FETAL HYPOGLYCEMIA STIMULATES EXPRESSION OF FETAL CEREBRAL CANNABINOID 1 RECEPTOR (CB1R)

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INTRODUCTION

- The endogenous cannabinoid system (ECS) plays an essential role in human homeostasis. Human cannabinoid receptor 1 (*CNR1)* gene encodes unique CB1R transcript variants.

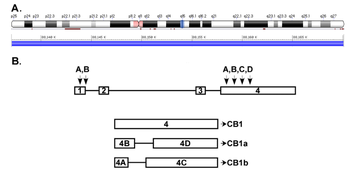


Figure 1. *CNR1* [*Homo sapiens* (human)] chromosomal location and structure diagram. **A.** Location: 6q15 (NCBI). **B.** Bars with numbers inside represent exons and horizontal lines represent introns. CB1 full length, CB1a and CB1b trasncript variants are shown [Modified from González-Mariscal et al., 2016].

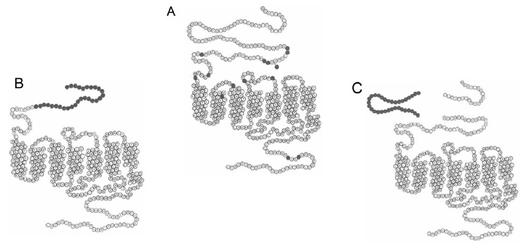
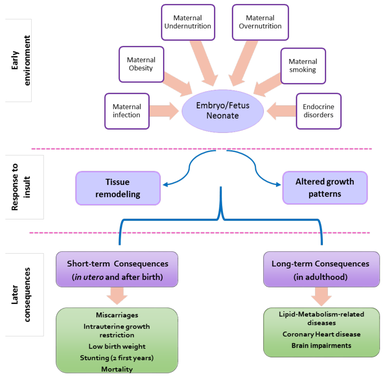


Figure 2. Human CB1R structure diagrams and its CB1a and CB1b isoforms. **A**. Human CB1R with rodent CB1R residues. **B**. CB1a isoform with the substituted amino-terminus residues added relative to CB1R. **C.** CB1b isoform with the missing amino-terminus region [Modified from Straiker, Wager-Miller, Hutchens, and Mackie, 2011].

- Maternal Nutrient Restriction (MNR) affects offspring development through fetal programming.

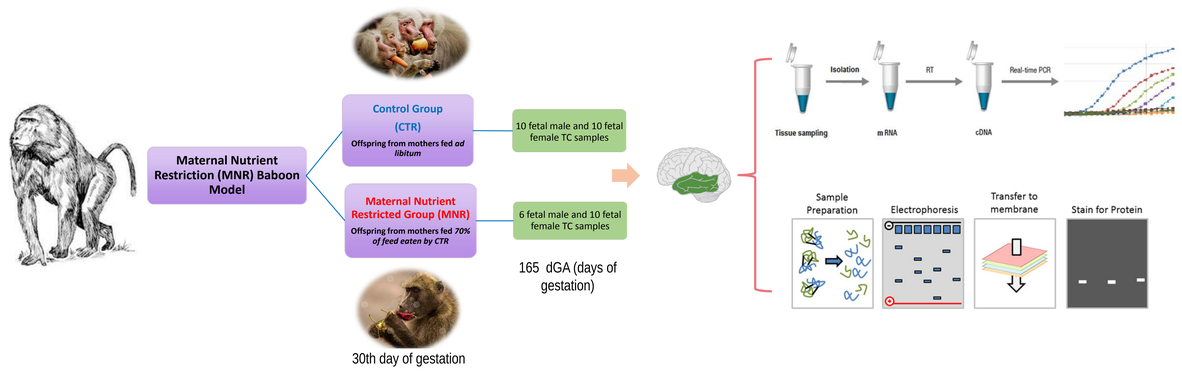


- The ECS modulates offspring's behavioral responses to nutritional stimuli through Temporal Cortex (TC) as a target of exo and endogenous cannabinoids.

OBJECTIVE

To determine the fetal sex-specific nutritional regulation of CB1R and $CB1_a$ transcript variants in temporal cortex of a baboon model (*Papio* spp.) of MNR near term**.**

MATERIALS & METHODS



RESULTS

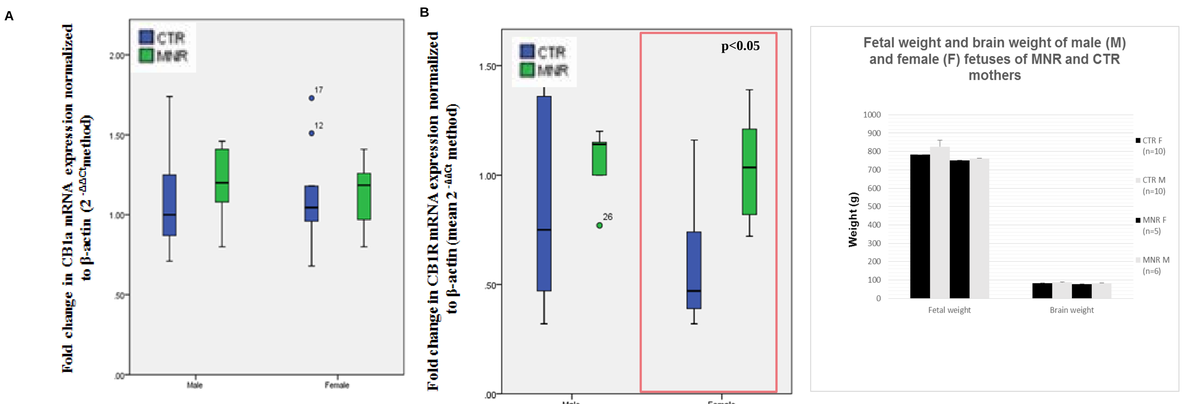


Figure 3. Fetal Temporal Cortex (TC) CB1a (A) and CB1R (B) expression at 165 dGA (days of gestation). CTR group (blue boxes; male (M) n=10; female (F) n=10) pregnant mothers fed *ad libitum*. MNR group (green boxes; M, n=6; F, n=6) mothers fed 70% of the global feed eaten by control group during pregnancy. There was an interaction between sex and diet. Sexes under MNR had the same responsiveness despite some differences in the control group. The CB1a did not show statistical significant results, but there was a trend of MNR group to increase the expression with small effect (Eta^2 = 0.022 is equivalent to Cohen-d= 0.296). The female CB1R expression showed large effect size (Eta^2= 0.1779 is equivalent to Cohen-d= 0.93). Fetal and brain weight did not differ between groups. (Data presented as mean ± SEM).

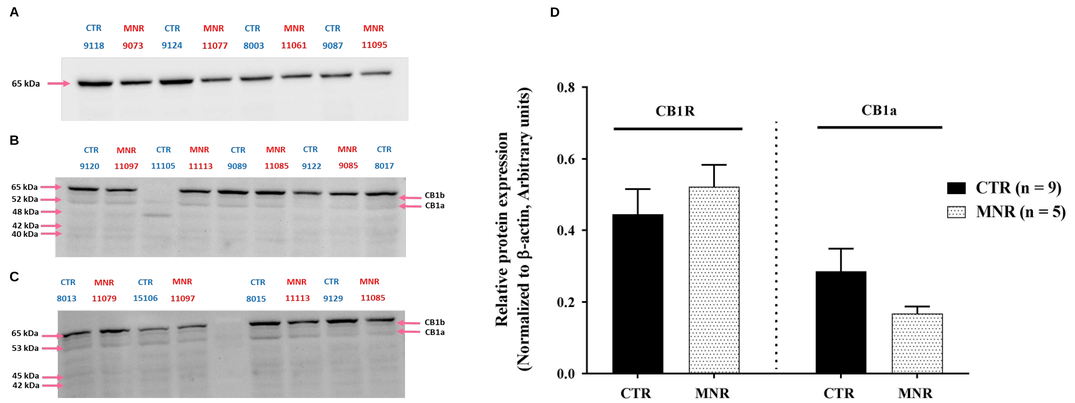


Figure 4. Protein Analyses of CB1R Isoforms. Relative protein band intensity normalized to B-actin for fetal temporal cortex of baboon female fetuses **(A)** and male fetuses **(B & C)** near term (165dGA). Bar diagram showing relative protein quantification of CB1R full-length and CB1a isoform in fetal temporal cortex of baboon male fetuses **(D)**. Software used: Image J. Data were presented as a mean ± S.E.M.

DISCUSSION

The only data available to date regarding MNR effects on the offspring's *CNR1* expression is available in rodent model (Fig.6); authors showed sex-specific behavioral and brain changes. In the female offspring of MNR mothers in non-human primate model low arousal, poor attention, and persistence, and difficulty modulating activities are reported (Figure 7).

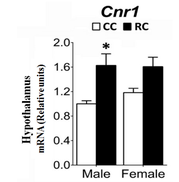


Figure 6. Effect of prenatal caloric restriction on the gene expression of *CNR1* in the hypothalamus of male and female Wistar rat's offspring at adulthood [*ad libitum* access of a standard chow (CC); 20%-restricted access of the same standard chow (RC)]. Source: [Ramírez-López et al., 2016]

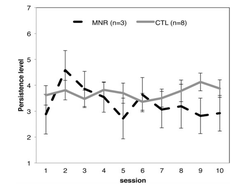
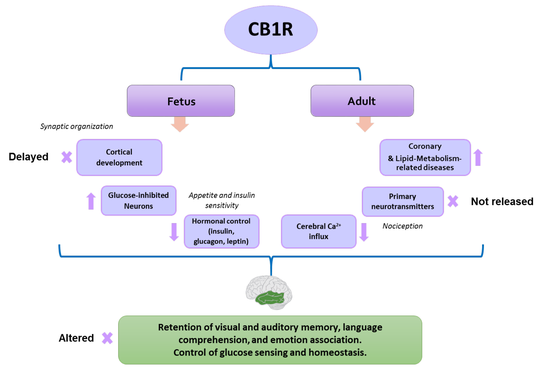


Figure 7. Persistence level for females by nutrition groups. There was an interaction effect of nutrition group and sex on persistence over time (F[9,126] = 2.19, P = 0.027, partial h2 = 0.16). CTL, control; MNR, maternal nutrition restriction. Source: [Keenan et al., 2013]



- For the 2-AG pathway analysis see poster Number S-096 in today's session: Fetus II by Dr. Kushal Gandhi.

CONCLUSIONS

- Endogenous activation of CB1R may serve as a compensatory mechanism for caloric restriction-associated decreased insulin and glucose concentrations.
- Our data might explain the more variable and lower levels of persistence and attention in the female offspring of nutritionally restricted mothers.

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