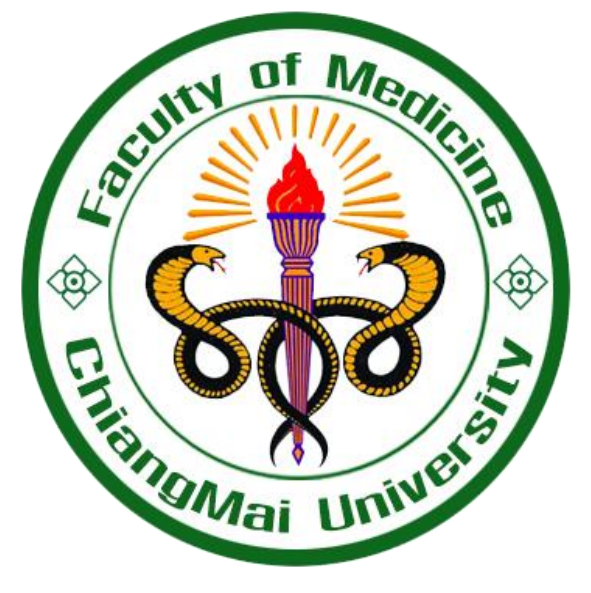


Pyroptosis Inhibitor Improves Anxiety and Brain Mitochondrial Function Independent of Tryptophan-kynurenine Restoration in Obese Rats



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These findings suggest that pyroptosis inhibition improves anxiety-like behavior and brain mitochondrial function without restoring brain tryptophan and kynurenine levels in obese rats. Overall, pyroptosis inhibition may represent a potential therapeutic strategy for reducing anxiety-like behavior under obese conditions.

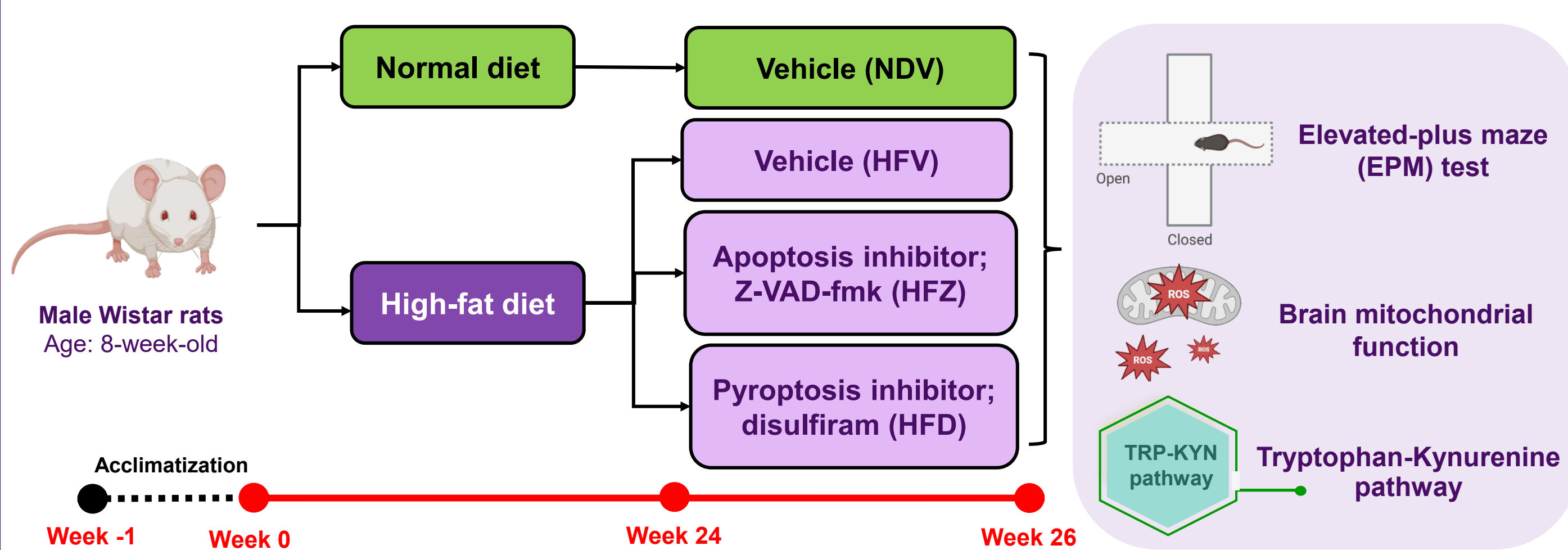
INTRODUCTION

- Pyroptosis and apoptosis are programmed cell death pathways implicated in anxiety^{1,2}. Inhibiting these pathways may reduce anxiety-like behavior by improving brain mitochondrial function and normalizing brain tryptophan metabolism.
- Z-VAD-fmk (apoptosis inhibitor) and disulfiram (gasdermin-mediated pyroptosis inhibitor) have shown neuroprotective effects in prior rodent models^{3,4}, but their roles in obesity-related anxiety remain unclear.
- Therefore, this study aimed to investigate whether Z-VAD-fmk or disulfiram attenuates anxiety-like behavior, brain mitochondrial dysfunction, and altered brain tryptophan-kynurenine levels in obese rats.

AIM

Aim: To investigate whether apoptosis (Z-VAD-fmk) and pyroptosis inhibitor (disulfiram) attenuates anxiety-like behavior, brain mitochondrial dysfunction, and altered tryptophan-kynurenine levels in obese rats.

METHODS



Twenty male Wistar rats (8-week-old) were assigned to a normal diet (ND; n=5) or high-fat diet (HFD; n=15) for 26 weeks. At week 24, HFD-fed rats were subdivided into 3 subgroups to receive either saline (control), Z-VAD-fmk (1 mg/kg, i.p.), or disulfiram (50 mg/kg/day, p.o.) for two weeks. After two weeks of treatment, anxiety-like behavior was assessed using the elevated-plus maze (EPM) test. Then animals were euthanatized, brain mitochondrial function and brain tryptophan-kynurenine metabolites were measured.

RESULTS

1 HFD-fed rats showed a lower preference index in the open arms and a higher preference index in the close arms of the EPM, compared with ND-fed rats (**Figure 1A-B**). HFD-fed rats also increased brain mitochondrial reactive oxygen species (ROS) production and induced mitochondrial swelling, accompanied by reduced brain tryptophan levels and increased kynurenine levels (**Figure 2A-D**).

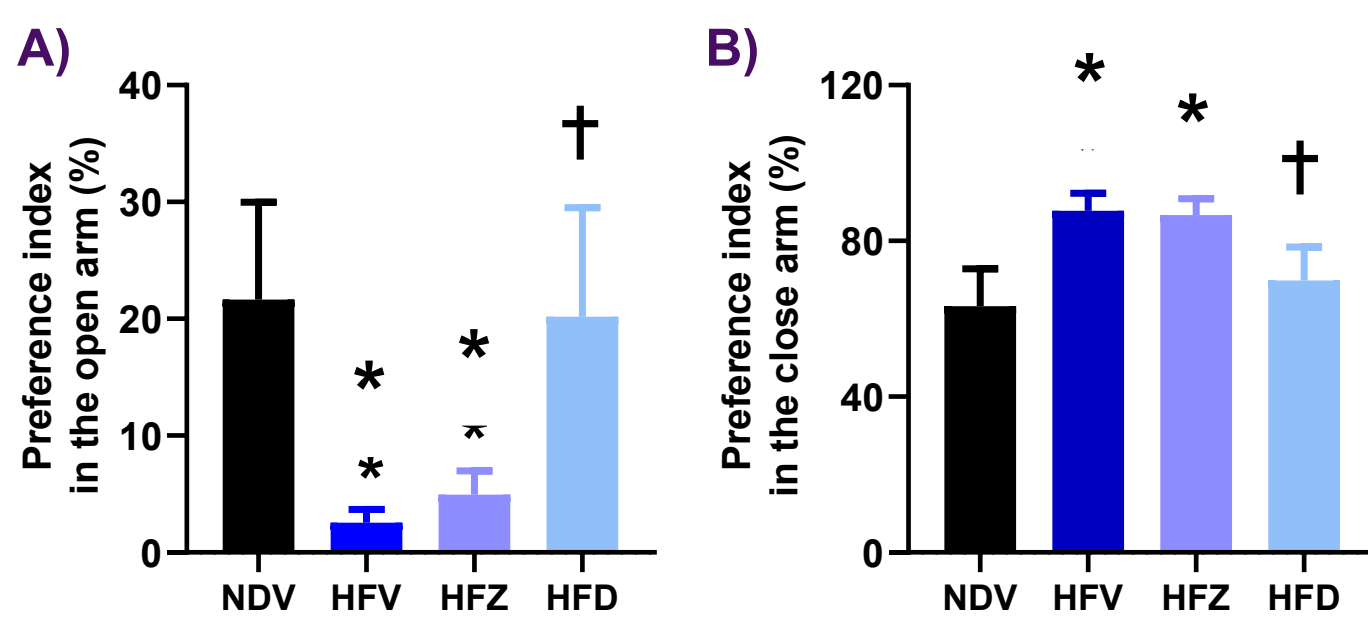


Figure 1. Effect of apoptosis and pyroptosis inhibitor on anxiety-like behavior in HFD-induced obese male rats. Anxiety-like behavior measured by elevated-plus maze; preference index in the open arm (**A**) and preference index in the close arm (**B**). *p<0.05 versus NDV, and † p<0.05 versus HFV. One-way ANOVA follow by post-hoc LSD (n=5/group)

ACKNOWLEDGEMENT

This work was supported by the Distinguished Research Professor Grant from the National Research Council of Thailand (No. N42A690147 to NC), the National Research Council of Thailand (No. N42A660432 to NA), and the Chiang Mai University Center of Excellence Award (to N.C.).



RESULTS

2 Only disulfiram significantly increased preference index in the open arms and decreased preference index in the close arms (**Figure 1A-B**). Both Z-VAD-fmk and disulfiram improved brain mitochondrial function by reducing ROS and attenuating mitochondrial swelling (**Figure 2A-B**). However, neither Z-vad.fmk nor disulfiram improved the alteration of brain tryptophane and kynurenine levels, compared to the HFD-fed rats (**Figure 2C-D**).

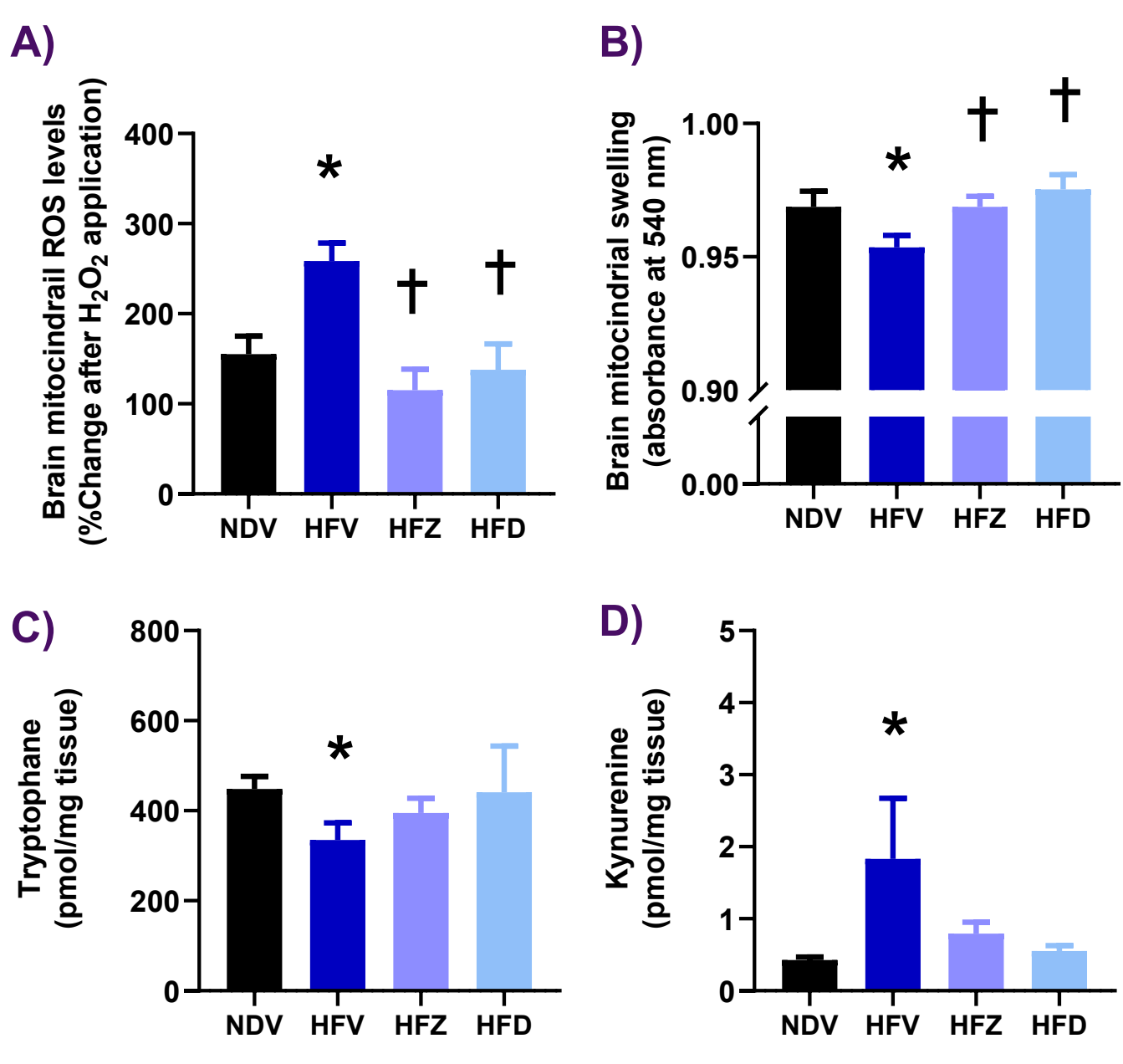


Figure 2. Effect of apoptosis and pyroptosis inhibitor on brain mitochondrial function and tryptophan-kynurenine levels in HFD-induced obese male rats. Brain mitochondrial function; ROS production (**A**) and mitochondrial swelling (**B**). The level of tryptophan (**C**) and kynurenine (**D**). *p<0.05 versus NDV, and † p<0.05 versus HFV. One-way ANOVA follow by post-hoc LSD (n=5/group)

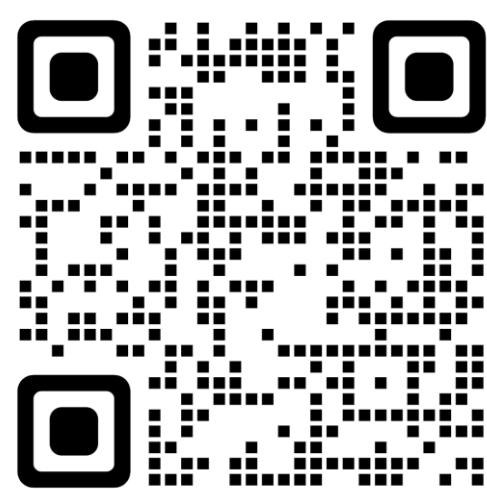
CONCLUSION

A pyroptosis inhibitor (disulfiram) improved anxiety-like behavior in HFD-induced obese rats. Both apoptosis inhibitor (Z-VAD-fmk) and disulfiram enhanced brain mitochondrial function by reducing mitochondrial ROS production and attenuating mitochondrial swelling. However, neither treatment normalized HFD-induced alterations in tryptophan nor kynurenine levels in obese rats.

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