KETAMINE INDUCES OLIGODENDROGLIA APOPTOSIS IN ADDITION TO NEURONAL LOSS IN DEVELOPING NON-HUMAN PRIMATE BRAIN

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BACKGROUND

Exposure of fetal or infant animals, including non-human primates (NHPs), to anesthetic drugs, at clinically relevant doses, causes brain injury and results in long-term neurodevelopmental impairment (NDI). The injury in fetal or infant macaque brains was originally described as apoptotic death of neurons, and was documented following exposure to ketamine, isoflurane or propofol (1,2,3). Subsequent reports demonstrated that the cell death response following isoflurane or propofol is more complicated and includes apoptotic death of both neurons and oligodendrocytes (oligos) (3,4). The present study was undertaken to determine whether ketamine-induced neuronal apoptosis in the developing NHP brain is also accompanied by apoptosis of oligos.

METHODS

With institutional approval, neonatal (postnatal day 6; P6) and pregnant (gestation day 120; G120; full term 165 days) macaques were exposed for 5 h to ketamine (intravenous infusion, ventricle perfusion controlled) or no anesthesia (controls). Ketamine was infused IV to maintain a surgical plane of anesthesia (no movement ± >10% raise in heart rate or systolic blood pressure to mosquito-clamp pinch; all movements ≤10% baseline measurements, IV saline and returned to their dams/cages. At 8 h from time zero, neonatal and fetal brains (G120) were perfusion fixed and analyzed using markers of apoptosis (activated caspase 3; AC3) and cell death (silver stain). Quantitative evaluation included counting all apoptosis-positive oligo profiles in serial sections at 2 mm intervals across the brain.

RESULTS

Fetal brains (G120) after ketamine-exposure (n=3) had a 4.45-fold higher number of apoptotic (AC3-positive) oligos compared to controls (n=4; Fig. 1). Neonatal brains (P6) after ketamine-exposure (n=4) had a 4.33-fold greater number of apoptotic oligos compared to controls (n=5; Fig. 1). The oligo apoptosis response reported here is approximately of the same magnitude as the neuronal apoptosis response to ketamine reported previously (2). Oligo-apoptosis in both fetal and neonatal brains was distributed throughout the white matter, but tended to be more heavily concentrated caudally in the fetus and rostrally in the neonate, which is consistent with the caudal to rostral progression of myelogenesis during early development.

REFERENCES

(3) Creeley MS, Farber NB, Smith DJ, Zhang X, Creeley MS, Farber NB, Smith DJ, Martin, LD, Olsen EA1, Noguchi KK3, Olney JW. Ketamine induces oligodendroglia apoptosis in the developing neonatal macaque brain. Anesthesiology 2010; 112: 834-41.
(4) Dissen CE, Dikranian K, Olney JW et al. The present study was undertaken to determine whether ketamine-induced neuronal apoptosis in the developing NHP brain is also accompanied by apoptosis of oligos.