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# 3-Hydroxy Fatty Acid Induce Trophoblast and Hepatocyte Lipoapoptosis

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## 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-hydroxyl 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  $\mu\text{M}$  of 3-hydroxy myristic acid (3-HMA), or 3-hydroxy octanoic acid (3-OHC8) for 24h in 1% BSA containing media

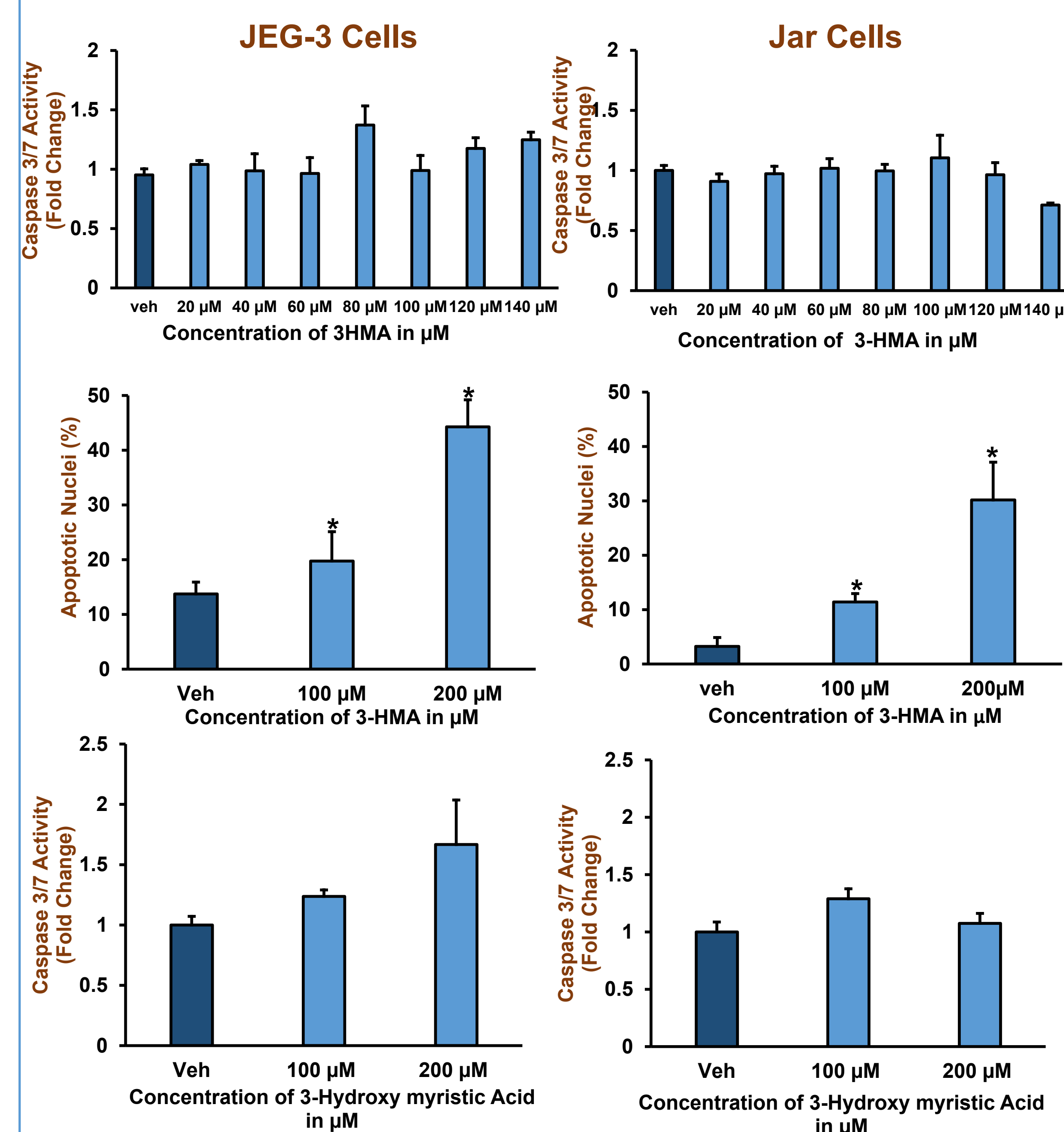
Control cells were treated with vehicle isopropanol (<1% in media)

Arachidonic acid (40, 80, 120  $\mu\text{M}$ ) were treated with or without 100  $\mu\text{M}$  of 3-hydroxy myristic acid (3-HMA) for 24h in 1% BSA containing media

Palmitoleate (200  $\mu\text{M}$ ) was co-treated with 100  $\mu\text{M}$  of 3-HMA for 24h in 1% BSA containing media.

## Results

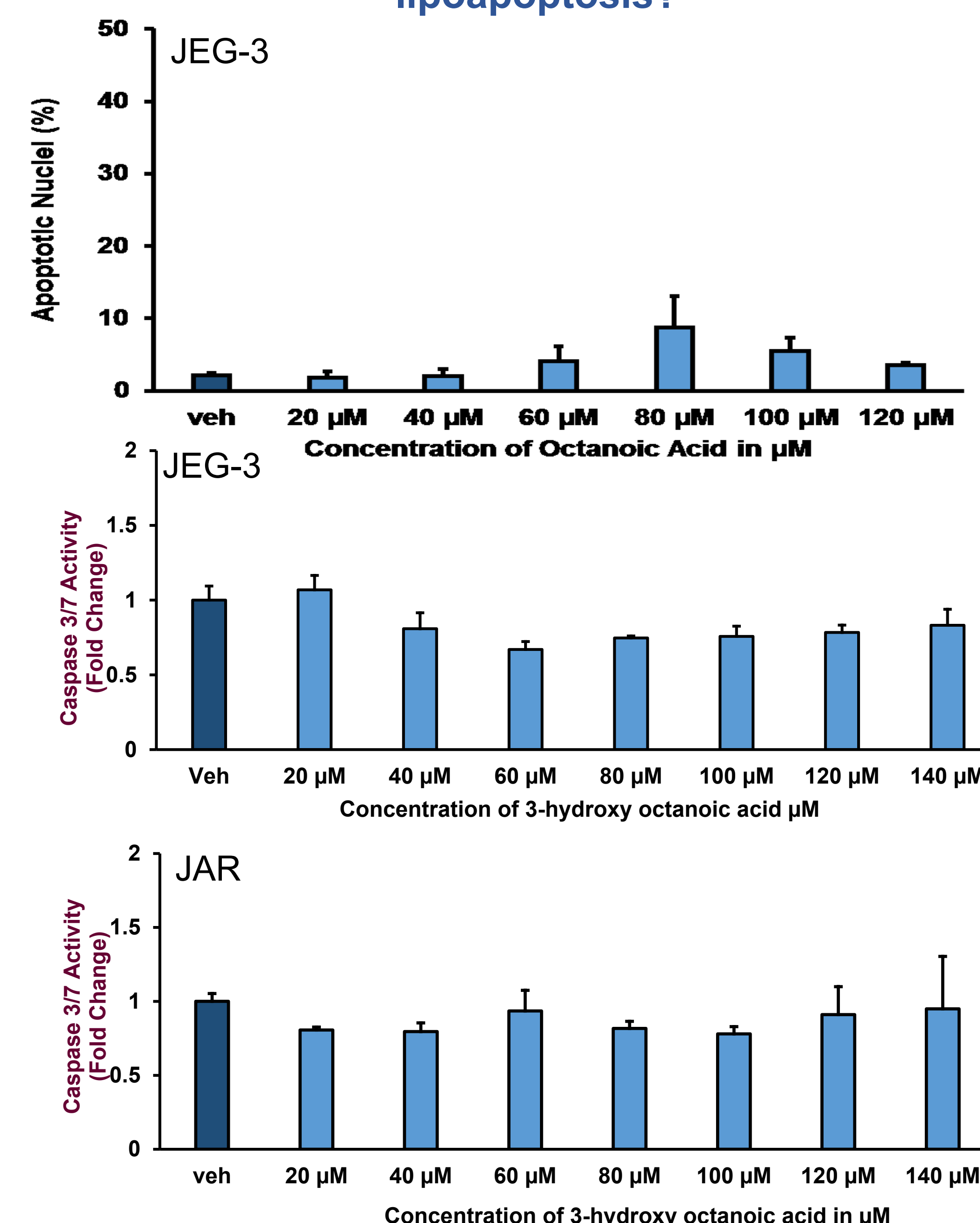
Can 3-hydroxy myristic acid induce trophoblast lipoapoptosis?



3-HMA induce caspase-independent trophoblast cell death

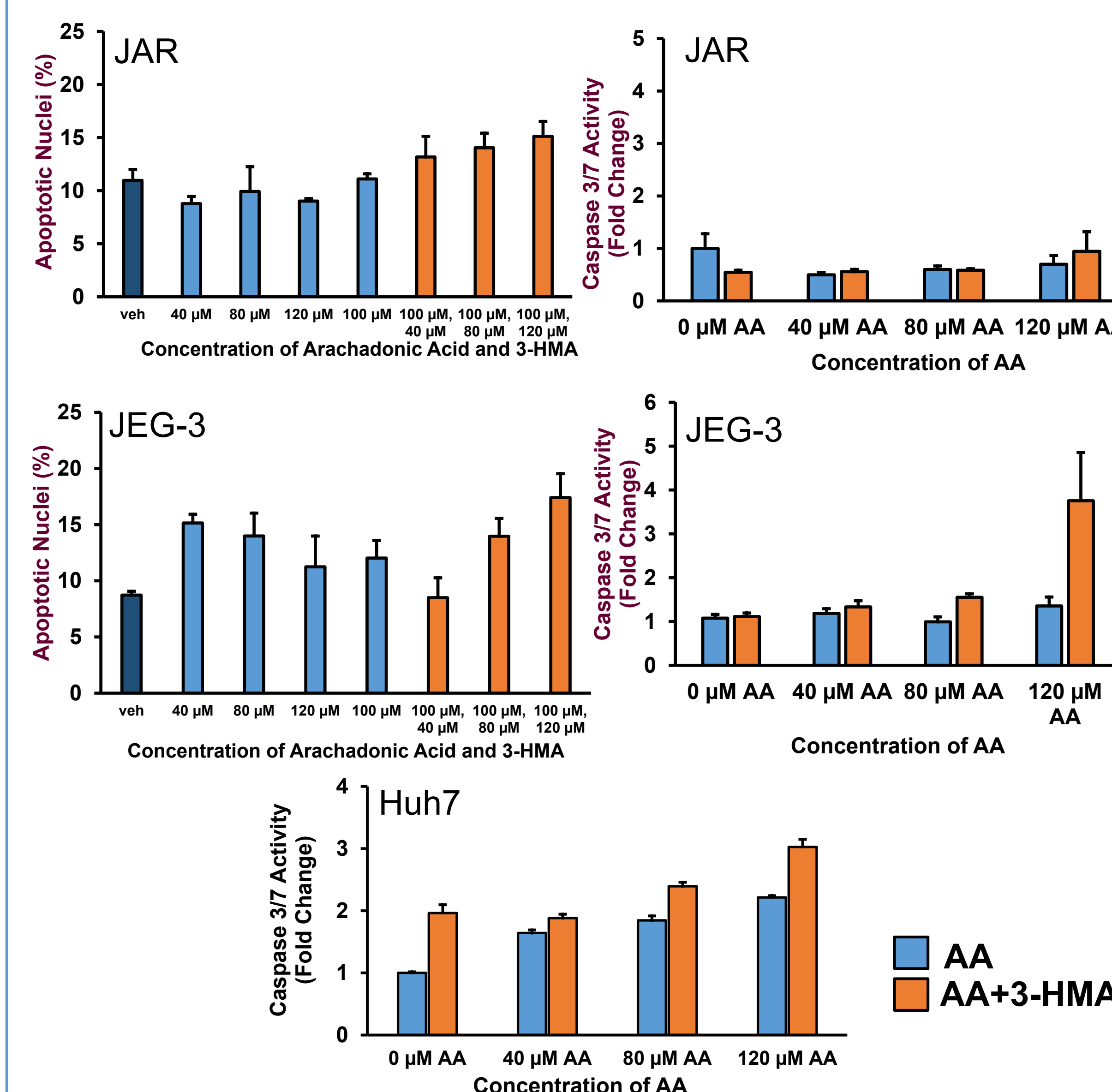
## Results

Can 3-hydroxy octanoic acid (3-OHC8) induce Trophoblast lipoapoptosis?

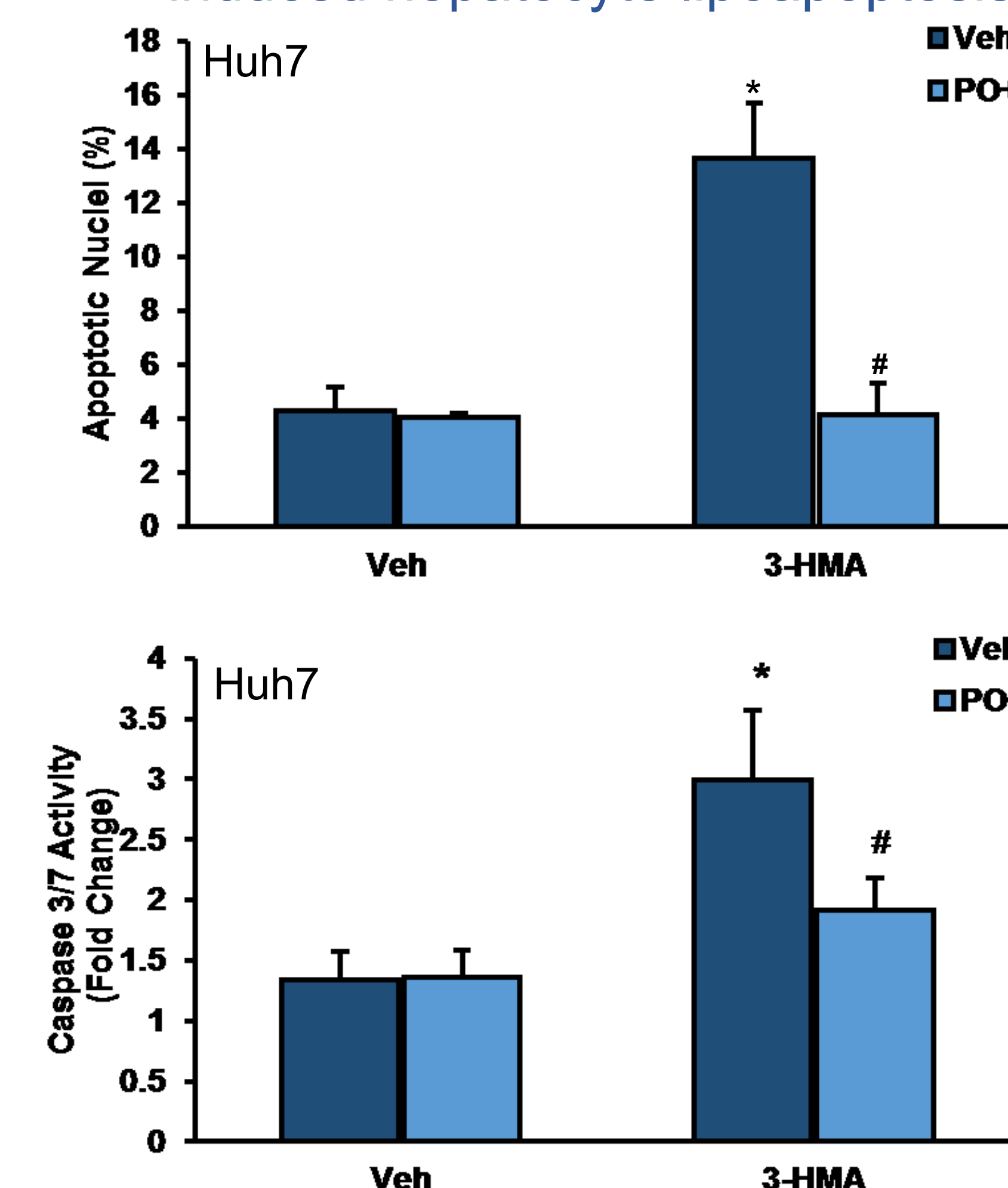


3-OHC8 did not induce trophoblast apoptosis

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/ Cas 9 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

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