Fetal exposure to Bisphenol A alters mitochondrial function

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Introduction

The fetal brain is susceptible to insults during pregnancy that can adversely impact brain development resulting in impaired brain function. Bisphenol A (BPA; 4,4'-isopropylidenediphenol) which is present in plastic food and drink containers, and dental materials, has been implicated as an endocrine-disrupting chemical during pregnancy due to its ability to mimic the action of endogenous steroidal hormones. Several laboratories have shown that exposure to BPA during gestation and/or lactation results in adverse effects for the offspring, as evidenced by accelerated growth and puberty, reproductive malformations, and behavior modifications [1,2]. The aim of the project was to evaluate the differential effect of BPA exposure during gestation and lactation in the developing rat brain using proton spectroscopy (^{1}H-MRS).

Methods

Female Sprague-Dawley dams (Charles River Laboratories, France) were used to program two groups of pups,(n=8 each): 2) Control group: 1% of ethanol was added in their drinking water from day 6 of gestation 1) BPA-treated group: 1mg/l BPA dissolved in 1% ethanol in their drinking water from day 6 of gestation. Rat pups were scanned at postnatal day 20 (P20) and were anesthetized by spontaneously breathing 1.2 to 1.8% of isoflurane in oxygen through a face mask.

All experiments were performed on an actively-shielded 9.4T 31 cm bore magnet (Varian/Magnex Scientific) with 12 cm gradient (400 mT/m in 120 µs). Following shimming with FASTMAP, localized 1H spectroscopy was performed on a 12µl voxel in the hippocampus (Fig. 1) using ultra-short echo time STEAM with as previously published [2] (TE/TM/TR = 2/20/4000 ms), combined with outer volume and VAPOR water suppression [2]. A 17 mm diameter two-loop quadrature transceiver coil was used. The measured data were corrected for small frequency drift and residual eddy-current effects. The neurochemical profile was obtained with LCModel [3] and absolute concentration was determined relative to tissue water signal.

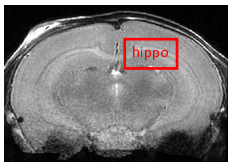

Figure 1: T2-weighted image showing the voxel position for localized spectroscopy on the hippocampus

Results and Discussion

The neurochemical profile in control rats was in excellent agreement with previous studies [4]. Overall, the neurochemical profile of the BPA-treated pups was very similar to the control one (c.f. Figure 2). However, Glutamate (Glu) showed a significant increase ($[Glu]_{control}$ = 8.95 ± 0.3 µmol/g ± SE, $[Glu]_{BPA}$ = 9.7 ± 0.2 µmol/g and p-value of 0.035, unpaired t-test). The Glu/Asp ratio was significantly increased from $[Glu/Asp]_{control}$ = 4 ± 0.3 µmol/g to $[Glu/Asp]_{BPA}$ = 5.5 ± 0.4 µmol/g (p-value = 0.02) whereas the sum of Asp and Glu concentrations did not change significantly.

Asparate and glutamate are metabolically linked by the aspartate aminotransferase reaction, a critical component of the malate aspartate shuttle (c.f. Figure 4) [5]. The increase of the Glu/Asp ratio reflects a relative increase in cytosolic dehydrogenase activity relative to the activity of the glutamate/aspartate antiporter, the critical rate-controlling step of the malate-aspartate shuttle. Similar changes in the Glu/Asp ratio have been reported in two previous studies in the rat [6] and in the human brain [7] during physiological stimulation. We conclude that BPA reflects an impaired relative ability of the mitochondrion to oxidize glucose, be it due to increased glucose metabolism or due to impaired mitochondrial function in the developing rat hippocampus.

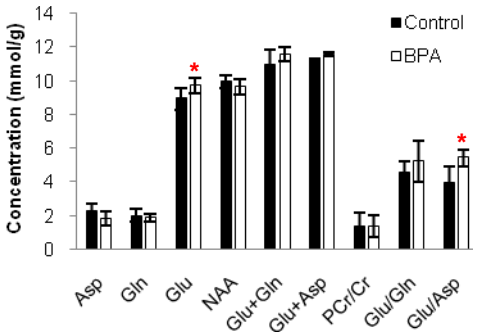

Figure 2: Absolute concentration of select constituents of the neurochemical profile of the control pups (white) and the BPA-treated animal (black). Errors bars = SD and *: p<0.05

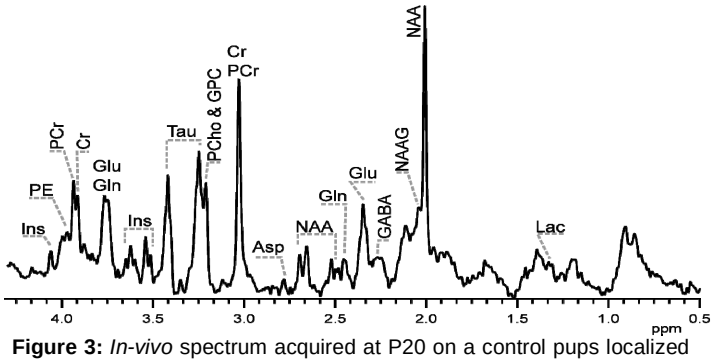

Figure 3: *In-vivo* spectrum acquired at P20 on a control pups localized in the hippocampus

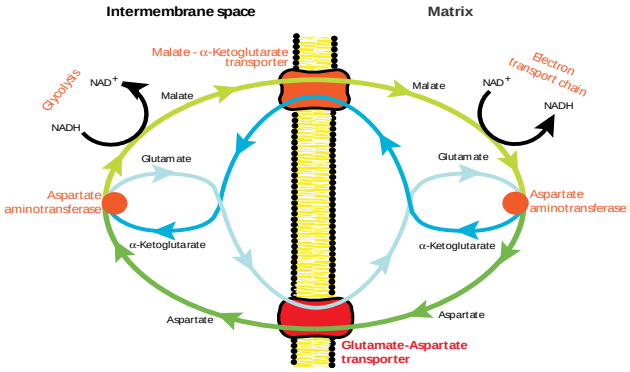

Figure 4: Malate-Aspartate shuttle in the mitochondrion

Acknowledgements

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