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Taylor Bruett  
*University of Nebraska Lincoln*, taylor.bruett@huskers.unl.edu

Taylor Heng  
*University of Nebraska Lincoln*, taylor_heng@hotmail.com

Sathish Kumar Natarajan  
*University of Nebraska - Lincoln*, snatarajan2@unl.edu

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Bruett, Taylor; Heng, Taylor; and Natarajan, Sathish Kumar, "3-Hydroxy Fatty Acid Induce Trophoblast and Hepatocyte Lipoapoptosis" (2016). UCARE Research Products. 130.  
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3-Hydroxy Fatty Acid Induce Trophoblast and Hepatocyte Lipoapoptosis

Taylor Bruett, Taylor Heng, Sathish Kumar Natarajan
Department of Nutrition and Health Sciences, and Nebraska Center for the Prevention of Obesity Disease (NPOD), University of Nebraska-Lincoln

Introduction
Acute Fatty Liver of Pregnancy (AFLP) is a rare and fatal condition for both the mother and the unborn offspring accompanied by severe maternal liver dysfunction.
AFLP is characterized by microvesicular steatosis, hepatic failure and encephalopathy develops in the last trimester of pregnancy.
Fetuses with defective in mitochondrial fatty acid oxidation are known to be associated with AFLP.
Mutation in the enzyme, long-chain 3-hydroxy acyl CoA dehydrogenase (LCHAD), involved in the mitochondrial beta-oxidation of fatty acid is highly associated with AFLP.
In the third trimester pregnancy induces maternal lipolysis.
In AFLP, a fetus with homozygous mutation for LCHAD will have his/her placenta defective to metabolize the long chain fatty acids resulting in the accumulation of 3-hydroxy fatty acids.
Accumulated 3-hydroxy fatty acids and other fatty acids due to maternal lipolysis enter the mother’s circulation and affects the maternal liver resulting in the complication of liver disease observed in AFLP.
Our lab previous work had demonstrated that placental oxidative stress and mitochondrial dysfunction were evident in patient’s with AFLP.
We also reported that there was an elevated level of free fatty acids and hydroxy-fatty acids in the systemic circulation of patients with AFLP.
Palmitoleate, a mono unsaturated fatty acids and can act as a lipokine.
Palmitoleate has been shown to protect free fatty acid-induced hepatocyte lipoapoptosis.

Hypothesis
3-hydroxy fatty acids that are released from the placenta induces trophoblast and hepatocyte lipoapoptosis.

Materials and Methods
Apoptosis was determined from caspase 3/7 activity and measurement of percent apoptotic nuclear morphology changes using fluorescent microscopy.
Trophoblast cell lines (JEG-3 and JAR) or Hepatocyte (Huh7) were used in this study.
Cell were treated either with 20-200 µM of 3-hydroxy myristic acid (3-HMA) or 3-hydroxy octanoic acid (3-OHCB) for 24h in 1% BSA containing media.
Control cells were treated with vehicle isopropanol (<1% in media).
Arachidonic acid (40, 80, 120 µM) were treated with or without 100 µM of 3-hydroxy myristic acid (3-HMA) for 24h in 1% BSA containing media.
Palmitoleate (200 µM) was co-treated with 100 µM of 3-HMA for 24h in 1% BSA containing media.

Results
Can 3-hydroxy myristic acid induce trophoblast lipoapoptosis?

Can arachidonic acid (AA) treatment aggravate 3-hydroxy myristic acid-induced cell death?

Can palmitoleate protect 3-hydroxy myristic acid-induced hepatocyte lipoapoptosis?

Conclusion
• 3-hydroxy myristic acid induces caspase-independent cell death in placental cells.
• 3-hydroxy octanoic acid did not induce apoptosis.
• 3-hydroxy myristic acid induces caspase-dependent hepatocyte lipoapoptosis.
• Palmitoleate protects against 3-hydroxy myristic acid-induced hepatocyte lipoapoptosis.

Future Directions
Knock down LCHAD using CRISPR/Cas9 technology and test 3-hydroxy fatty acid toxicity.
We will test 3-hydroxy palmitic Acid toxicity in trophoblasts and hepatocytes.
We will also look at the role of necroptosis with 3-hydroxy myristic acid-induced trophoblast cell death.

Acknowledgements
UCARE (Undergraduate Creative Activities and Research Experience), University of Nebraska-Lincoln
BORG, NPOD Core Laboratory, UNL
National Institute of Health-NIH P20GM104320
Nebraska Tobacco Settlement Biomedical Research Enhancement Fund.