Pretreatment with erythropoietin improved the long-term neurological function induced sevoflurane exposure in neonatal rats.

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Introduction

- Sevoflurane exposure induced neural apoptosis and degeneration in the neonatal immature brain.
Paediatr Anaesth 26: 6-36, 2016.
- Erythropoietin (EPO) has been shown to protect neonatal animals from hypoxic ischemic injury.
Pediatr Res 74: 658-667, 2013.
- EPO exerts its neuroprotective effects through multiple mechanisms, including anti-apoptotic, anti-inflammatory, neuroregenerative, neurotrophic, and anti-oxidant. Clin Perinatol 42: 469-481, 2015.
- EPO can protect against anesthetic-induced neurodegeneration remains largely unknown.
Paediatr Anaesth 24: 749-759, 2014, Paediatr Anaesth 21: 1209-1213, 2011.

Purpose

- EPO administration could ameliorate neurodegeneration triggered by sevoflurane in the developing rat brain and improve cognitive function in the long-term.

Methods

- On P7, rat pups were injected intraperitoneally with saline or 0-600 U of recombinant human EPO.
Group (n=5, each group)
EPO 0 U: saline
EPO 60 U: EPO 60 U
EPO 120 U: EPO 120 U
EPO 600 U: EPO 600 U
- After 30 minutes, rats were exposed to 3% sevoflurane anesthesia for 4 hours with 21% oxygen.
- Cognitive function was evaluated using the Morris water maze on P27-P29 (acquisition trial) and P47-P49 (retention trial).
- Fear conditioning test (FC) was conducted 5 weeks (P42) and 6 weeks (P49) after anesthesia exposure.
- Brains were stained with NeuN on P49.
- The number of NeuN-positive cells in a 500 $\mu\text{m} \times 300 \mu\text{m}$ area was counted bilaterally in the CA1 hippocampus and cerebral cortical layer 3.

- Data (mean $\pm$ SD) were analyzed using one-way and two-way ANOVA.

Results

Acquisition trials of water maze test (P27-29)

Retention trials of water maze test (P47)

Fear conditioning test

Number of NeuN positive cells

NeuN staining of brain sections

Representative NeuN staining at -2 ± 0.2 mm from bregma is shown. NeuN-positive cells in the entire image at lower magnification (A), CA1 hippocampus at higher magnification (B), and cortex at higher magnification (C) are shown for each group. Squares indicate the measuring field in the cortex and CA1. Scale bar: 2 mm (A) or 100 μm (B and C). EPO, erythropoietin.

Conclusion

- A single administration of EPO (600 U) before sevoflurane exposure reduced the neurologic impairment.
- Even a small dose of EPO increased the number of intact neurons in the cortex and hippocampus exposed to sevoflurane as infants.
- Pretreatment with EPO is likely to improve long-term cognitive function and ameliorate neuronal degeneration induced by sevoflurane exposure in neonatal rats.