Neurotoxic and Behavioral Effects of Prenatal Ketamine Exposure: A Literature Review

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Abstract

Prenatal exposure to ketamine, a widely used anesthetic and analgesic, poses risks to the developing fetus due to its ability to cross the blood-brain and placental barriers. This literature review examines the effects of prenatal ketamine on offspring neurodevelopment and behavior. Animal studies indicate that ketamine exposure during pregnancy leads to increased apoptosis, neuronal death, and altered dendritic growth in the prefrontal cortex. These neurotoxic effects are associated with affective disorders, cognitive impairments, and anxiety-like behaviors in adulthood. Prenatal ketamine exposure is also linked to schizophrenia-like behaviors, including cognitive deficits, social withdrawal, and aggressive behaviors. However, postnatal use of ketamine shows antidepressant benefits and can attenuate stress-induced neuronal changes. Dexmedetomidine (DEX), an alternative sedative/anxiolytic agent, has shown promise in mitigating the neurotoxic effects of ketamine. DEX administration along with ketamine reduces apoptosis and neuronal degeneration, particularly in the frontal cortex. DEX also exhibits neuroprotective effects when combined with other anesthetics, such as propofol. Further research is needed to explore the precise mechanisms and long-term consequences of prenatal ketamine exposure, as well as to optimize the use of DEX as a neuroprotective agent.

Introduction

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist widely used for its anesthetic and analgesic properties, has a history of abuse as a recreational drug due to its psychotropic effects (1). More recently, ketamine has also been utilized as an antidepressant. It is known that ketamine can cross the blood-brain and the blood-placenta barrier. Indirect administration of ketamine to a fetus involves the transfer of the drug through the maternal-fetal barrier/placenta or given to a baby through breast milk. One minute 37 seconds after intravenous injection of ketamine to the mother, ketamine levels in newborn cord blood reaches the same levels as the mother's venous blood (1). As seen in lactating mice, phencyclidine, which is pharmacologically similar to ketamine, readily crosses into breast milk, increasing concentrations to levels 10-fold higher than in plasma (1). This rapid entry of ketamine into fetal/neonatal circulation alters neurodevelopment due to its accumulation in the brain. The presence of ketamine in the developing brain can lead to increased apoptosis and necrosis in neuronal cells, decreased proliferation of neural stem cells, increased reactive oxygen species, increased cell death of immature GABAergic interneurons, and decreased dendritic growth (1).

Mothers often suffer from postpartum depression (PPD) as a complication of cesarean section. When given intravenously during surgery, S-ketamine can help prevent PPD despite its neurotoxic effects (2). For example, s-ketamine given through patient-controlled intravenous analgesia (PCIA) reduced PPD within 14 days and relieved pain within 48 hours after cesarean delivery without increasing the adverse effects compared to the control group (2).

Methods

A review of the literature was conducted pertaining to the use of ketamine prenatally and its effects on offspring. References were obtained from PubMed, Google Scholar, and Geisinger Libraries with publication years ranging from 2012 to 2022. Keywords screened for in the database search included: prenatal ketamine, ketamine, ketamine misuse, dexmedetomidine, schizophrenia. The research did not include any exclusion criteria.

Discussion

Ketamine-Induced Neurotoxicity

The prefrontal cortex (PFC) is important for emotional and cognitive processes. Prenatal ketamine use harms development as it contributes to offspring suffering from affective disorders and cognitive impairments. Based on animal models, exposure of fetal rats to ketamine results in cell apoptosis and neuronal death. There is more dendritic branching in PFC neurons due to prenatal ketamine exposure when compared to the control (3). Increased neuronal cell death is evident in the frontal cortex of newborn mice after prenatal exposure to ketamine compared to the parietal cortex (4). Cortical layers II-IV are especially impacted by the loss of Gad67-GFP interneurons, along with a significant reduction in their dendritic spine density (5).

Ketamine and Behavior

Embryonic and infant exposure to ketamine harms the developing brain, and behavioral changes accompany this ketamine-induced neurotoxicity. Through the use of an open field test and an elevated plus maze, it was determined that mice prenatally exposed to ketamine did not show any effects during puberty. However, they later portrayed anxiety-like behaviors during adulthood (6). Using cFos to map neuronal activity, it was discovered that there was abnormal activity in the bed nucleus of the stria terminalis (6). Once this abnormal activity was silenced, the anxiety-like behavior induced by ketamine was reduced, leading to the conclusion that prenatal exposure to ketamine was the cause of the abnormal activity (6).

MAOA-LPR is a gene that regulates monoaminergic neurotransmission (7). Animals prenatally exposed to ketamine expressed the sensitivity MAOA-LPR genotype especially following first and second-trimester exposures (7). Ketamine administration in the first trimester correlated the sensitivity genotype with inhibited behaviors, such as less emotional expression in responsiveness observations and less contact with novel objects (7). Exposure in the second trimester showed a positive correlation between ketamine dosage and activity level seen in responsiveness observations (7). Postnatal ketamine, in combination with the low activity variant of monoamine oxidase A (MAOA), led to poor performance on a visual memory test (8).

Disturbances to the prenatal immune system can contribute to the pathophysiology of neuropsychiatric disorders. Maternal immune activation (MIA) increases oxidative stress and metalloproteinase expression in the fetal brain and amniotic fluid (9). Injection with ketamine on postnatal day 54 after MIA was induced led to memory impairment and deficits, in addition to observed behavioral deficits in adult rats (9). However, administration of (R)-ketamine twice weekly for four weeks in juvenile and adolescent offspring of maternal rats who experienced MIA blocked the development of cognitive defects and decreased dendritic spine density in the medial prefrontal cortex (mPFC) (10).

Despite its negative behavioral changes, there is an antidepressant benefit to the postnatal use of ketamine. A rat prenatal stress model of depression showed that mGluR5 is associated with depression-like behaviors and is increased in rats exposed to prenatal stress (11). However, ketamine can attenuate the stress-induced increase of mGluR5 (11).

Ketamine and Schizophrenia

Schizophrenia is a mental disorder characterized by cognitive impairments pertaining to attention, working memory, verbal learning, processing speed, and executive functioning (12). Exposure to prenatal ketamine has been strongly linked with schizophrenia-like behaviors in animal models (13). There is disinhibition and hyperactive behavior in pubertal rats exposed to ketamine, followed by cognitive impairments, social withdrawal, anxiety, depression, and aggressive-like behaviors in adulthood (13). Transplantation of mesenchymal stem cells into rodents who experienced a schizophrenic decrease in hippocampal neurogenesis due to ketamine exposure led to an improvement in social novelty and prepulse inhibition as well as behavioral improvement, increased hippocampal neurogenesis, and increased gene expression (14).

Is Dexmedetomidine an Alternative to Ketamine?

Dexmedetomidine (DEX) is an a2-adrenoreceptor agonist with sedative, anxiolytic, and analgesic effects (15) that has a mechanism of action different from ketamine. Ketamine exposure leads to apoptosis and degeneration in the frontal cortex; however, DEX exposure causes no or minimal neuroapoptotic and neurodegenerative lesions in the frontal cortex at low doses (16). Although DEX is a neuroprotectant in clinical doses, high doses result in neuroapoptosis (17). Its current dosing schedules in humans yield plasma levels below the concentrations required to induce neurotoxicity (17).

When comparing the effects of ketamine and DEX on the primary sensory and limbic brain regions, ketamine causes significant cell degradation and apoptosis in the limbic regions and insignificant changes in the primary sensory brain areas. In contrast, DEX produces opposite results (18). It causes significant cell degradation and apoptosis in the primary sensory brain regions and insignificant changes in the limbic regions (18).

General anesthetics can cause developmental neurotoxicity, such as neuronal cell death, long-term memory deficits, and learning abnormalities (19). It has been discovered that while ketamine causes apoptosis and impaired brain function in the developing brain, DEX can attenuate these effects when administered with ketamine (20). As a result, Ketamine and DEX have been increasingly used in combination for pediatric patients (20). Propofol is another anesthetic widely used in pediatric patients; however, previous studies have indicated that it can also induce apoptosis and damage cognitive and memory functions (21). Similar to its effects when administered with ketamine, DEX attenuates the effect of propofol-induced neurotoxicity on hippocampal neurons (21).

Conclusion

Ketamine is widely used as an analgesic, anesthetic, and antidepressant. Due to its hydrophilic and lipophilic properties, it can cross the blood-brain barrier as well as the placental barrier, making ketamine detrimental to developing fetuses. Ketamine is known to induce neurotoxicity and behavioral deficits following prenatal exposure. Prenatal ketamine administration is linked to apoptosis, neuronal death, anxiety-like behaviors, and schizophrenia-like behaviors. Ketamine, like other anesthetics, has been proven to promote neurotoxicity; however, DEX can attenuate the effects of ketamine when used in conjunction. DEX also reduces the neurotoxic effects of propofol. This decrease in neurotoxicity due to DEX may lead to a new age of anesthetic and antidepressant practices.

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