

Effects of Lactoferrin on altered brain metabolism in pup rats after prenatal exposure to Dexamethasone

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Introduction:

In utero exposure to synthetic dexamethasone mimics maternal stress and the clinical situation when glucocorticoids are administered to pregnant women at risk of premature delivery. The rat model of glucocorticoids exposure during gestation has shown reduction in brain weight. Histological analysis revealed a delay in myelination and a persistence of radial glial fibres, suggesting a delay in the normal involution of radial glia and maturation into astrocytes. At postnatal day 7 (P7), alterations of cerebral metabolism in the cortex and the hippocampus have been observed by *in vivo* Proton Magnetic Resonance Spectroscopy (¹H-MRS) [1]. These results have suggested an impairment of brain structure, cerebral energy metabolism and neurotransmitter action after gestational dexamethasone exposure [1]. Lactoferrin (Lf) is an iron-binding glycoprotein secreted in milk which has an antioxidant activity [2]. In mouse after oral administration, Lf is rapidly transferred from the intestine into various organs including the brain [3]. Lf is also synthesized in brains of both human suffering from Alzheimer's dementia and mouse model of Parkinson's disease, indicating that Lf potentially plays a role in neurodegenerative diseases. The aim of this work was to evaluate the neuroprotective effect of Lf following prenatal exposure to glucocorticoids by high field localized ¹H-MRS.

Materials and Methods:

Animal preparation: Sprague-Dawley rats were divided in 3 groups: two groups treated with DEX (100 µg/kg/day) during the third week of gestation. One had access *ad libitum* to a standard diet (Ctrl-DEX), the second received Lactoferrin-enriched food (1 g/kg/day) *ad libitum* during both gestation and lactation (Lf-DEX). The third group represents sham rats fed with standard diet (Ctrl-Veh).

¹H-MRS: All experiments were performed on an actively-shielded 9.4T/31cm magnet (Varian/Magnex) equipped with 12-cm gradient coils (400mT/m, 120µs) with a quadrature transeceive 17-mm surface RF coil. At P7, Fast Spin Echo (FSE) images (TR/TE = 6000/80 ms; FOV = 25×25 mm and matrix size = 256×128) were acquired to position MRS voxel of interest (VOI = 1.5×1.5×2.5 mm³). First and second order shims were adjusted using FASTMAP [4]. The water line-widths ranged between 8 and 15 Hz. Spectra acquisitions both within the cortex and hippocampus were performed using an ultra-short echo time (TE/TR = 2.7/4000 ms) SPECIAL spectroscopy method [5]. 30 series of FIDs (16 averages each) were acquired, individually corrected for frequency drift, summed together and corrected for residual eddy current effects using the reference water signal. Proton spectra were analyzed with LCModel [6] using the unsuppressed water signal corrected for age-dependent changes in brain water content as an internal reference [7]. Metabolites were quantified resulting in a neurochemical profile of both the hippocampus and the cortex for each group and compared using a Kruskal-Wallis test.

Results and Discussion:

Compared to Ctrl-Veh group (Figure 1), the Ctrl-DEX group showed significant decreased concentration of NAA+NAAG in the hippocampus (2.55 mM ± 0.26 vs 3.37 mM ± 0.10, p<0.05). In addition a significant decrease of Glu+Gln was observed in both the hippocampus (3.74 mM ± 0.85 vs 5.32 mM ± 0.66, p<0.05) and the cortex (2.95 mM ± 0.66 vs 5.62 mM ± 0.78, p<0.05). No statistical differences have been found between Lf-DEX and Ctrl-Veh groups. Variation of NAA+NAAG and Glu+Gln concentrations, considered as markers of neuronal integrity and function, have confirmed the altered brain development after Dex exposure and revealed the potential protective effect of the lactoferrin given to gestational and lactating dams in a rat model of prenatal exposure to adverse conditions.

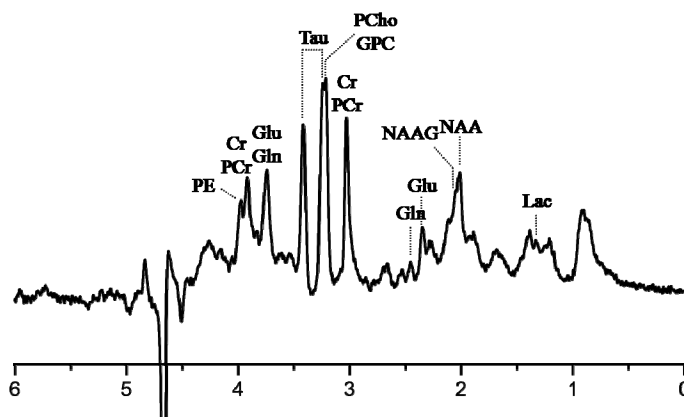


Figure 1: Typical spectrum of the hippocampus of a sham P7 rat.

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