ADVERSE LIFE EXPERIENCES MAY REINFORCE NEURODEVELOPMENTAL ABNORMALITIES INITIATED BY GENERAL ANESTHETIC EXPOSURE DURING THE EARLY POSTNATAL PERIOD

Millions of neonates undergo anesthesia every year. Paradoxically, many human studies report neurocognitive abnormalities in children after testing those who had anesthesia-requiring procedures despite the fact that the duration of anesthesia is normalized to the life span, the length of typical anesthesia exposure in humans is much shorter than that shown to induce developmental abnormalities in animal models. We investigated whether developmental abnormalities in rodents, initially programmed by a relatively short exposure to etomidate anesthesia, can be exacerbated by post-anesthesia stressful environmental factors and whether neonatal anesthesia exposure combined with post-anesthesia stress induces a dysregulation of stress response systems in adulthood.

Postnatal days (P) 4, 5, or 6, Sprague-Dawley rats received the Na+-K+-2Cl- (NKCC1) inhibitor, bumetanide, or saline prior to 2 h of etomidate (8 mg/kg, IP) for induction followed by second injection (4 mg/kg, IP.) 50 min later. To simulate subsequent stress, a subgroup of the animals was subjected to a single episode of maternal separation for 3 h at P10. Two cohorts of animals were studied. Neonatal rats in cohort one were used for gene expression studies to determine etomidate-induced changes immediately and 3-7 days after exposure to etomidate, the time period at which maternal separation was administered. Rats in cohort two were used for behavioral and neuroendocrine studies, as well as for gene expression measurements in adulthood. Rats were sequentially evaluated in the elevated plus maze (EPM) starting at P60, for prepulse inhibition (PPI) of the acoustic startle response at P70 and for the corticosterone response to physical restraint for 30 min at 8P120.

Post-anesthesia stressors may exacerbate/unmask neurodevelopmental abnormalities even after a relatively short anesthetic with etomidate, leading to dysregulated stress response systems and neurobehavioral deficiencies in adulthood, with more profound changes in males.

Amelioration by bumetanide suggests a mechanistic role for etomidate-enhanced gamma-aminobutyric acid type A receptor-mediated depolarization in initiating long-lasting alterations in gene expression that are further potentiated by subsequent maternal separation.

Significant alterations in gene expressions, neuroendocrine and neurobehavioral abnormalities in adult rats neonatally exposed to etomidate anesthesia and a single maternal separation suggest that even relatively mild environmental stressors may reveal long-term developmental abnormalities initiated by a relatively short exposure to a general anesthetic during an early period of life, and that a neonatally administered anesthetic may program abnormal functioning of the stress response systems and behavioral deficiencies in adulthood.