FETAL SYNDROME OF ENDOCANNABINOID DEFICIENCY (FSECD) IN AN EXPERIMENTAL MODEL OF MATERNAL HIGH FAT DIET

TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER at the Permian Basin

SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER SNPRC

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Introduction

Cannabinoids have been used for the treatment of chronic pain for millennia with documented results of numerous clinical trials in non-pregnant patients. Exogenous cannabinoids act through the mechanism of "kick-starting" the components of the endogenous cannabinoid system (endocannabinoid [eCB] system, ECS). ECS is a pharmacological target for the treatment of obesity, inflammation, cardiovascular and neuronal damage, and pain. The clinical syndrome of endocannabinoid deficiency (CECD) is linked to numerous pain-related conditions in adults. First described by Russo in 2004, the concept of CECD has been developed and applied to such conditions as irritable bowel syndrome, fibromyalgia, migraine, and autism [9]. The clinical definition of the syndrome is important, since it leads to the therapeutic application of the cannabis derivatives to its treatment.

The "developmental programming" hypothesis opens the opportunity for understanding the origin of adult diseases and their prevention at the most adaptable stage of individual's life – in the womb.

Maternal obesity (MO), affects 64% of all pregnant and has increased in a linear fashion between 2005 and 2014,and is associated with significant health risks for mothers and their offspring. However, the results of numerous maternal lifestyle changing trials (i.e. UPBEAT, LIMIT) and surgical interventions for weight reduction remain controversial and unable to demonstrate the benefits of such for fetal and maternal health. Therefore, there is a clear need to identify novel mechanisms and pharmacological targets underlying gene-environment interactions in MO. Remarkably, there is experimental and epidemiological evidence that the spectrum of the diseases which are included in the definition of CECD are "programmed in utero" by MO; however there are no reports available connecting MO and CECD.

Hypothesis

We hypothesize that MO programs offspring health at least in part through the mechanism of the Fetal Syndrome of Endocannabinoid Deficiency (FSECD).

This hypothesis differs from the present explanation of the phenomenon of fetal programming and brings all present theories under the umbrella of one syndrome.

FSECD hypothesis is evident from the perspective of 1) the involvement of ECS in obesity, 2) experimentally-proven shared phenotypes of CECD and diseases, programmed by MO, and 3) evidence from human and non-human primate studies regarding fetal and placental ECS disbalance in MO.

Evaluation of the hypothesis

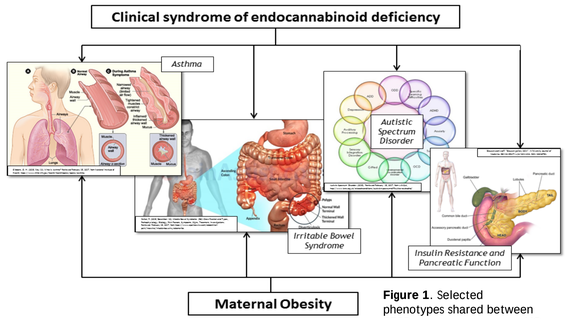
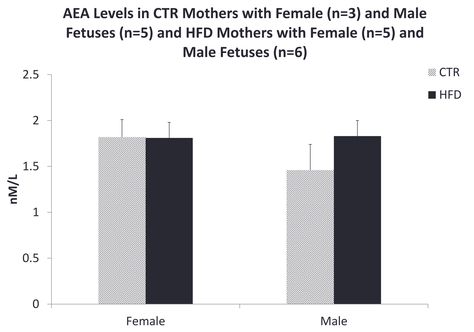


Figure 1. Selected phenotypes shared between CECD and programmed by MO

Materials and Methods

Baboons ate 45% fat (HFD; n=11) or 12% fat (C; n=9) from at least 9 months prior to conception. Fetal and maternal serum collected at term Cesarean Section. Concentrations of eCB Anandamide (AEA) and 2-Arachidonoyl Glycerol (2-AG) were measured using LC-MS. Statistical methods used P-values, estimated by Scheirer-Ray-Hare extension of Kruskal-Wallis test. < 0.05, for significance.

Results



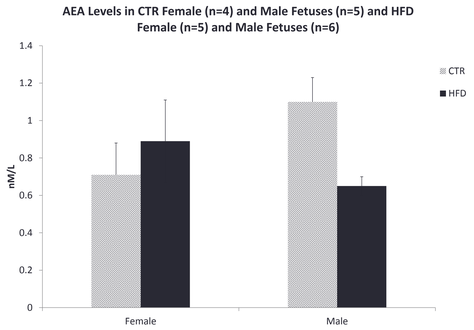


Figure 2. Quantification of Anandamide (AEA) levels (nM/L;data are mean ±SEM) in maternal and fetal serum from CTR and HFD specimens.

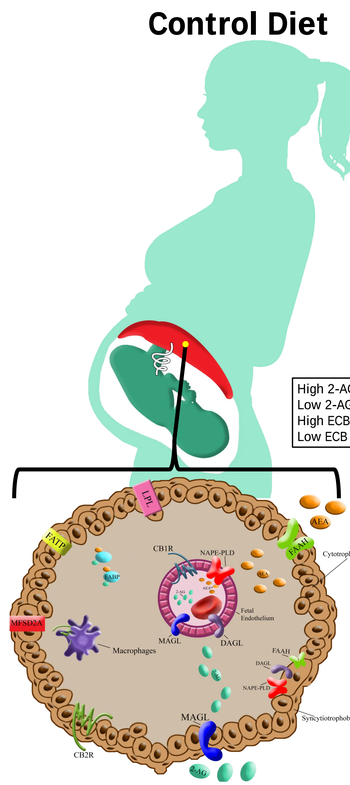
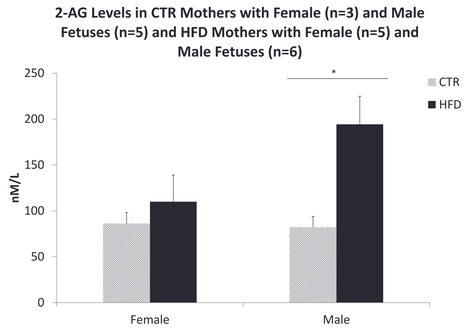


Figure 4. Graphic representation of a transverse section of a chorionic villus exposed to a control diet.

Figure 5. Graphic representation of a transverse section of a chorionic villus exposed to a high fat diet.



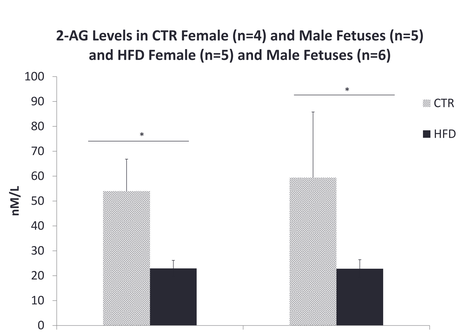


Figure 3. Quantification of 2-Arachidonoyl Glycerol (2-AG) levels (nM/L;data are mean ±SEM) in maternal and fetal serum from CTR and HFD specimens.* p<0.05

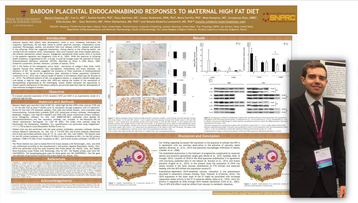
	Female				Male						
	CTR		HFD		CTR		HFD		p-value		
	n	M ± SEM	n	M ± SEM	n	M ± SEM	n	M ± SEM	diet	sex	Diet x sex
Fetal wt (g)	7	712.75 ± 64.62	4	767.43 ± 31.32	4	798.84 ± 28.66	6	853.43 ± 16.24	0.220	0.045	0.195
Mat CS wt	6	17.49 ± 1.27	4	20.72 ± 0.88	4	17.69 ± 0.56	6	20.24 ± 0.88	0.055	0.744	5.156
Plac wt (g)	6	171.8 ± 5.03	4	202.59 ± 14.06	2	159.25 ± 4.75	5	229.38 ± 6.36			
Liver (g)	3	20.82 ± 2.56	4	26.03 ± 1	1	24.4 ± 0	5	24.89 ± 0.97			

Table 1. Maternal and fetal weight. Note: HFD – animals fed a diet of 45% fat, CTR – animals fed a diet of 12% fat. Since placental and liver weights presented an important number of missing values, only descriptive data are presented for these variables.

Discussion and Conclusion

ECS role in metabolic regulation is well described. Hepatic accumulation of the ectopic fat in HDF (NAFLD) has been associated with increase of circulating 2-AG (but not AEA) and increased hepatic CB1R expression in animal models and in humans. The increase in 2-AG concentrations in HFD dams agrees with these data. However, the effect of HFD on AEA/2-AG levels in systemic circulation is controversial: in a non-pregnant canine model and in lean and obese subjects, HFD did not affect AEA, but decreased 2-AG concentrations. In opposite to this observation 2-AG and AA concentrations were increased in obesity and hyperphagia, associated with Prader-Willi syndrome, in obese postmenopausal women with insulin resistance and women with PCOs. Our data is in agreement with our own data in baboon model of natural obesity, associated with over-eating (Brocato et al., 2013). Consumption high fat diet during pregnancy results in systemic fetal eCB deficiency, which might result in programming of Clinical Endocannabinoid Deficiency Syndrome later in life.

See poster T-155 for more information regarding placental changes



Title: BABOON PLACENTAL ENDOCANNABINOID RESPONSES TO MATERNAL HIGH FAT DIET
Presenting Author: Marcel Chuecos, SRI Member *In-training*
Presentation date and time: **Thursday 10:00 am - 11:30 am**
Program Page #: 59

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