs	[29, 30]
		PND 7	6 h	PND 21–28	Long-lasting disturbances in inhibitory synaptic neurotransmission	[31]
		PND 7	6 h	PND 29–33	Deficits in hippocampal synaptic function	[16]
		PND 7	6 h	PND 20–131	Persistent memory/learning impairments	[16]
	Mouse	PND 7	6 h	PND 14	Lasting increase in frequency of mIPSCs	[28]
		PND 7	4 h	PND 21	Reduction in long thin spines; Impairment in long-term potentiation; Deficits in acute object recognition	[26]

PND: postnatal day; G: gestation; eIPSCs: evoked inhibitory postsynaptic currents; eEPSCs: evoked excitatory postsynaptic currents; mIPSCs: miniature inhibitory postsynaptic potentials.

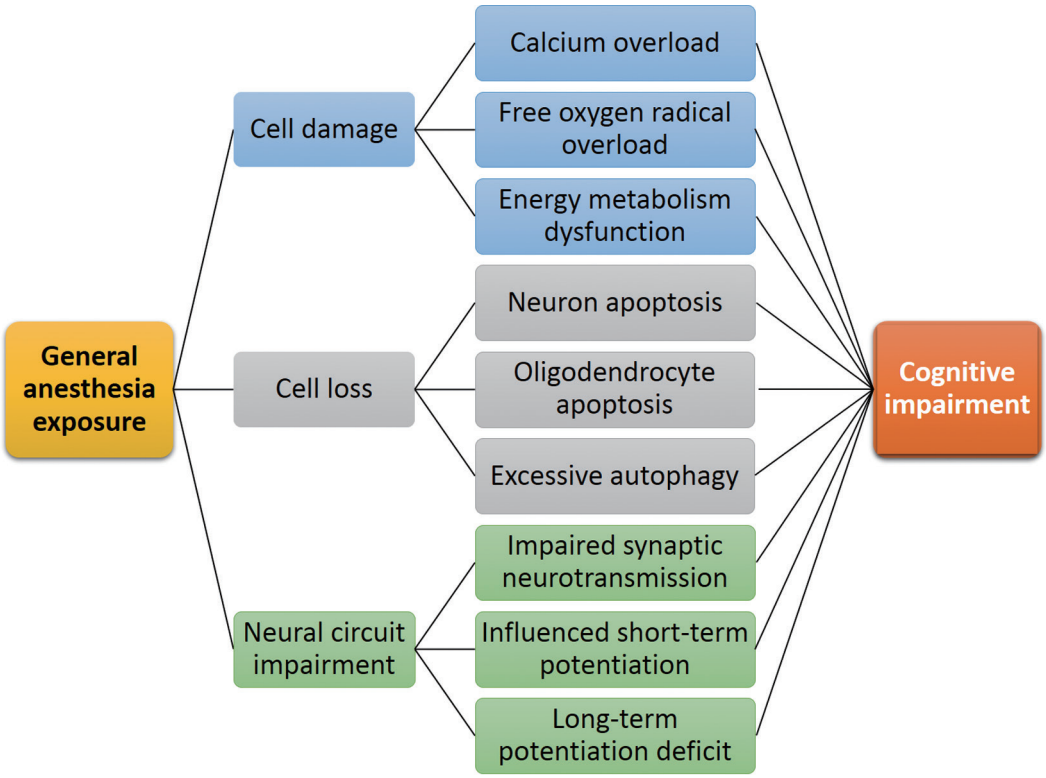

图 1. 发育期全麻药暴露影响认知功能机制示意图

Fig. 1. A schematic of mechanism responsible for cognitive impairment induced by early exposure to general anesthesia. An early exposure to general anesthesia induces cell damage. General anesthetics may induce cytosolic Ca^{2+} overload, cause a significant and long-lasting disturbance in mitochondria, which in turn causes free oxygen radical overload and energy metabolism dysfunction in cells and newly developing synapses. General anesthesia activates the mitochondria-dependent apoptosis and excessive autophage, which then leads to cell loss. General anesthesia-induced cell loss involves neurons and oligodendrocytes. Cell damage and cell loss together promote the damage of neural circuit, including synapse structure, transmission and plasticity. Due to all these mechanisms, early general anesthesia exposure causes the impairment of cognitive function.

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