Ketamine-induced neurotoxicity in neurodevelopment: A synopsis of main pathways based on recent in vivo experimental findings

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Abstract

Ketamine, a phencyclidine derivative and N-methyl-D-aspartate (NMDA) receptor antagonist, is widely used as an anesthetic, analgesic, and sedative agent in daily pediatric practice. Experimental studies have suggested that early prenatal or postnatal exposure to ketamine can induce neuroapoptosis, and establish neurobehavioral deficits that are evident in adulthood. However, most of the currently available clinical evidence is derived from retrospective and observational clinical studies. We, herein, attempt a brief review of the cellular and molecular mechanisms suggested to mediate ketamine-induced developmental neurotoxicity, utilizing a selected number of recent in vivo experimental evidence.

Keywords: Ketamine, neurodevelopment, neurogenesis, NMDA receptors, oxidative stress

Introduction

Although intravenous anesthetic agents are typically considered as safe to be administered during pediatric surgery, preclinical and clinical evidence has recently emerged regarding their potential neurotoxicity. Several studies have demonstrated that anesthetic exposure in early age may lead to long-term cognitive impairment as well as learning deficits.[1-4] The United States Food and Drug Administration has raised the concern of pediatric anesthetic neurotoxicity as a major public health issue,[5] and toward that direction, the Smart-Tots initiative has been carried out.[6,7] Moreover, a number of clinical studies have been performed in recent years,[8,9] and symposia are now assessing both the preclinical and clinical data on the potential correlation between anesthetic exposure and developmental neurocognitive impairment.[10] A central role in the ongoing debate on the potential developmental neurotoxicity of anesthetic agents is played by ketamine [Figure 1a], a N-methyl-D-aspartate (NMDA) receptor antagonist that is widely used in the pediatric anesthesia practice and in sub-anesthetic doses for sedation during diagnostic procedures.

Most of the currently available clinical evidence is derived from retrospective and observational clinical studies, and thus, very little can be concluded from them with regard to the mechanisms involved. We, herein, attempt a brief review of the cellular and molecular mechanisms suggested

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Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/joacp.JOACP_415_19

How to cite this article: Kalopita K, Armakolas A, Philippou A, Zarros A, Angelogianni P. Ketamine-induced neurotoxicity in neurodevelopment: A synopsis of main pathways based on recent in vivo experimental findings. J Anaesthesiol Clin Pharmacol 2021;37:37-42.

Submitted: 07-Dec-2019 Accepted: 07-Jan-2020 Published: 10-Apr-2021

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Recent experimental evidence suggests that the same deregulation of the NMDA receptors’ expression leads to premature differentiation of NPCs.\(^\text{[26]}\) It is well-established that ketamine downregulates receptor subunit NR1 in the PND7 frontal cortex.\(^\text{[20]}\) An earlier study investigating gene expression profiling in frontal cortical areas of age-matched (PND7) Sprague-Dawley rats that received ketamine, identified perturbations and confirmed an upregulation of NMDA receptors.\(^\text{[21]}\)

The deregulation of the expression of the NMDA receptors contributes to the neuronal susceptibility to the excitotoxic effects of Glu after the clearance of ketamine, leading to a major deregulation of the neuronal Ca\(^{2+}\)-signaling, and to the generation of oxidative stress.\(^\text{[20]}\) Moreover, due to the fact that Glu is an established regulator of neural progenitor cell (NPC) differentiation, and as NMDA receptors are considered to promote neuronal differentiation (through the overexpression of NeuroD as a result of neuronal excitation), premature neuronal differentiation becomes an additional consequence of the exposure to ketamine during neurodevelopment \([\text{Figure 1b}]\).\(^\text{[26]}\)

**Mitochondrial dysfunction and oxidative stress/mitochondrial apoptotic pathway**

The deregulation of the neuronal Ca\(^{2+}\) signaling as a result of the increased susceptibility to the excitotoxic effects of Glu has been reported to provoke mitochondrial dysfunction and the generation of oxidative stress in the hippocampi of rats exposed to ketamine during neurodevelopment.\(^\text{[15,18,19,22]}\) Mitochondrial dysfunction in ketamine-exposed rat brains has been associated with a downregulation of critical components of the extracellular signal regulated kinase (ERK) signaling cascade,\(^\text{[15,18]}\) implying a decreased capacity to perform critical gene transcription and translation. In the hippocampus, the latter could result to an impairment of synaptic consolidation and to a difficulty in the maintenance of long-term potentiation.\(^\text{[30]}\)
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Journal of Anaesthesiology Clinical Pharmacology | Volume 37 | Issue 1 | January-March 2021

Table 1: Selected recent (2009-2019) in vivo experimental studies providing critical insight to the cellular and molecular mechanisms underlying ketamine-induced developmental neurotoxicity

| Study | Species used; age at exposure | Exposure details (ED); main findings (MF); importance of the study (IMP) |
|-------|-------------------------------|------------------------------------------------------------------------|
| Aligny et al.\[11\] | FVB-Tg(GadGFP)45704Swn transgenic mice; from GD15 to GD20 | ED: pregnant mice received ketamine at 50 mg/kg, daily, subcutaneously, via injection; MF: (i) at PND45, mice exposed to ketamine demonstrated significant loss of Gad67-GFP interneurons in cortical layers II-IV, accompanied by a significant reduction in the dendritic spine density of these same interneurons; (ii) GABA levels as well as GAT-1 and GAT-3 expression levels were found increased in PND45 ketamine-exposed male mice (but not in the female ones) as compared to controls; (iii) an exacerbated Glu-induced Ca\(^{2+}\) mobilization was evident in PND45 ketamine-exposed female mice only, accompanied by higher levels of spontaneous locomotor activity; IMP: this study has targeted a time-window in which the migration of GABAergic precursors occurs in the developing murine brain, has utilized a dose of ketamine that can induce anesthesia for 3 h, and has demonstrated that although the ketamine-induced interneuronal loss is evident in both male and female mice, a sex-dependent adaptation of the GABAergic neurotransmission seems to provoke sex-specific behavioral deficits in adulthood |
| Brambrink et al.\[12\] | rhesus macaques; fetuses (GD120) and neonates (PND6) | ED: pregnant macaques (on GD120) received ketamine intravenously at a dose scheme of 10 mg/kg bolus, followed by a continuous infusion of 10-85 mg/kg of ketamine per h, for 5 h (supplemented with additional anesthetic-depth maintenance boluses); neonate macaques received ketamine intravenously at a dose scheme of 20 mg/kg bolus, followed by a continuous infusion of 20-50 mg/kg of ketamine per h, for 5 h (supplemented with additional anesthetic-depth maintenance boluses); MF: (i) both fetal and neonatal macaque brains exposed to ketamine demonstrated a significant increase of activated caspase-3 positivity as compared to controls; (ii) the pattern of the ketamine-induced neuroapoptosis was different in macaque fetuses than that in the respective neonates; IMP: this study has used a ketamine perfusion protocol of 5 h in order to match the depth and duration of anesthesia considered as “standard” in anesthetic drug testing and is among the few studies ever to demonstrate the differences in ketamine-induced neuroapoptotic injury as a result of different exposure time-windows, in nonhuman primates |
| Dong et al.\[13\] | Sprague-Dawley rats; GD17 | ED: pregnant rats on GD17 were exposed to ketamine via intraperitoneal injection at different doses (1, 2, 10, 20, 40, and 100 mg/kg), followed by an intraperitoneal injection of BrdU 24 h later; MF: GD19 fetuses demonstrated a dose-dependent reduction of BrdU-positive cells in the VZ and SVZ of their brain cortex, just 48 h after their exposure to ketamine; IMP: this study demonstrates that even in low doses, ketamine can inhibit cell proliferation in critical neurogenic regions of the developing rat brain |
| Huang et al.\[14\] | Sprague-Dawley rats (male); PND7 | ED: rats were exposed to 4 intraperitoneal injections of ketamine (40 mg/kg each) at 1 h intervals; MF: (i) ketamine-exposed rats demonstrated a transient disruption of their NSC proliferation and differentiation, as revealed by a series of well-devised experiments using BrdU along with a panel of other immunofluorescence stains; (ii) exposure to ketamine caused an inhibition of neuronal migration and in the granule cell layer of the hippocampal dentate gyrus of PND37 and PND44 rats, accompanied by a reduced growth of astrocytes in the hippocampal dentate gyrus; (iii) 2-month-old rats previously exposed to ketamine demonstrated a lower performance in the Morris water maze test than their age-matched controls; IMP: this is a critical study for the understanding of the role of the hippocampus in the ketamine-induced developmental neurotoxicity, with important leads regarding neuronal migration and glial growth |
| Huang et al.\[15\] | Sprague-Dawley rats; PND7 to PND9 | ED: rats were exposed to ketamine via intraperitoneal injections, at various doses (25, 50, and 75 mg/kg), once daily for 3 days; MF: 24 h after the last injection, ketamine-exposed rats demonstrated an increased number of apoptotic cells in the dentate gyrus and the CA1 region of their hippocampi only at the highest dose scheme (75 mg/kg), supported by decreased expression levels of p-ERK\(_{1/2}\), p-ERK\(_{1/2}\); (ii) female rats of the same treatment group (75 mg/kg) demonstrated a decreased performance in the Morris water maze test at PND60; IMP: this study provides evidence of a PKC\(_{\gamma}\)-ERK signaling pathway-mediated rat hippocampal neurodegeneration as a result of exposure to ketamine at a high dose (75 mg/kg) during the PND7-PND9 time-window, that is consistent with learning and memory impairment as assessed in adulthood in female only rats |

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Table 1: Contd...

| Study                  | Species used; age at exposure | Exposure details (ED); main findings (MF); importance of the study (IMP) |
|------------------------|-------------------------------|------------------------------------------------------------------------|
| Jeevakumar et al.\[16\]| CB6-Tg[ Gad1-EGFP ] G422Zjh/J mice (male); PND7 to PND11 | ED: rats received subcutaneous injections of ketamine at 30 mg/kg on PND7, PND9, and PND11; MF: (i) rats exposed to ketamine demonstrated a significant reduction of PV-expressing interneurons in the medial prefrontal cortex, in adulthood; (ii) adult rats exposed to ketamine demonstrated schizophrenia-like behavioral performance when assessed on a battery of behavioral experiments between PND90 and PND120; IMP: the authors claim this method of utilizing the neurodevelopmental exposure to ketamine could act as a model for the experimental simulation of the “cognitive and negative symptoms of schizophrenia” |
| Kanungo et al.\[17\]  | Transgenic (hb9:GFP) Danio rerio (zebrafish); embryos | ED: zebrafish embryos were exposed to 0.5 and 2 mM of ketamine for 2 or 20 h; MF: (i) when administered for 20 h, ketamine at 2 mM decreased cranial and motor neuron populations, as well as the axon length of the latter; (ii) ketamine suppressed the expression of the Notch 1α gene and downregulated the expression of the motor neuron-inducing NeuroD and Gl2b, while it upregulated the expression of Ngn1; IMP: this is a unique experimental study that describes a new pathway of ketamine-induced developmental neurotoxicity through the manipulation of differentiating and differentiated neurons (for more details, see Figure 1) |
| Li et al.\[18\]        | Wistar rats; GD14             | ED: pregnant rats received an intravenous injection of ketamine (200 mg/kg) for 3h; MF: (i) PND30 offspring rats exposed to ketamine during gestation demonstrated decreased levels of ERK, p-ERK, PKA, p-PKA, p-CREB, and BDNF in their hippocampi; (ii) these same rats demonstrated an impaired performance in a battery of behavioral tests as a result of their exposure to ketamine on GD14; IMP: this is a representative study of this group of authors, demonstrating the role of the ERK-CREB signaling pathway in ketamine-induced developmental neurotoxicity |
| Li et al.\[19\]        | Wistar rats; GD19             | ED: pregnant rats received an intravenous injection of ketamine (200 mg/kg) for 3h; MF: (i) GD19 rat embryos exposed to ketamine demonstrated the induction of oxidative stress in parallel to increased levels of cleaved-caspase-3, Bax, LC3-II, and ATG5 protein levels, as well as decreased Bcl-2, ATG4, and P62 protein levels in their hippocampi; IMP: this study provides evidence of a potential ketamine-induced ROS-mediated activation of the mitochondrial apoptotic pathway in the developing hippocampus, as well evidence of autophagy as a result of the exposure to ketamine under the specific experimental conditions |
| Liu et al.\[20\]       | Sprague-Dawley rats; PND7    | ED: rat pups received ketamine at different doses (5, 10, and 20 mg/kg) in 1, 3, or 6 subcutaneous injections at 2-h intervals, on PND7; MF: only the rats receiving 6 injections of 20 mg/kg of ketamine demonstrated significantly increased apoptotic death in their frontal cortex, while in situ hybridization revealed an overexpression of the NR1 subunit of the NMDA receptor of these same rats’ frontal cortex; IMP: this simple study demonstrates a ketamine-induced “compensatory” upregulation of the NMDA receptors and apoptosis, both after repeated exposures of ketamine at the highest dose tested |
| Shi et al.\[21\]       | Sprague-Dawley rats; PND7    | ED: rat pups received ketamine at 20 mg/kg in 6 subcutaneous injections at 2-h intervals, on PND7; MF: the rats receiving ketamine had their frontal cortical areas’ RNA profiled and identified perturbations were further investigated with the use of other techniques, revealing an upregulation of NMDA receptors; IMP: this study is supplementary to that of Liu et al.\[20\] |
| Yan et al.\[22\]       | Sprague-Dawley rats; PND7 to PND10 | ED: rat pups received ketamine at 75 mg/kg, in 3 intraperitoneal injections at 24-h intervals, starting on PND7; MF: (i) exposure to ketamine provoked an increase of HIF-1α, cleaved-caspase 3 and p53 protein levels in the PND11 rat hippocampi, in addition to a decreased Bcl-2/Bax ratio; (ii) the administration of YC-1, L-carnitine or nimodipine; IMP: this study suggests that the ROS/HIF-1α pathway is activated in ketamine-induced hippocampal neurodegeneration |
| Ye et al.\[23\]        | C57BL/6 mice; PND10 to PND17 or PND30 to PND37 | ED: mice were administered ketamine at 100 mg/kg per day for 7 consecutive days via intraperitoneal injection; MF: the levels of pyroptosis-related proteins (caspase-1, caspase-11, NLRP3, IL-1β, and IL-18) were found to be significantly increased after multiple doses of ketamine administration; IMP: this is a unique study suggesting the caspase-1-dependent pyroptosis could be an essential component of the mitochondrial apoptotic pathway triggered by ketamine |

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Also, triggering of the mitochondrial apoptotic pathway has been reported to evolve autophagy and caspase-1-dependent pyroptosis in rodents.\textsuperscript{19,23}

**Deregulation of neurogenesis through premature neuronal differentiation**

An experimental study on transgenic zebrafish embryos\textsuperscript{17} has put forward a new candidate pathway of ketamine-induced developmental neurotoxicity through the manipulation of differentiating and differentiated neurons [Figure 1c]. More specifically, zebrafish embryos were exposed to 0.5 and 2 mM of ketamine for 2 or 20 h; when administered for 20 h, ketamine at 2 mM was found not only to decrease cranial and motor neuron populations, and the axon length of the latter, but also to: (i) suppress the expression of the Notch 1a gene, (ii) downregulate the expression of the motor neuron-inducing NeuroD and Gli2b, and (iii) upregulate the expression of Ngn1.\textsuperscript{17}

The reported ketamine-induced downregulation of Notch 1a\textsuperscript{17} is expected to affect negatively the ligand-dependent Notch signaling in the proneural domain. The latter inhibition would upregulate Ngn1 in the NPCs and decrease the possibility of neuronal survival in differentiated neurons. In the first case, the ketamine-induced upregulation of the Ngn1 expression could lead to an upregulation of NeuroD expression, leading to premature neuronal differentiation.\textsuperscript{26} A downregulation of the NeuroD expression has been reported\textsuperscript{17} and it was suggested to be a result of fewer surviving differentiated neurons as a result of the exposure to ketamine [Figure 1c].

This—yet to be confirmed in mammals—mode of ketamine-induced developmental neurotoxicity could explain the findings of Aligny et al.\textsuperscript{11} on FVB-Tg(GadGFP) 45704Swn transgenic mice, where both the migration and the cytomorphology of GABAergic interneurons in the cortical layers II-IV were significantly affected by maternal exposure to ketamine from GD15 to GD20. It could also account for the dose-dependent inhibition of cell proliferation in critical rat neurogenic regions such as the ventricular and the subventricular zones by a single intraperitoneal injection of ketamine on GD 17.\textsuperscript{11}

**Other findings of interest**

Interestingly, the reduction of parvalbumin-expressing interneurons in the adult murine medial prefrontal cortex as a result of exposure to ketamine during the PND7 to PND11 time-window seems to be compatible with the expression of a phenotype that could act as a model for the experimental simulation of the "cognitive and negative symptoms of schizophrenia".\textsuperscript{16} Moreover, a critical and noteworthy study for the understanding of the role of the hippocampus in the ketamine-induced developmental neurotoxicity, with important leads regarding neuronal migration and glial growth, has been performed by Huang et al.\textsuperscript{14} In that well-designed study on Sprague-Dawley rats, ketamine-exposed rats on PND7 demonstrated a transient disruption of their neural stem cell proliferation and differentiation, and an inhibition of neuronal migration and in the granule cell layer of the hippocampal dentate gyrus upon reaching PND37 and PND44, which were accompanied by reduced growth of astrocytes in the hippocampal dentate gyrus.\textsuperscript{14}

**The “bigger picture” and translational perspectives**

Despite the progress recorded regarding the understanding of the neurodevelopmental toxicity of ketamine, the clinical translation of the aforementioned experimental findings should be done with caution and only after...
considering that: (i) in clinical pediatric or obstetric practice, ketamine is rarely used as a stand-alone anesthetic agent,[12] (ii) sex-dependent differences with regards to the developmental neurotoxicity of ketamine seem to exist,[11] and (iii) in vivo experimental studies involving a maternal exposure to ketamine rarely provide details of the maternal hemodynamic and respiratory stability; the latter being a critical interfering factor for the reliability of that type of study.[13] The pathways presented in this review seem to form a bigger picture in which the extent and the nature of the neuronal susceptibility to ketamine during neurodevelopment is strongly dependent on the experimental conditions employed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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