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Relationship between anesthetic-induced toxicity and NMDA receptor-mediated calcium influx in developing neurons

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Ketamine is a non-competitive NMDA receptor antagonist and is used as a general anesthetic. Recent data suggest that anesthetics can cause neuronal damage when exposure occurs during development. To elucidate the underlying mechanisms associated with ketamine neurotoxicity, neural cells were harvested from the forebrain of newborn rats and neural stem cells were isolated from gestational day-16 rats. To determine the effect of ketamine on developing neurons and undifferentiated neural stem cells, cultures were exposed to 10 μ M ketamine for 24 hours. Ketamine exposure resulted in elevated NMDA receptor (NR1) expression in primary cultures, and enhanced damage of developing neurons including those differentiated from the neural stem cells. However, the viability and proliferation rate of neural stem cells were not significantly affected after ketamine exposure. Calcium imaging data indicated that 50 μ M NMDA did not cause a significant influx of calcium in typical neural stem cells; however, it has produced an immediate elevation of intracellular free Ca2⁺ [Ca²⁺] i in neurons differentiated from the same neural stem cells. These findings suggest that prolonged exposure of developing neurons to ketamine produces an increase in NMDA receptor expression, which allows for a higher/toxic influx of calcium into neurons once ketamine is removed from the system, leading to neuronal cell death likely due to elevated reactive oxygen species generation.

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