HEPATIC AND PLACENTAL ENDOCANNABINOID SYSTEM (ECS) IN MATERNAL OBESITY

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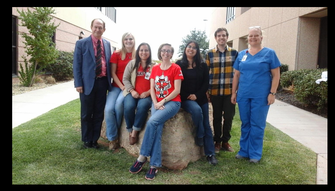
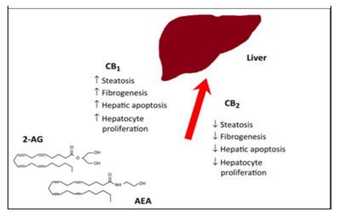


Introduction

The endogenous cannabinoid (or "endocannabinoid" (eCB)) system (ECS) comprises N-arachidonylethanolamide (anandamide, AEA), 2-arachdonoyl glycerol (2-AG), endocannabinoid receptors (cannabinoid 1 and 2 receptors (CB1Rs and CB2Rs), and synthesizing/degrading enzymes (FAAH, fatty-acid amide hydrolase; MAGL, monoacylglycerol lipase; DAGL-α, diacylglycerol lipase-alpha). ECS are a family of lipid derivatives. The CB1Rs are expressed in brain and peripheral tissues, while the CB2Rs are expressed in microglia, immune and hematopoietic tissues. We and others described the presence of ECS in placenta. The concentrations of AEA and 2AG are increased at the end of gestation. Recent data showed a direct role of ECS in alcoholic and non-alcoholic (obesity-related) fatty liver diseases (NAFLD). Fatty liver has been documented already in fetuses of obese women and in healthy pregnant women as early as the first trimester of pregnancy. However, the markers to diagnose these conditions in pregnancy do not exist.



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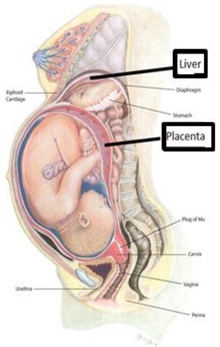


Figure 1. The endocannabinoid (eCB) system (ECS) of … liver. N-arachidonoylethanolamine (anandamide) (AEA), 2-arachidonoylglycerol (2-AG)…are synthesized in the gut and liver, acting locally and in the brain. In the liver, the type 1 cannabinoid receptor (CB1) and CB2 have opposing effects, with CB1 promoting steatosis, fibrogenesis, apoptosis, and proliferation and CB2 inhibiting these effects (modified from Maccarrone et al., 2015).

Objectives

The goal of this study was to evaluate the expression of CB1 and CB2 receptors in maternal and fetal liver in the baboon model of maternal obesity and compare this expression to human placenta.

Methods

Archived liver and placental tissues from a pervious study collected from obese and non-obese baboons (*Papio spp*) (Farley et al., 2009), were evaluated using Reverse Transcription- real-time quantitative PCR method (q-RT-PCR). The TRIzol method was used to isolate RNA from tissue samples (Life Technologies, USA), and cDNA was synthesized according to the manufacturer's instructions (Applied Biosystems/ Roche, USA). qPCR was performed using Fast start Essential DNA Probe Master Mix (Roche, USA), and TaqMan Gene Expression Assay Probes (Life Technology, USA). The TaqMan probes used were CB1 (Hs01038522), CB2 (Hs00275635), and 18S (Hs99999901). A secondary analysis of the previously published data was performed, as well as immunhistochemistry, using conventional methodology (adipophilin prrimary antibody) (ABBIOTEC, San Diego, CA).

Results

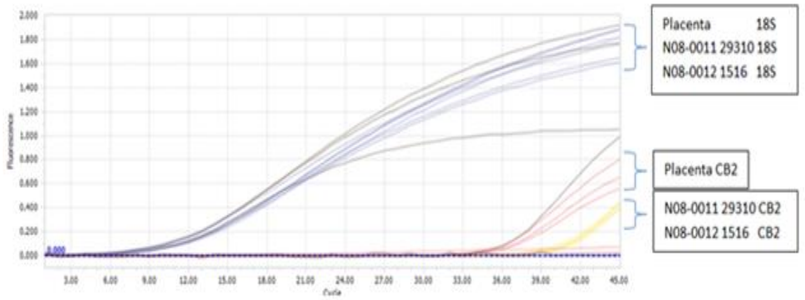


Figure 2. Amplification curve for CB2 and 18S (as the housekeeping gene).

Sample ID		CT		
		18s	CB2	ΔΔCT
N08-0011 29310	FETAL	8.42	39.39	0.055
N08-0012 1516	MATERNAL	9.38	40.04	0.068
PAD014	PLACENTA	8.63	35.41	1
RT neg control		0	0	0
PCR ned control		0	0	0

Table 1. The relative expression of CB2 in fetal, maternal and placental tissues.

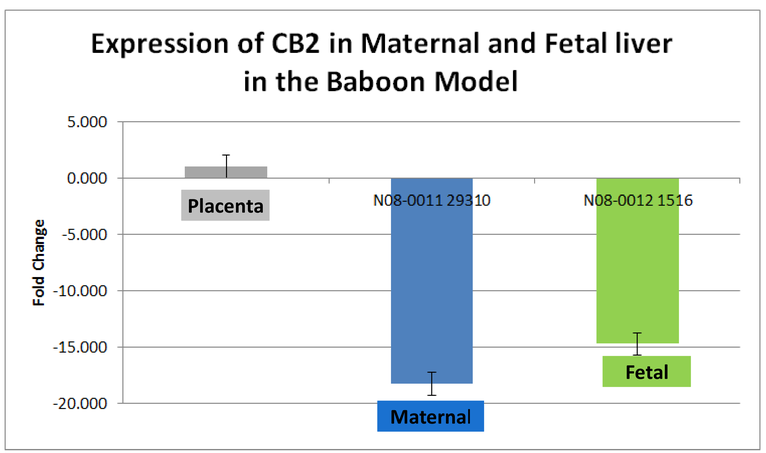


Figure 3. The relative CB2 expression in maternal and fetal and placental tissues.

Results Cont.

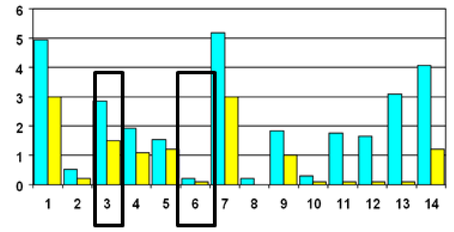
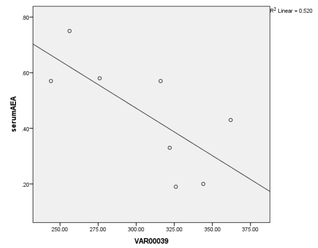


Figure 4. Real time PCR results. Endocannabinoid receptors [CB1 (blue) and cb2 (yellow)] tissue distributions and relative abundance analyses. (1.-stomach, 2.-hypothalamus, 3.-liver, 4.-ovary, 5.-kidney, 6.-placenta, 7.-mononuclear cells, 8.-colon, 9.-omental fat, 10.-subcutaneous fat, 11.-pancreas, 12.-muscle, 13.-small intestine and 14.-lung).



Weight of maternal liver (g)

Figure 5. Direct negative correlation of serum AEA (nM/L) with the weight of maternal liver (secondary analyses of the data from Brocato, 2013).

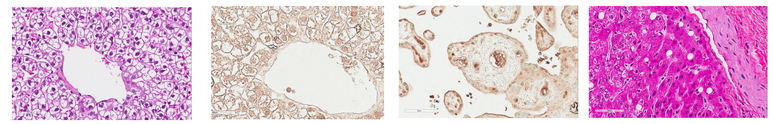


Figure 6. Representative images of fetal (A) and maternal liver (D). B and C-Expression of adipophIllin -lipid droplet marker in fetal liver and placenta Note: glycogen deposits in fetal liver.

Conclusion

This is the first report demonstrating the presence of both ECS receptors in fetal and maternal hepatic tissues. Changes in the ECS could be markers of NAFLD in pregnancy

References

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