# MATERNAL NUTRIENT RESTRICTION AUGEMENTS FETAL CORTICAL ENDOCANNABINOID 2-ARACHIDONOYLGLYCEROL (2-AG) PATHWAY


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## INTRODUCTION

Prenatal exposure to maternal undernutrition (Figure 7) is associated with altered brain structure and decreased cognitive function during adulthood. In the context of the "developmental origins of health and disease" (DOHaD) paradigm it has been proposed that maternal nutrient restriction (MNR) during pregnancy triggers long-lasting effect on the epigenome of the differentiating cell, thus resulting in changes in organ structure and metabolic adaptions to ensure immediate survival of the fetus.

Exogenous and endogenous cannabinoids (eCB) have diverse and critical effects on the central and peripheral body systems. Exogenous cannabinoids act through the mechanism of "kick-starting" the components of the endogenous cannabinoid system (ECS). ECS is a pharmacological target for the treatment of obesity, inflammation, cardiovascular and neuronal damage. ECS modulates a diverse array of behavioral and physiological processes through the modulation of endocannabinoid receptors type 1 (CB1R) and type 2 (CB2), by two major endogenous ligands, anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Endocannabinoid receptors are the members of a family of GPCRs best known for mediating effects of the active components of marijuana.

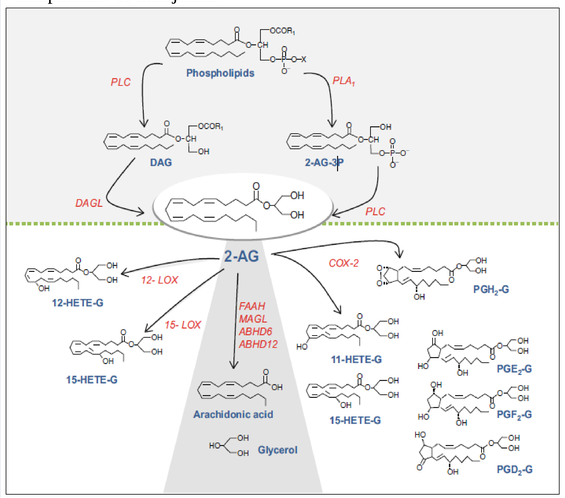
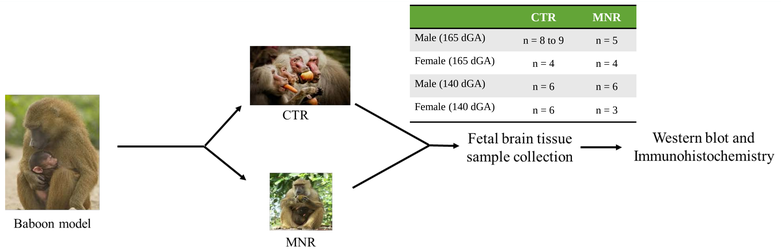



**Figure 1:** Biosynthetic, degradative and oxidative pathways of 2-AG and congeners. AA: arachidonic acid; *2-AG-3P*: 2-arachidonoylglycerol-3-phosphate; COX-2: cyclooxygenase-2; DAG: diacylglycerol; DAGL: diacylglycerol lipase; *12-HETE-G*: 12-hydroxy-arachidonoyl glycerol; *ABHD6/12*: α/β-hydrolase domain 6/12; *12-LOX*: 12-lipoxygenase; *MAGL*: monoacylglycerol lipase; *PLC*: phospholipase; *PGE2-G*: prostaglandin glycerol E2-G (Endocannabinoid signaling book written by Mauro Maccarrone, 2016)

## OBJECTIVE

To evaluate temporal changes in main 2-AG (2-Arachidonoyl Glycerol) cannabinoid binding receptor (CB2R) and degrading enzyme MAGL (Monoacylglycerol Lipase) in offspring of maternal nutrient restricted pregnant baboons (MNR) and control (CTR) group.

## MATERIALS AND METHODS




| | CTR | MNR |
|---|---|---|
| Male (165 dGA) | n = 8 to 9 | n = 5 |
| Female (165 dGA) | n = 4 | n = 4 |
| Male (140 dGA) | n = 6 | n = 6 |
| Female (140 dGA) | n = 6 | n = 3 |

**Figure 2:** Experimental Design

## RESULTS

**Fetal sex dependent cerebral "Endocannabinoidome" in baboon (*Papio spp.*) model of maternal nutrient restriction**

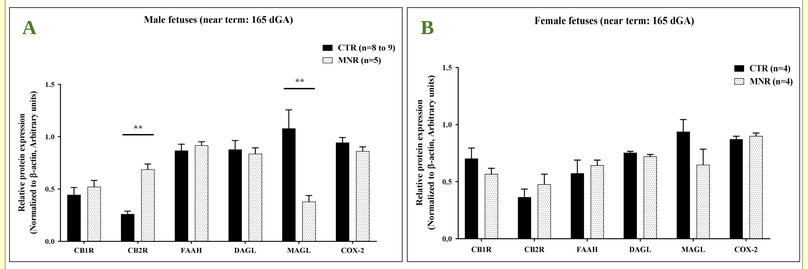



**Figure 3:** Cerebral protein expression of endocannabinoid receptors (CB1R and CB2R) and ECS metabolic enzymes (FAAH, DAGLα, MAGL and COX-2) were analyzed by Western blot analysis in Control (CTR) and MNR group of baboon (*Papio* spp.) model at 165 dGA. (A) Male fetuses and (B) Female fetuses. The bar diagram shows relative band intensity, quantified using Image J software, normalized to control β-actin expression. Data were presented as the mean ± SEM. $p<0.05$ indicates a significant difference between groups. ($^*p<0.05$)

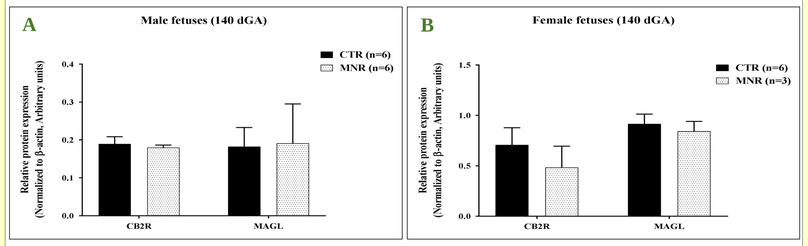



**Figure 4:** Cerebral protein expression of endocannabinoid receptor type 2 (CB2R) and ECS metabolic enzyme (MAGL) were analyzed by Western blot analysis in Control (CTR) and MNR group of baboon (*Papio* spp.) model at 140 dGA. (A) Male fetuses and (B) Female fetuses. The bar diagram shows relative band intensity, quantified using Image J software, normalized to control β-actin expression. Data were presented as the mean ± SEM.

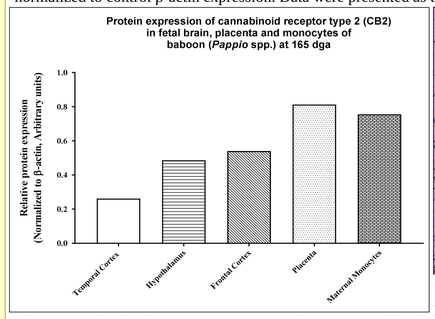



**Figure 5:** Cerebral protein expression of endocannabinoid receptor type 2 (CB2R) in fetal brain, placenta and monocytes of baboon (*Papio* spp.). The bar diagram shows relative band intensity, quantified using Image J software, normalized to control β-actin expression.

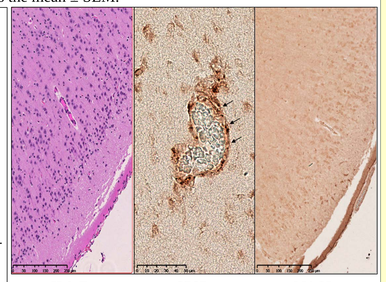



**Figure 6:** Fetal cerebral cortical CB2R and MAGL protein expression of baboon (*Papio* spp.) near term (165 dGA). The CB2R staining is positive in all layers neurons and fetal cerebral endothelial cells. MAGL staining is observed in neurons, located in layer 2-3. (Scale bar: 200 μM)

## REFERENCES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## DISCUSSIONS

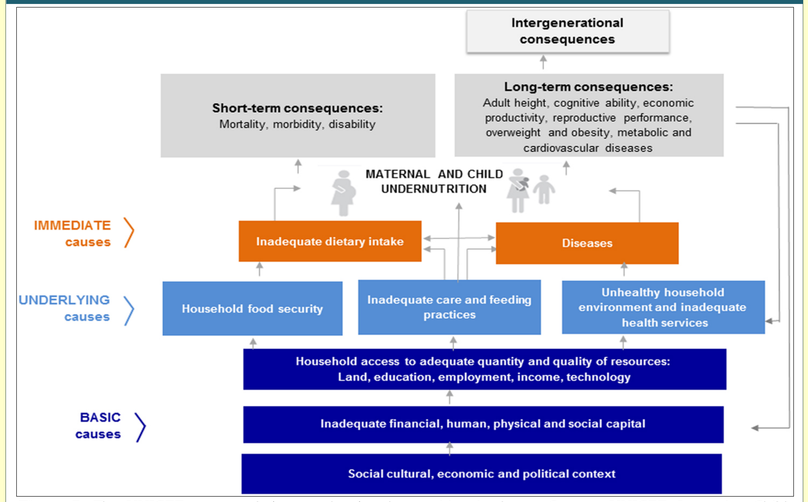


**Figure 7:** The UNICEF conceptual framework of under nutrition is shown. **Source:** UNICEF. Improving Child Nutrition: The achievable imperative for global progress. (Kristina Reinhardt *et al.* 2014)

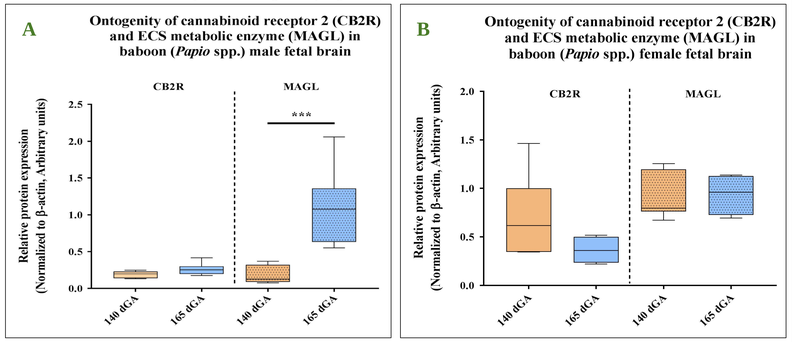


**Figure 8:** Cerebral protein expression of endocannabinoid receptor type 2 (CB2R) and ECS metabolic enzyme (MAGL) were analyzed by Western blot analysis in baboon (*Papio* spp.) at 165 dGA. (A) Male fetuses and (B) Female fetuses. The bar diagram shows relative band intensity, quantified using Image J software, normalized to control β-actin expression. Data were presented as the mean ± SEM. $p<0.05$ indicates a significant difference between groups. ($^*p<0.05$)

Lower level of MAGL might be associated with increased 2-AG concentrations since this molecule is principally degraded by MAGL. Increased level of endocannabinoid 2-AG has neuroprotective effect in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse model of Parkinson's disease (Ross Mounsey *et al.* 2015). Thus our data might provide explanation for fetal sex-dependent MNR effect on the F1 female, but not male offspring: more variable and lower level of persistence and attention. In humans MNR induced alterations in brain structure have been associated with cognitive and behavioral deficits, behavioral and psychiatric disorders, as well as later-life neurodegenerative disorders (Katja Franke *et al.* 2017). Increased in CB2R expression might have protective anti-inflammatory effect (Yuri Persidsky *et al.* 2015). In addition, our research group worked on CB1 isoform in MNR baboon model (Please Refer: Abstract No. S-069, Presenter: Vanessa Montoya-Uribe, Poster Session today: Developmental Programming I).

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