Relatively short neonatal anesthesia with etomidate alters resilience to the adverse effects of stressors in rats

Ling-Sha Ju,[1] Jiao-Jiao Yang,[1] Christoph N. Seubert,[1] Nikolaus Gravenstein,[1,2] Timothy E. Morey,[1] Anatoly E. Martynyuk,[1,2]

[1]Department of Anesthesiology and the [2]McKnight Brain Institute, University of Florida College of Medicine, Gainesville, FL.

Background

Relatively long exposures of neonatal rats to either sevoflurane, an anesthetic whose actions include enhancement of gamma-aminobutyric acid type A receptor ($GABA_AR$) activity, or propofol, a relatively selective enhancer of $GABA_AR$ activity, induce long-term exacerbated corticosterone responses to stress and neurobehavioral abnormalities. Similar developmental abnormalities may be induced by excessive postnatal stress, e.g. repeated maternal separations throughout the first weeks of life. Here we tested whether a relatively short exposure to etomidate, another $GABA_AR$ enhancer, and a single episode of maternal separation, i.e. two mild interventions incapable to produce significant abnormalities by themselves can together induce significant abnormalities that resemble those induced by relatively long exposure to anesthesia.

Methods

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.

Results

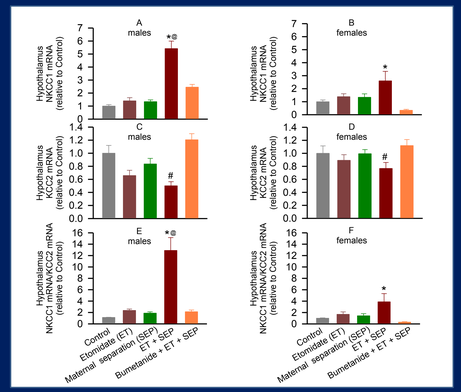

Figure 1: Anesthesia with etomidate for 2 h at postnatal days (P) 4, 5 or 6 followed by maternal separation for 3 h at P10 lead to increased hypothalamic levels of NKCC1 mRNA reduced hypothalamic levels of KCC2 mRNA in adult male and female rats. These effects were alleviated by pretreatment with bumetanide prior to anesthesia with etomidate.

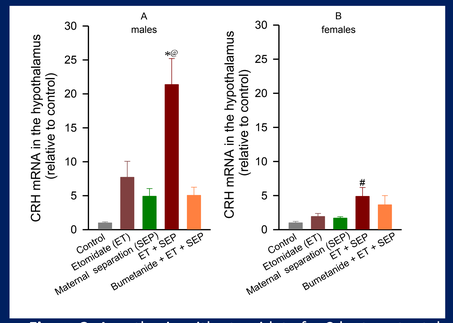

Figure 3: Anesthesia with etomidate for 2 h at postnatal days (P) 4, 5 or 6 followed by maternal separation for 3 h at P10 lead to increased hypothalamic levels of corticotropin releasing hormone (CRH) mRNA in adult male and female rats, with greater effects in male rats.

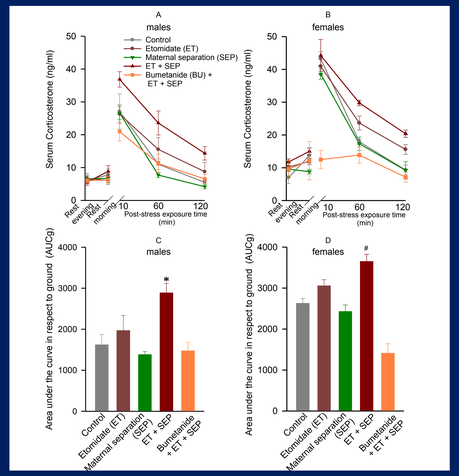

Figure 2: Anesthesia with etomidate for 2 h at postnatal days (P) 4, 5 or 6 followed by maternal separation for 3 h at P10 lead to increased serum levels of corticosterone after physical restraint for 30 min in adult male and female rats.

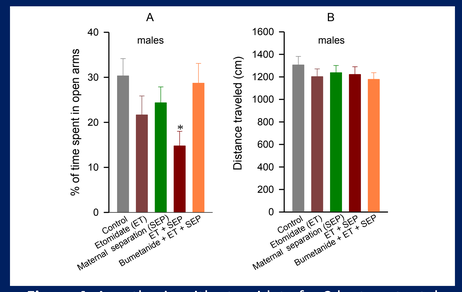

Figure 4: Anesthesia with etomidate for 2 h at postnatal days (P) 4, 5 or 6 followed by maternal separation for 3 h at P10 lead to reduced time spent in open arms of the elevated plus maze (EPM) in adult male, but not female rats, an effect that was alleviated by pretreatment with bumetanide prior to anesthesia with etomidate.

Summary

The results of this study together with our previously published data[1-6] show that:

- 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.
- These findings imply that etomidate may induce developmental abnormalities through a previously unknown long-lasting alteration in gene expression.
- Our current findings together with previous reports on the effects of propofol and sevoflurane[3-6] add a new type of early life experience, namely neonatal exposure to general anesthesia, as an early programming event that may contribute to stress-related cognitive disorders in adulthood.

References

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Acknowledgements

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