Environmental Enrichment Ameliorates the Epigenetic Reduction of BDNF and Memory Deficiency Induced by Neonatal Anesthesia

Abstract: Although neonatal exposure to commonly used anesthetic drugs has been associated with persisted memory deficiency in rodent models and possibly in pediatric patients, the underlying mechanisms are not known. Brain-derived neurotrophic factor (BDNF) and its cognate receptor tyrosine receptor kinase B (TrkB) play a substantial role in regulating the synthesis of synaptic proteins and in modulating synaptogenesis, synaptic plasticity and memory. Here, we found a substantial reduction of hippocampal BDNF, resulting from the transcriptional factors-mediated epigenetic modification in the promoter region of *Bdnf* exon IV (**Fig. 1a,b**) and decreased histone H3 acetylation in the *Bdnf* exon IV (**Fig. 1c**), but not *Gapdh*, promoter region of rats exposed postnatally (P7) to isoflurane anesthesia (2.5% induction, 1.5% maintenance) for 6h. This BDNF reduction led to the insufficient drive for the synthesis of synaptic protein (**Fig. 1d**) and was associated with significantly decreased synaptic density, dendritic spine number (**Fig. 1e,f**), impaired glutamatergic long-term potentiation (LTP) in the hippocampal CA1 neurons (**Fig.1g**) and extended escape latencies and less time (during the probe trial) spent in the target quadrant (TQ) in the Morris water maze test (**Fig.1h,i**), indicating an impaired synaptic plasticity and cognitive dysfunction induced by neonatal anesthesia in the adult rats (P65). Blocking TrkB receptor activity in naïve rats using TrkB-Fc microinjected into the hippocampal CA1 area resulted in synaptic and cognitive dysfunction (**Fig.1j-l**) similar to that induced by neonatal anesthesia. We also found that exposure to enriched environment (EE) significantly mitigated the epigenetic suppression of BDNF and restored hippocampal synaptic plasticity and cognitive functions (**Fig. 1b,d,e-i**). Our findings elucidated the epigenetic mechanism underlies the memory deficiency induced by neonatal anesthesia and proposed environmental enrichment as a potential therapeutic approach.

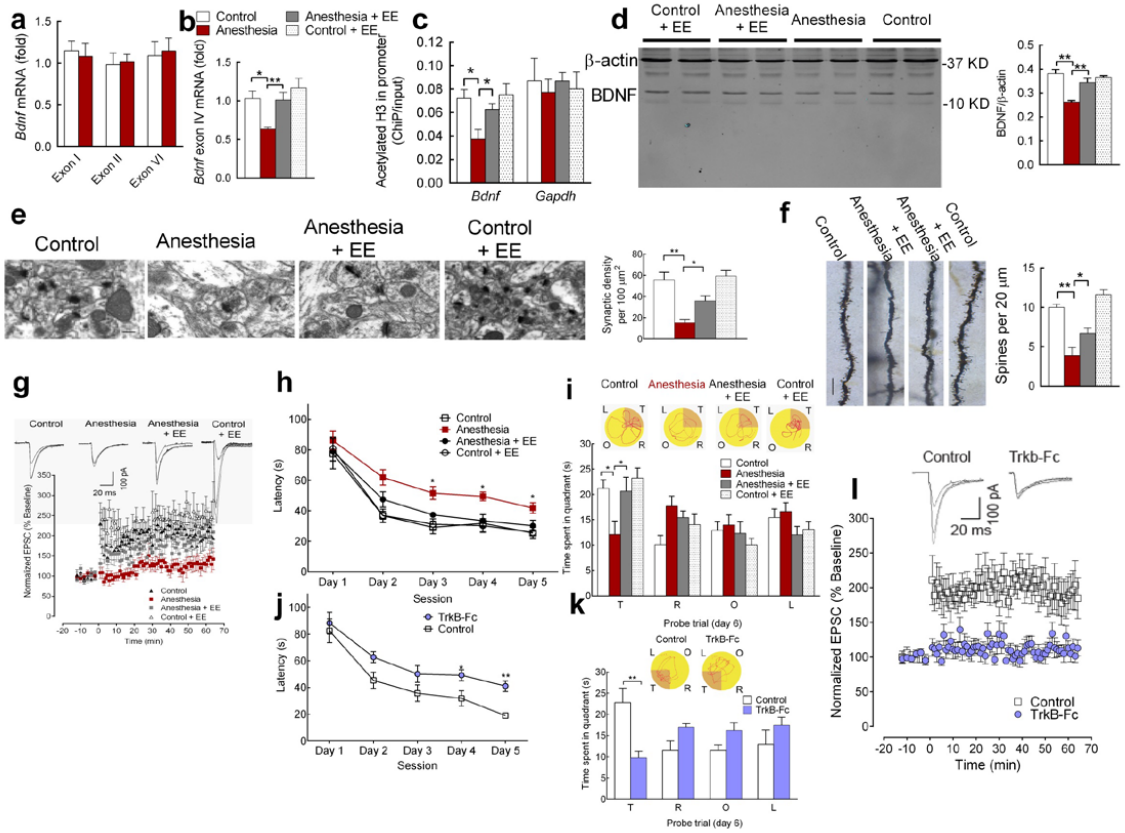

Figure 1. Neonatal (P7) exposure to anesthetics significantly decreased *Bdnf* exon IV mRNA (**a,b**), decreased histone H3 acetylation in the *Bdnf* exon IV, but not *Gapdh*, promoter region (c) and decreased protein expression (d) in the hippocampal CA1 tissue in the adult rats (P65). Hippocampal synaptic density (**e**, scale bar = 0.25 μm), dendritic spine numbers (**f**, scale bar = 10 μm) and HFS-induced LTP (g, n = 9-12 neurons in each group) were significantly reversed by EE in rats with neonatal exposure to anesthetics. Representative path tracings (**i**) in each quadrant during the probe trial of the Morris water Maze test on day 6 (T, target quadrant; R, right quadrant; O, opposite quadrant; L, left quadrant). Bilateral microinjection of Trkb-Fc (2 μg×7 days) into the hippocampal CA1 significantly extended the escape latencies (**j**), and shortened the time spent in the target quadrant (k) in the Morris water maze test and impaired HFS-induced LTP (**l**) in the hippocampal CA1 neurons. *, P<0.05; **, P<0.01. Data represent mean ± s.e.m.