**Graphic abstract**

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**Highlight**

1. BCAAs supplementation leads to severely hepatic metabolic disorder, damaged hepatic lipid buffer capability in HF diet-induced obese mice

2. BCAAs supplementation exacerbates muscle and renal ectopic lipid accumulation in HF diet-induced obese mice

3. BCAAs supplementation resulted in severe hepatic insulin resistance through deeply inhibition of Akt2 signaling in HF diet-induced obese mice

4. BCAAs supplementation suppressed Akt2 activation through mTORC1 and mTORC2-dependent pathways and promoted Akt2 ubiquitin-proteasome-dependent degradation via mTORC2

5. E3 ligase Mul1 contributed to BCAAs induced Akt2 ubiquitination and degradation