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Neural stem cell models to studying pediatric anesthetic neurotoxicity

Cheng Wang

FDA, USA

Abstract

Propofol is a widely used anesthetic agent for adults and children. A growing body of data suggests that exposure to anesthetics during certain periods of perinatal development has long-term deleterious effects. At the cellular level there is evidence in the developing brain that anesthetic agents induce cell death, cause synaptic remodeling, and alter brain cell morphology. Acetyl-L-carnitine (aLc), an anti-oxidant dietary supplement, has been reported to prevent neuronal damage from a variety of causes both *in vitro* and *in vivo*. To evaluate the ability of aLc to protect against propofol-induced neuronal toxicity, a rat embryonic neural stem cell model was used.

Brain cortices were collected from fetal rats [gestational day (GD) 14] for neural stem cell isolation and subsequent culture in commercial rat growth medium in a humidified atmosphere. On the 8th day *in vitro* (DIV), confluent neural stem cells were exposed to propofol at concentrations of 10, 50, 100, 300 and 600 µM or propofol plus aLc (10 µM) for 24 hours. Neural stem cells were identified using monoclonal anti-nestin antibody. Markers of cellular proliferation (EdU), mitochondrial health (MTT), cell death/damage (LDH) and oxidative damage (8-oxo-dG) were monitored to determine: 1) the effects of propofol on neural stem cell proliferation; 2) the nature of propofol-induced neurotoxicity; 3) the degree of protection afforded by aLc; and 4) to provide information regarding potential underlying mechanisms.

The EdU data demonstrated that after exposure to propofol for 24 hrs at a clinically-relevant concentration (50 µM), the number of dividing cells was significantly decreased. Propofol exposure also resulted in a substantial dose-dependent reduction in mitochondrial health as evidenced by significant decreases in the metabolism of MTT. No significant effect on LDH release was observed at propofol concentrations of 10, 50 or 100 µM. 50 µM propofol significantly increased oxidative DNA damage as evidenced by increases in 8-oxo-dG formation and this effect was blocked by aLc. No significant effect on 8-oxo-dG formation was observed when aLc was administered alone.

These data suggest that clinically-relevant concentrations of propofol induce dose-dependent adverse effects on rat embryonic neural stem cells: 24 h exposures slow or stop cell division/proliferation and cause cellular damage. The presence of elevated levels of 8-oxo dG and its analogs in the culture medium suggest the occurrence of oxidative damage due to increased generation of reactive oxygen species. Co-administration of aLc effectively blocks at least some of the toxicity of propofol, presumably by scavenging ROS and/or reducing ROS production.

Biography

Cheng Wang, M.D., Ph.D. is a Senior Scientist at the National Center for Toxicological Research (NCTR)/US Food and Drug Administration (FDA). He is also an Adjunct Faculty member in the Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences (UAMS).

Wang is currently the P.I. on 4 research protocols supported by the NCTR/FDA, National Toxicology Program and NICHD. He is currently responsible for leading a research team that provides unique and highly specialized skills in toxicology, pharmacology and systems biology research. Dr. Wang has published about 55 peer-reviewed research articles in prestigious journals and 10 book chapters. Dr. Wang is Co-Editor-in-Chief of the book entitled "Developmental Neurotoxicology Research: Principles, Models, Techniques, Strategies, and Mechanisms." He also serves on the editorial board of 3 reputed journals and as a reviewer of 10 other journals.

Wang was awarded the Outstanding Performance Award at the Society of Toxicology 44th Annual Meeting and the 2007 FDA Scientific Achievement Award for Excellence in Laboratory Science. He also was awarded a 2008 FDA Group Recognition Award for his participation in the Pediatric Anesthesia Research Group.