

Effect of morphine exposure on developing rat hippocampus

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INTRODUCTION

Opioids are used in the neonatal intensive care unit (NICU) for pain management and sedation of infants requiring mechanical ventilation [1]. Adult rats exposed to recurrent administration of opioids in the absence of pain have decreased neurogenesis and altered neurotransmitters in the dentate gyrus of the hippocampus [2, 3]. Prenatal exposure to opioids causes long-term learning and memory impairments in rats [4]. However, effects of morphine given postnatally to premature infants on the neurochemical profile of the hippocampus are unknown. The purpose of this study was to investigate effects of morphine on the neurochemical profile of the developing rat hippocampus.

METHODS

All NMR measurements were performed with a Varian INOVA spectrometer interfaced to a 9.4 T magnet, equipped with powerful 2nd-order shim coils (Magnex). First and second order shims were adjusted by FASTMAP [5]. Ultra-short echo-time STEAM (TE = 2 ms) combined with outer volume suppression and VAPOR water suppression was used for localization [6]. Metabolite concentrations were quantified using LCModel with macromolecule spectra included in the database and the unsuppressed water signal was used as an internal reference as in our previous studies [7-9]. Morphine sulfate (2 mg/kg, i.p.) or normal saline were administered twice daily to rat pups from postnatal day (P) 3 to P7. Rats were studied on P8 (control=6, morphine=7) and P29 (n=6 per group). In addition, the brains of littermates were harvested on P8 to evaluate neurogenesis by labeling with bromodeoxyuridine, a synthetic nucleoside that is an analogue of thymidine which is incorporated into the DNA of replicating cells during the S-phase of the cell cycle.

RESULTS AND DISCUSSION

Morphine exposure resulted in a 70% decrease in new cell production within the granule cell layer of the hippocampus ($p < 0.01$). Highly resolved *in vivo* ¹H NMR spectra measured from the left hippocampus (Fig. 1) allowed reliable quantification of fifteen brain metabolites (Cramer-Rao lower bounds < 30%). On P8, differences between the morphine and control groups were observed for multiple metabolites, such as GABA, GSH, GPC+PC, myo-Ins, PE, and Tau (Fig. 2). Concentration changes seen on P8 had resolved by P29, except that Glc was decreased in morphine exposed pups. Biochemical changes indicated effects of morphine on inhibitory neurotransmission (GABA, Tau), glial development and myelination (Gln, myo-Ins), osmoregulation (myo-Ins, Tau) and antioxidant processes (GSH). In conclusion, these results indicate that morphine exposure during hippocampal development may lead to hippocampal-dependent cognitive deficits in premature infants.

REFERENCES

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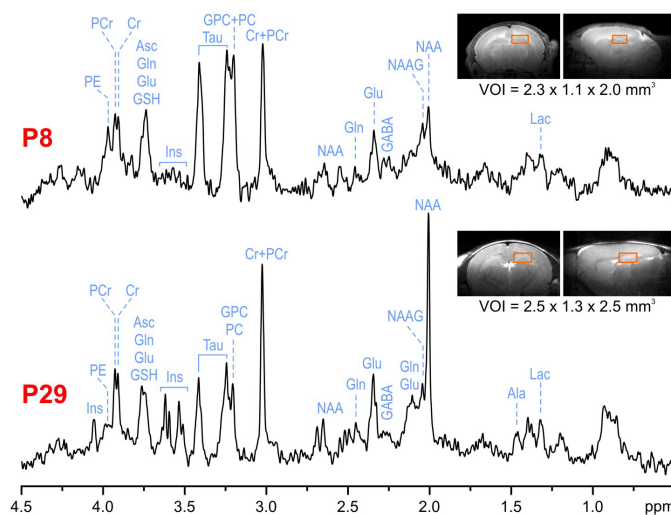


Fig. 1 *In vivo* ¹H NMR spectra measured from the hippocampus of rat pups on postnatal day (P) 8 and P29. Rat pups were exposed to morphine from P3 – P7. STEAM, TE = 2 ms, TR = 5 s, NT = 240. Insets: RARE images with the selected VOI in left hippocampus.

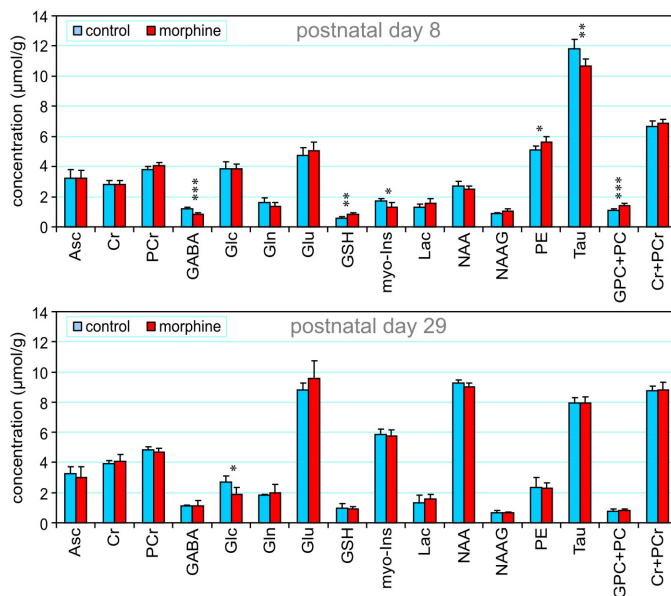


Fig. 2 Comparison of neurochemical profiles of rat pups exposed to morphine (2 mg/kg, twice a day, from P3 to P7) relative to littermate controls. Metabolite concentrations were measured from left hippocampus on P8 and P29. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.