Effects of exercise training on hepatic steatosis in high fat diet-induced obese mice

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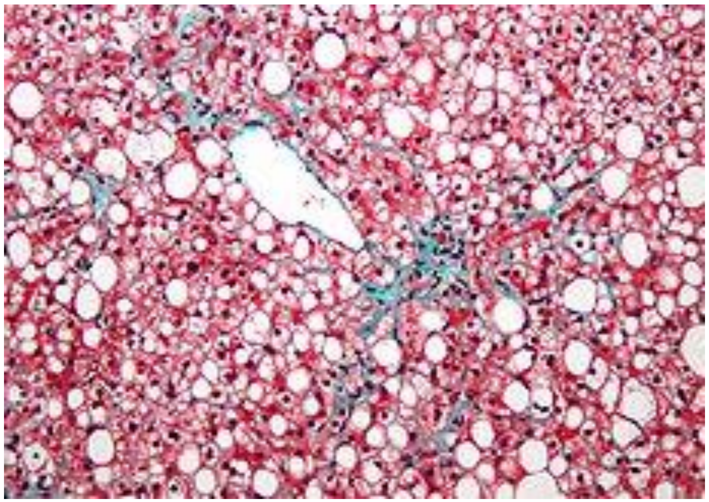
Non-Alcoholic Fatty Liver Disease (NAFLD)



(Source: Wikipedia, the free encyclopedia)

"A reversible condition that is characterized by hepatic lipid accumulation in the absence of significant alcohol consumption".

NAFLD—Spectrum of Disease

- Steatosis
- Steatohepatitis (NASH)
- NASH with Fibrosis
- Cirrhosis

By 2020

Prevalence of NAFLD and NASH

- Too much fat in the liver (NAFLD)
  - > 30% of adults
  - 13% of children
- Fat plus significant injury (NASH)
  - 3-4% of all adults
  - 15-20% of obese adults
  - 25-70% of people having bariatric surgery

Risk Factors for NAFLD

- **Obesity**
- **Type 2 DM**
- **Dyslipidemia**
- **Metabolic syndrome**

Insulin Resistance (IR)

(modified from J Clin Gastroenterol., 40: S1, 2006)

"NAFLD is a hepatic manifestation of insulin resistance"

Current Guidelines for NAFLD

- **Dietary restriction plus increased physical activity** shows clear hepatic benefits when weight loss approximately 3%-10% of body weight is achieved (Sreenivasa et al., 2006 J Gastroenterol Hepatol; Larson-Meyer et al., 2006 Diabetes Care).

- **The poor sustainability of weight loss** challenges the current therapeutic focus on weight loss and highlights the need for alternative strategies for NAFLD management.

- Epidemiologic data show **an independent relationship between fatty liver, physical activity and physical fitness** (Church et al., 2006 Gastroenterology; McMillan et al., 2007 Appy Physiol Nutr Metab).

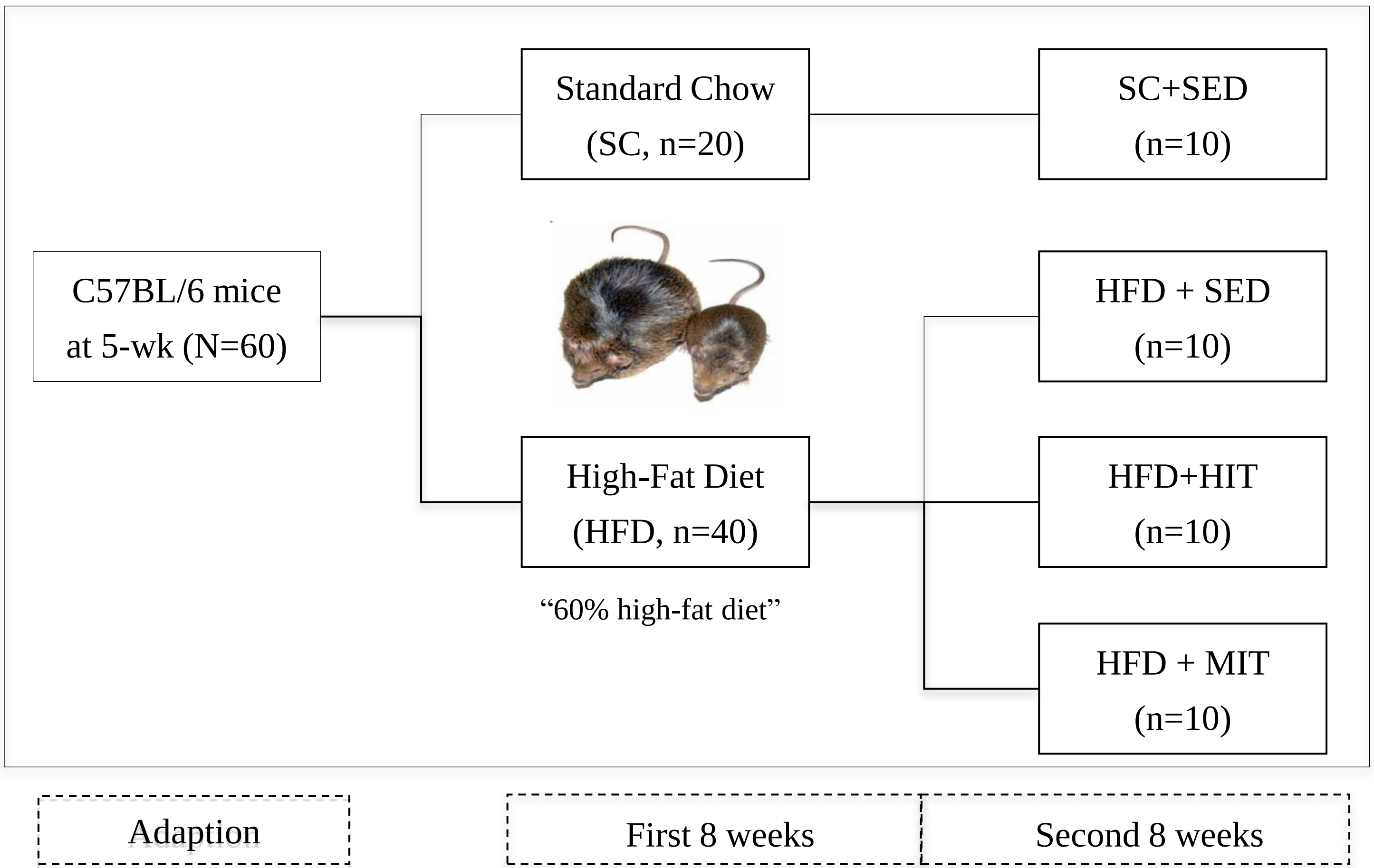
- A growing body of longitudinal research demonstrates that **increased physical activity per se** significantly reduces hepatic steatosis and serum aminotransferase in individuals with NAFLD, independent of weight loss (St George et al., 2009 Hepatology; Kantartzis et al., 2009 Gut).

Aims of the Study

- To study the role(s) of physical activity *per se* as a therapeutic means against obesity-induced NAFLD.

- To delineate the mechanistic insights to explain the hepatic benefits of increased physical activity.

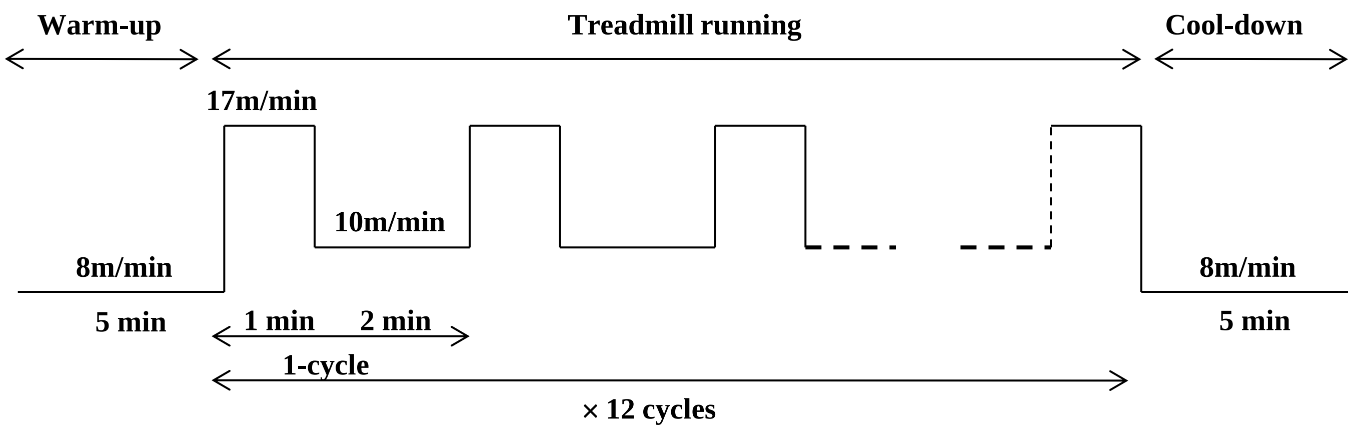
Description of Study Design



**SED: sedentary; MIT: moderate-intensity training; HIT: high-intensity training

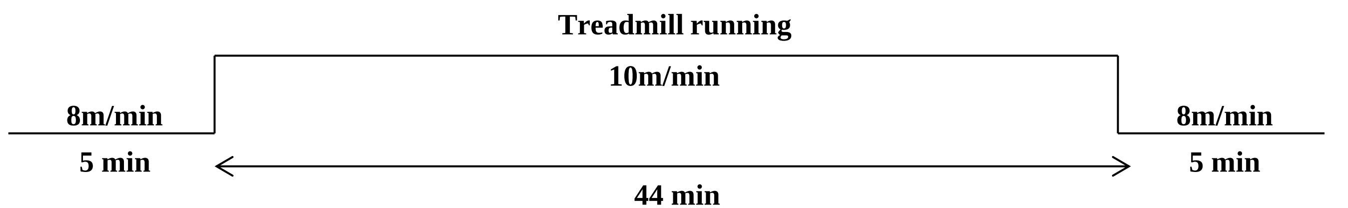
Exercise Training Protocol

A. High-intensity training (HIT)



Total exercise time: 46 min
Total distance: 524 m

B. Moderate-intensity training (MIT)



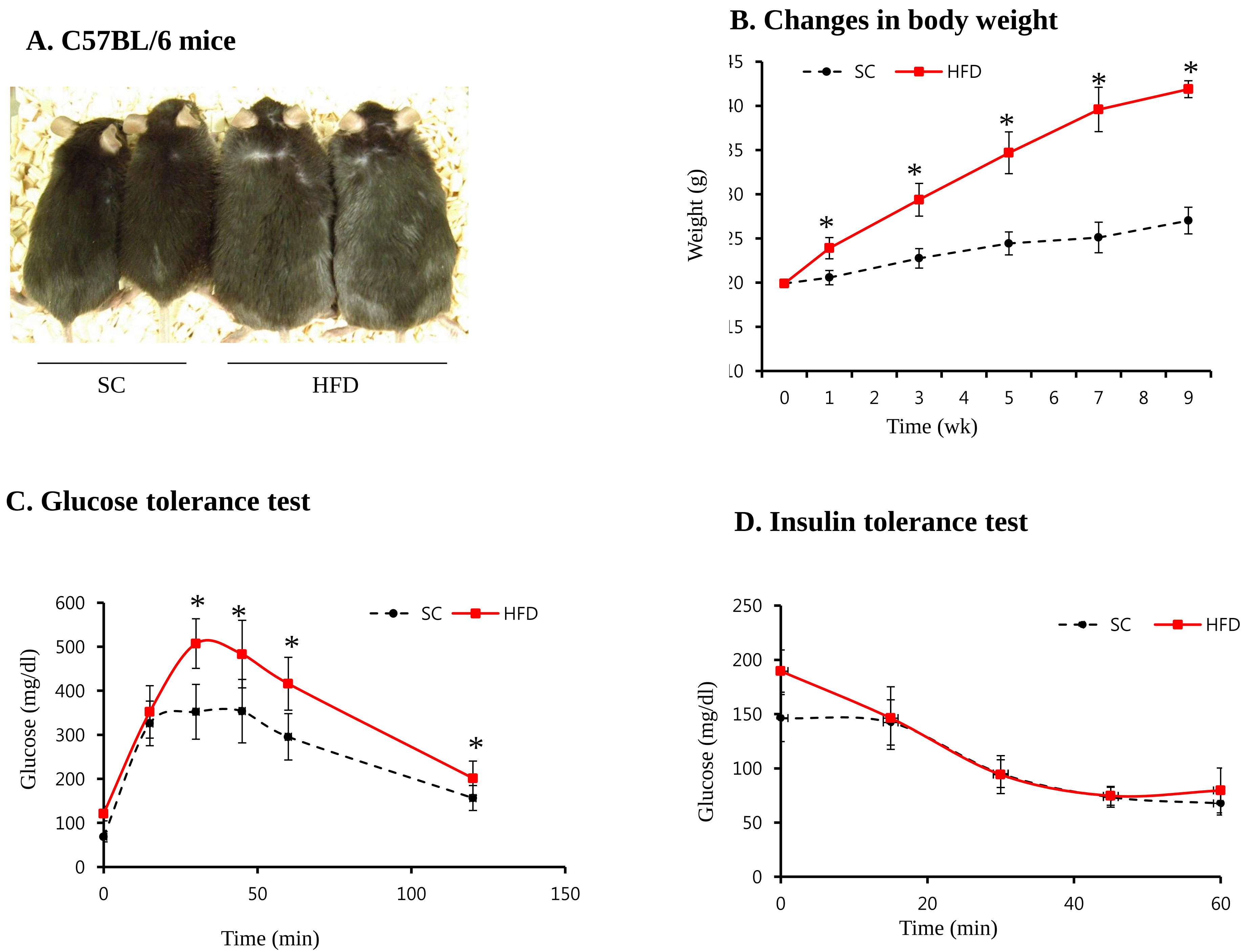
Total exercise time: 54 min
Total distance: 524 m

Primary Measurements of the Study

- Body mass
- Immunostaining (i.e., Oil-Red O, H & E, Trichome staining)
- Glucose tolerance test (GTT) and insulin tolerance test (ITT)
- Blood lipoprotein lipids
- Asparate aminotransferase (AST) and alanine aminotransferase (ALT)
- Adiponectins in serum and adipose tissue
- Real time-PCR for mRNAs and Western blot for proteins

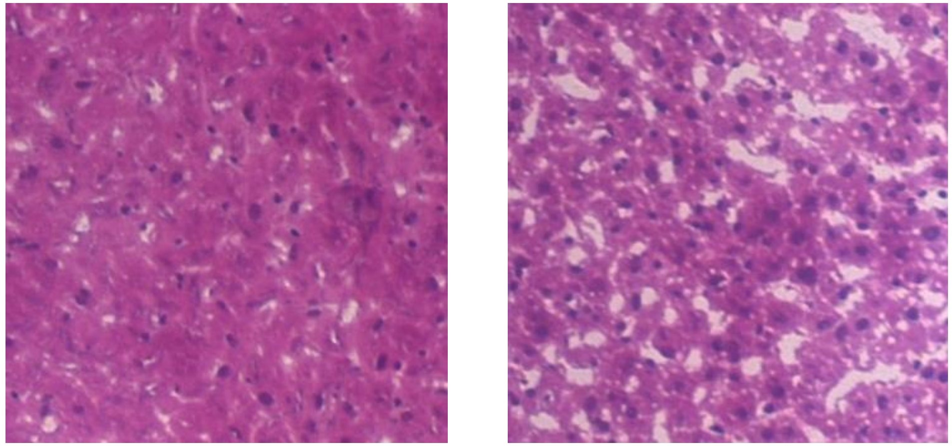
RESULTS

After the initial 8 weeks of a High-Fat Diet



A. C57BL/6 mice
SC
HFD
B. Changes in body weight
SC
HFD
Weight (g)
0
1
2
3
4
5
6
7
8
9
Time (wk)
C. Glucose tolerance test
SC
HFD
Glucose (mg/dl)
600
500
400
300
200
100
0
0
50
100
150
Time (min)
D. Insulin tolerance test
SC
HFD
Glucose (mg/dl)
250
200
150
100
50
0
0
20
40
60
Time (min)

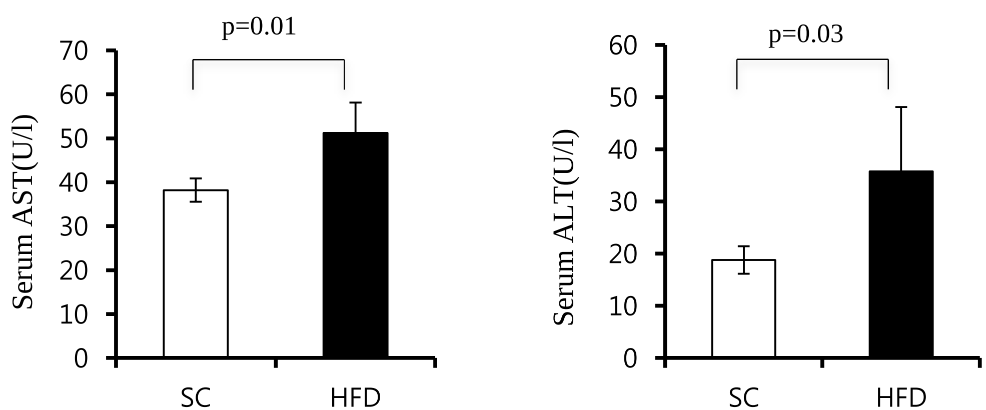
A. H&E staining in hepatic tissue



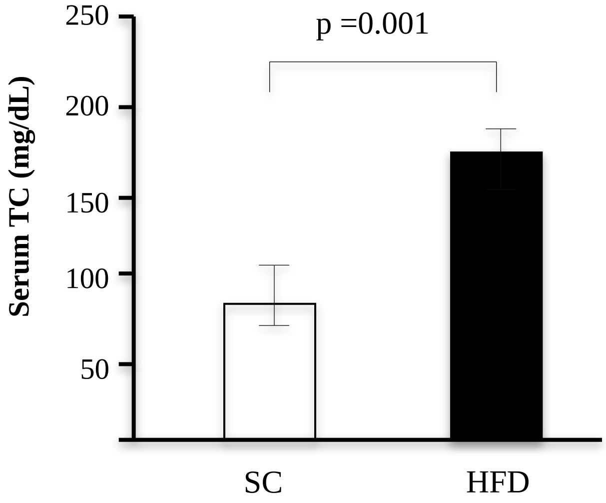
SC HFD

"macrovesicular steatosis"

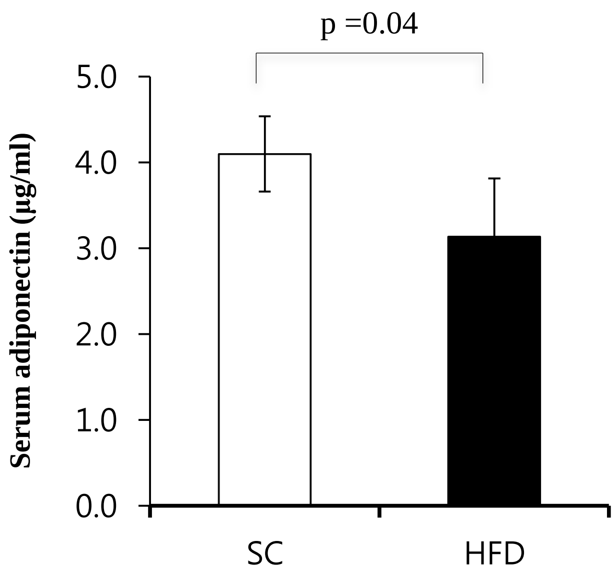
B. Serum aspartate- and alanine-aminotransferase



A. Serum total cholesterol (TC) levels



B. Serum total adiponectin levels



A 60% HFD for 8 weeks results in :

1) an obese and insulin resistance phenotype,

2) hepatic steatosis and injury,

3) elevated risk for artherosclerosis,

4) hypoadiponectinemia.

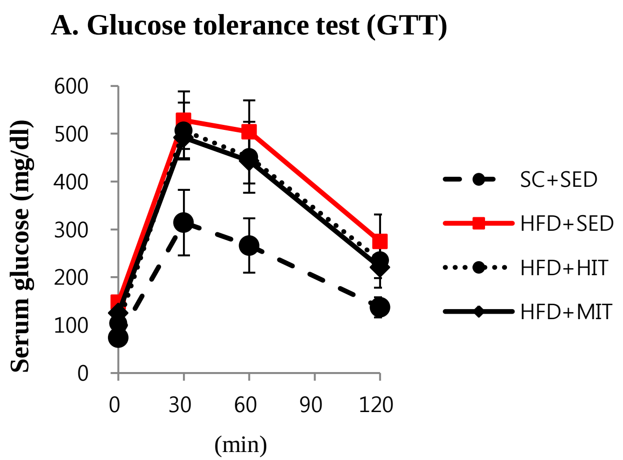
Effects of exercise training intervened at the second half of the 16-week high-fat diet regimen

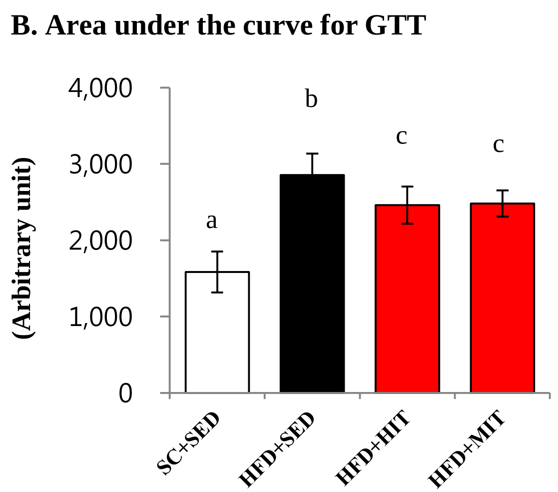
Exercise training attenuates weight gains, hepatic injury, and artheroscleorosis secondary to HFD, with no significant intensity-dependent differences.

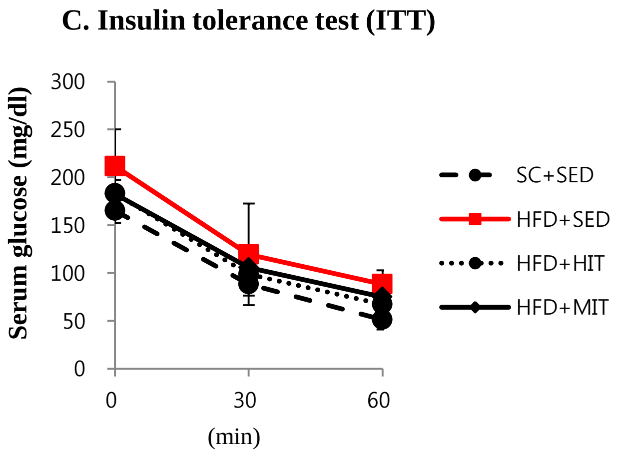
Table 1. Metabolic profiles after the 16-wk HFD and/or exercise training

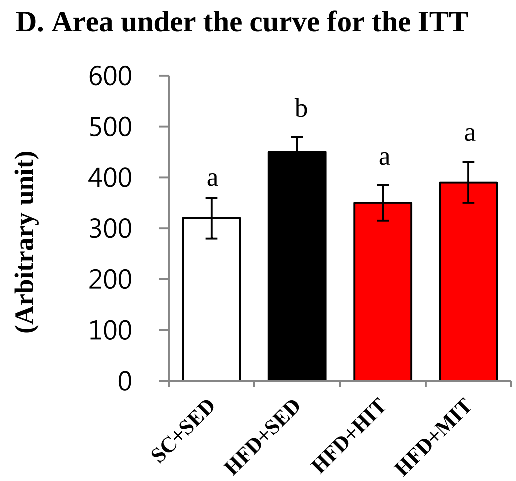
	SC+SED	HFD+SED	HFD+HIT	HFD+MIT
Final body mass, g	32.5±1.8[a]	48.0±1.6[b]	45.2±2.0[c]	46.0±1.7[c]
ALT, U/l	31.5±7.2[a]	236.0±49.3[b]	145.8±50.5[c]	182.8±19.9[c]
AST, U/l	54.0±17.2[a]	167.4±27.9[b]	155.8±40.1[b]	147.4±32.8[b]
FFA, mEq/L	2.1±0.35	2.4±0.33[a]	2.0±0.09[b]	2.0±0.18[b]
TG, mg/dl	61.2±11.6	64.2±16.8[a]	60.8±7.2[b]	61.8±9.4[b]
TC, mg/dl	88.2±9.0[a]	208.2±34.1[b]	160.0±22.2[c]	180.2±12.5[d]
HDLC, mg/dl	43.6±11.2[a]	134.0±15.0[b]	165.0±17.3[c]	160.4±17.5[c]

Exercise training attenuates insulin resistance phenotype secondary to HFD, with no significant intensity-dependent differences.



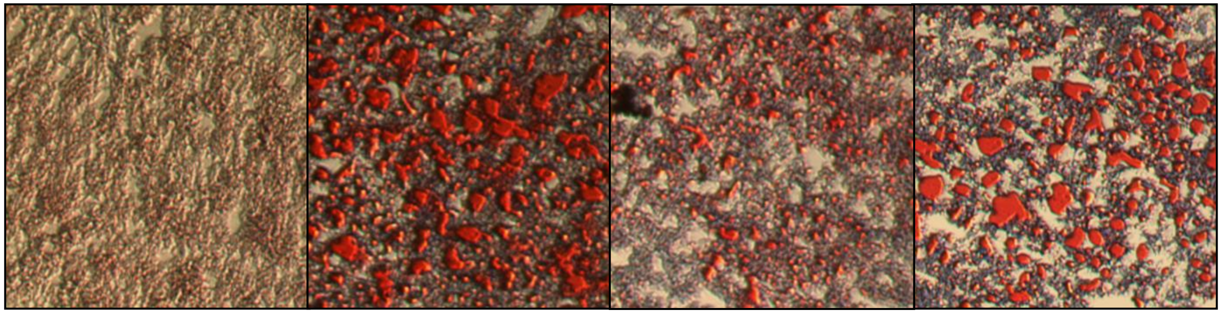






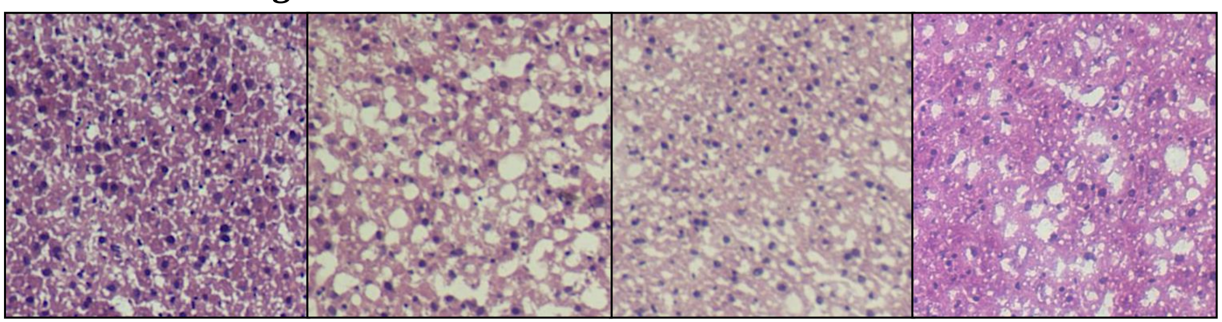
Exercise training, especially at the high-intensity, alleviates hepatic steatosis secondary to HFD.

A. Oil Red O staining



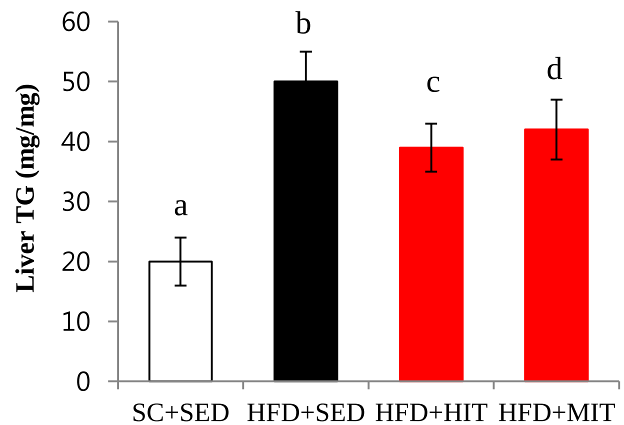
SC+SED **HFD+SED** **HFD+HIT** **HFD+MIT**

B. H&E staining



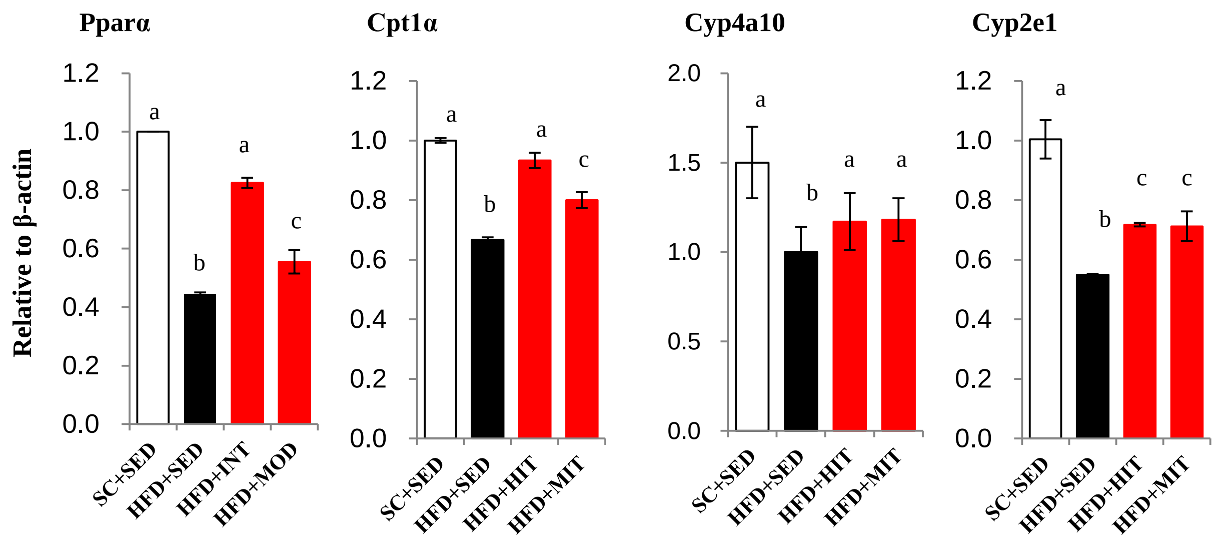
SC+SED **HFD+SED** **HFD+HIT** **HFD+MIT**

C. TG contents in the liver

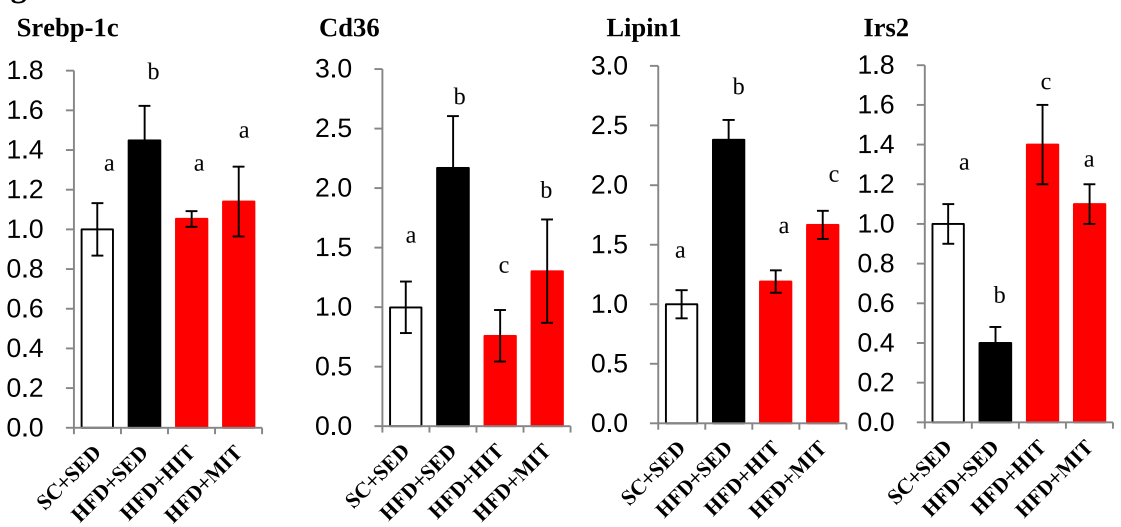


Exercise training suppresses decreased mRNA markers for fatty acid ox./MRC capacity as well as increased mRNA markers for lipogenesis secondary to HFD in the liver

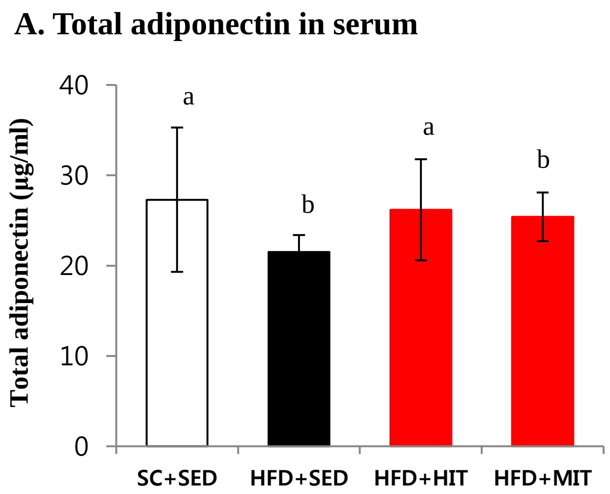
A. mRNAs of FA OX/MRC activity

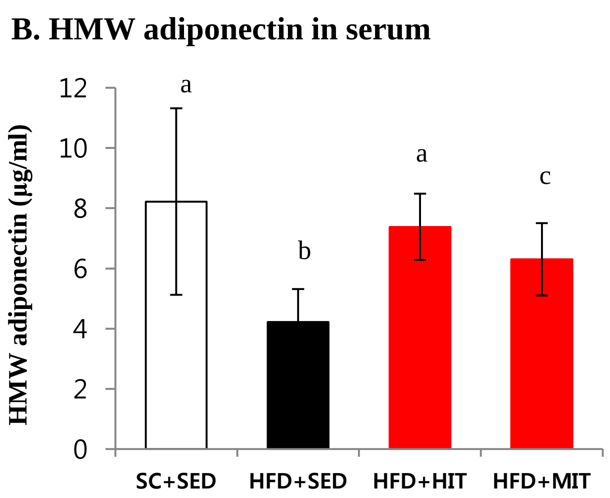


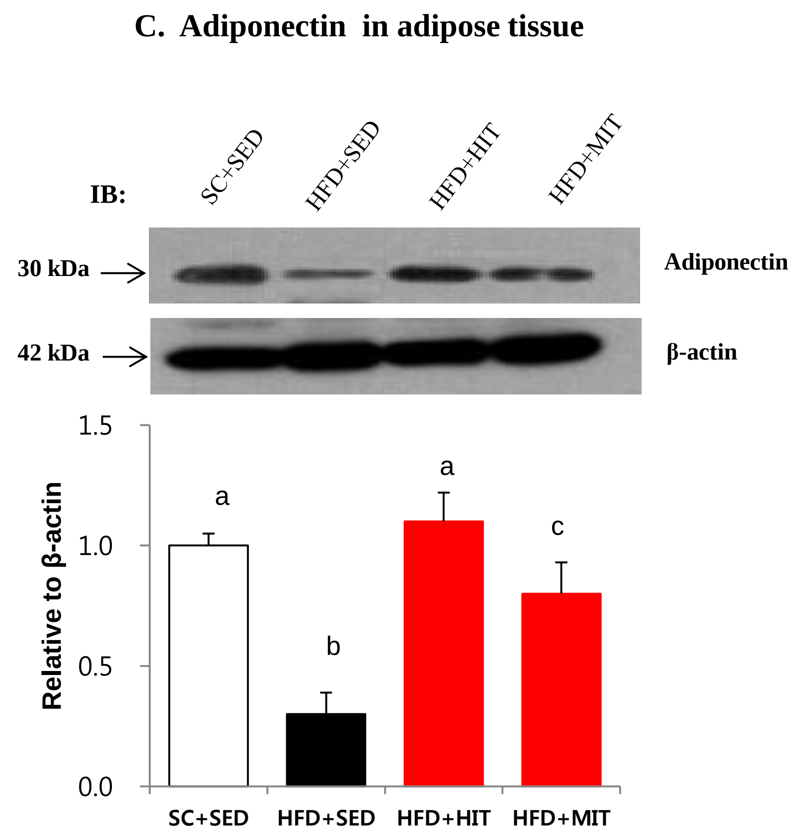
B. mRNAs of *de novo* lipogenesis



Exercise training, especially at the high-intensity, suppresses hypoadiponectinemia secondary to HFD.

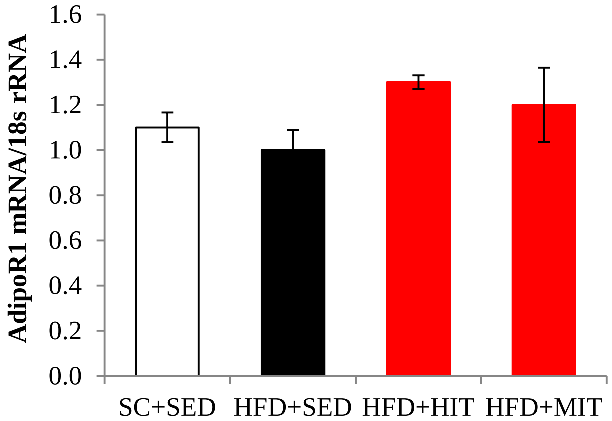




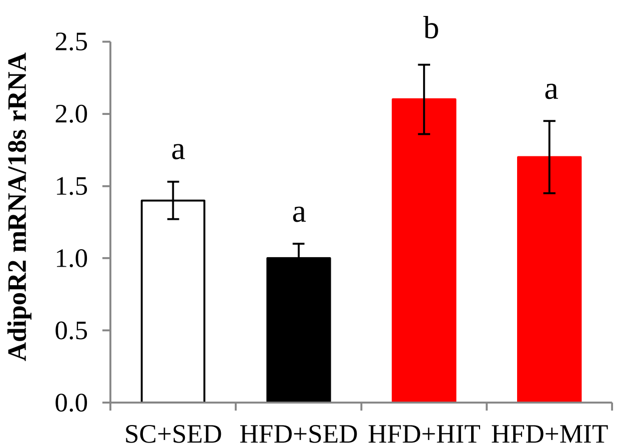


Exercise training, especially at the high-intensity, increases adiponectin receptor-2 in the liver.

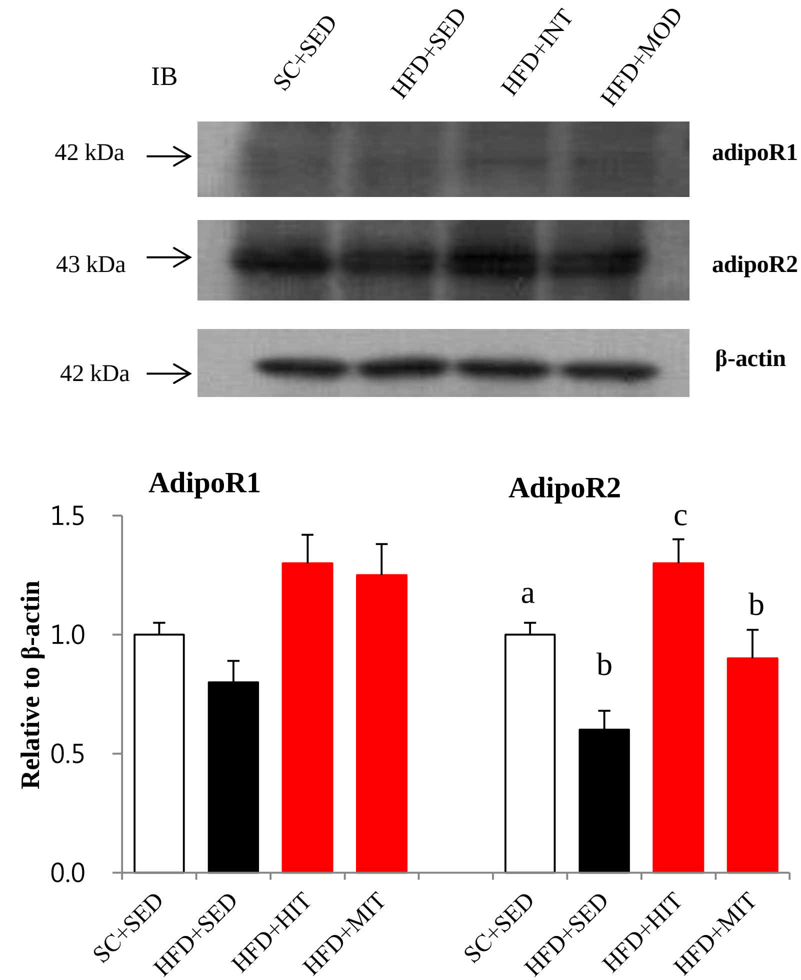
A. Adiponectin receptor 1 (AdipoR1) mRNA



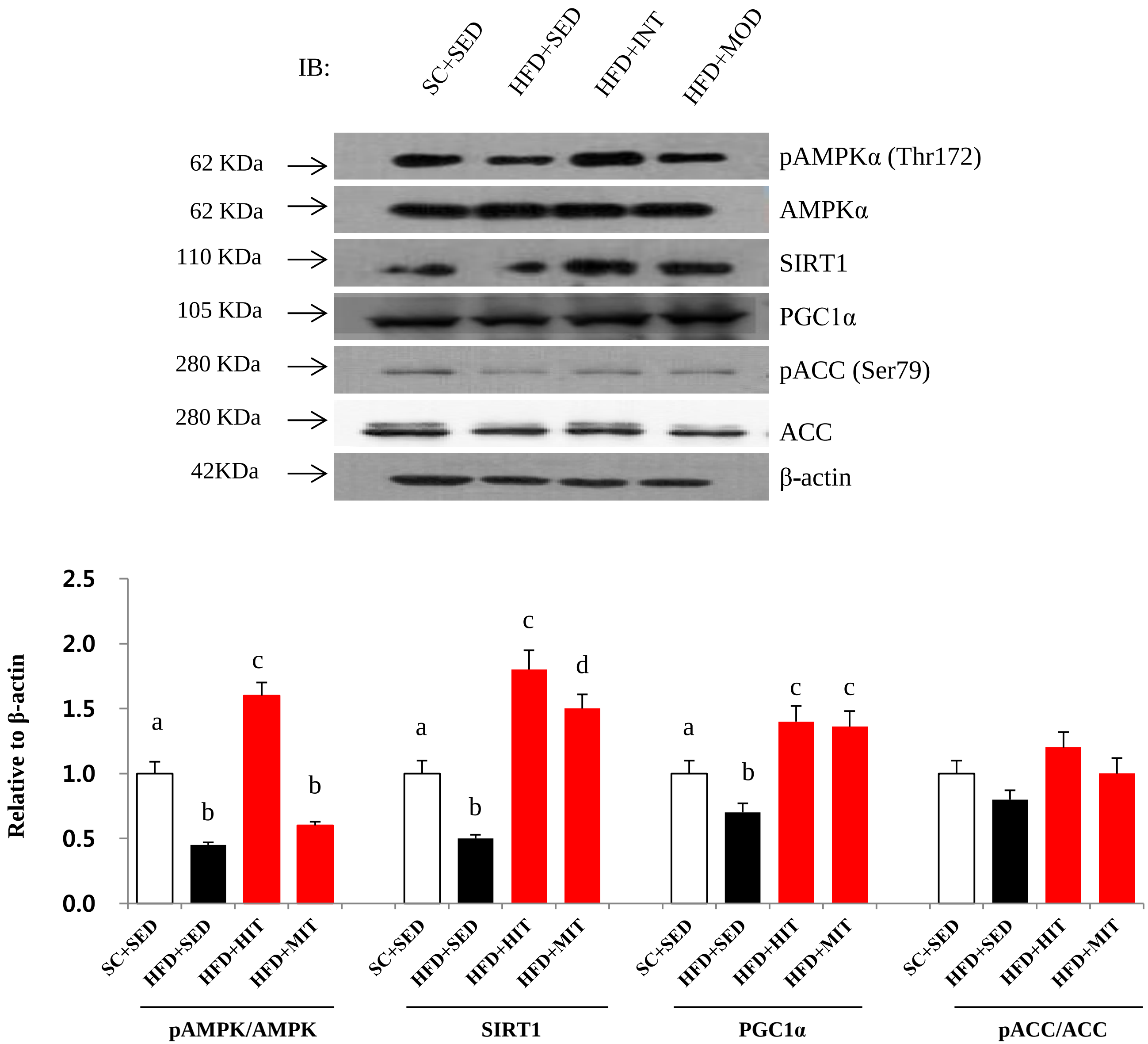
B. Adiponectin receptor 2 (AdipoR2) mRNA



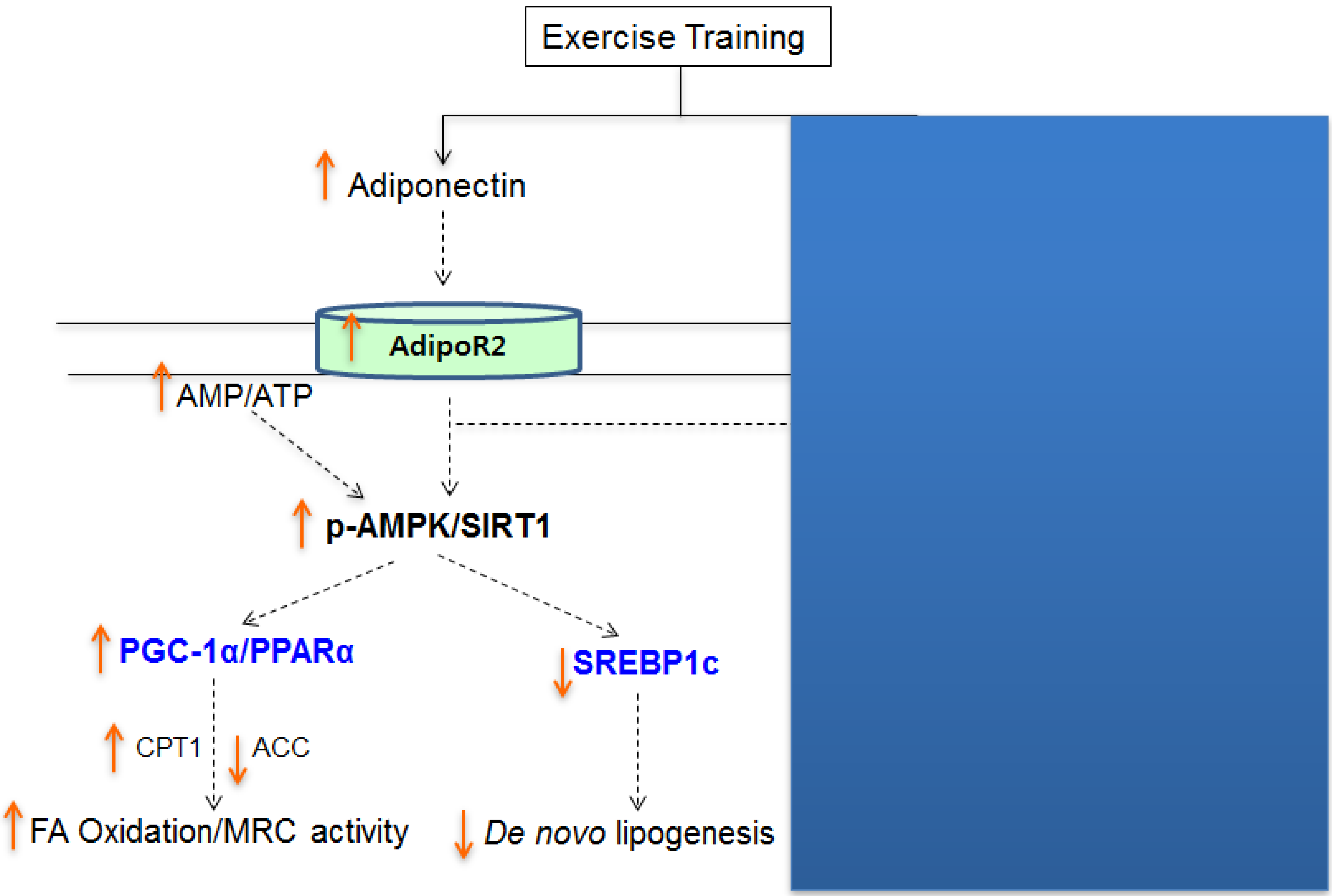
C. AdipoR1/2 proteins



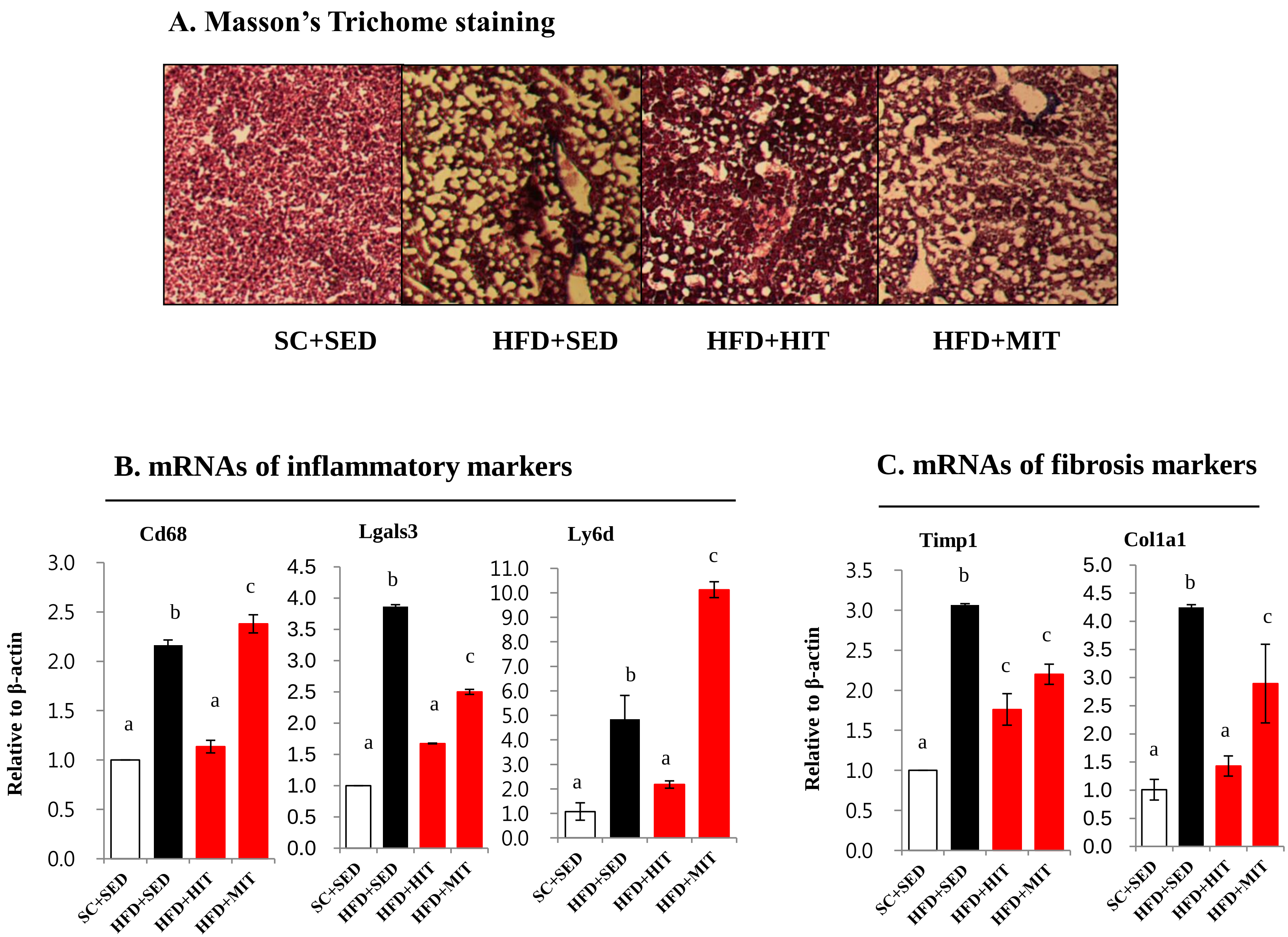
Exercise training, especially at the high-intensity, reverses decreased expression of AMPK /SIRT1 proteins secondary to HFD in the liver.



Exercise training suppresses HFD-induced hypoadiponectinemia while activating adiponectin/AdipoR2-mediated AMPK/SIRT1 pathway in the liver.

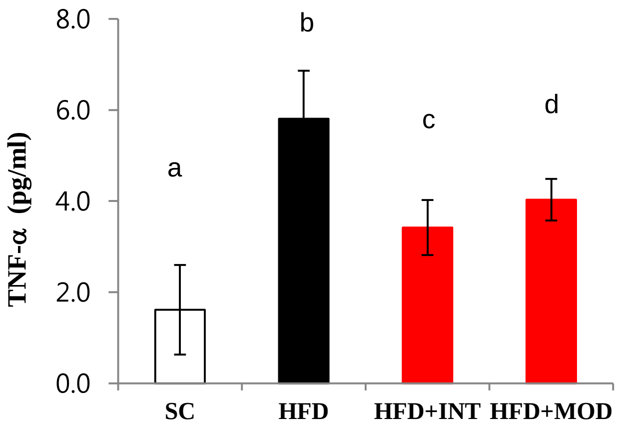


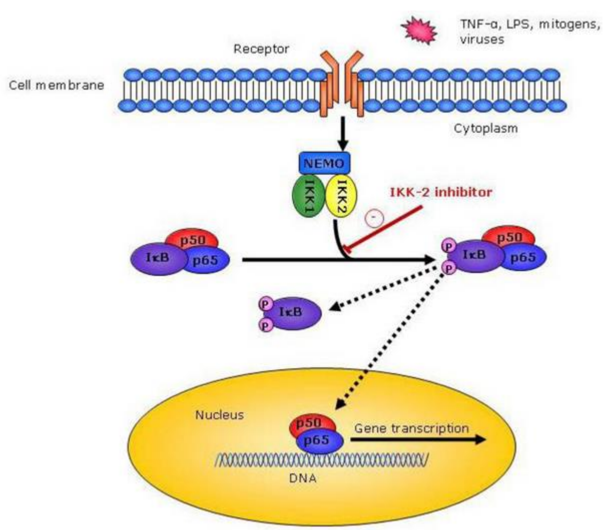
Exercise training suppresses elevated mRNA markers for inflammation and fibrosis secondary to HFD in the liver.



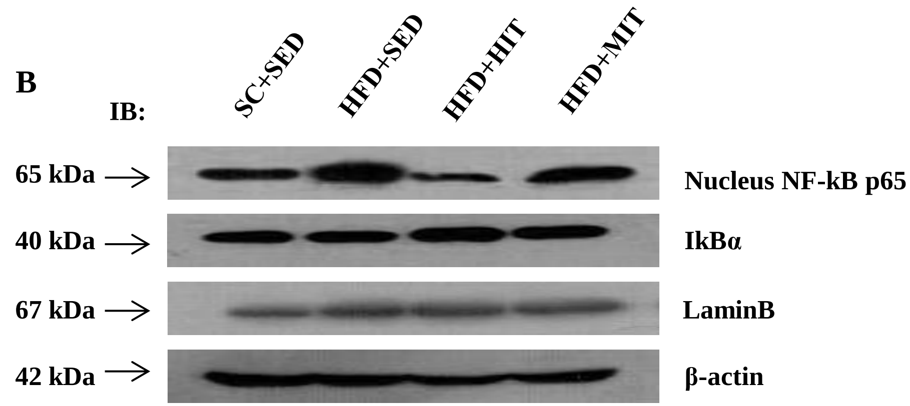
Exercise training, especially at a high-intensity, suppresses elevated TNF-α as well as activated NF-kB proteins secondary to HFD in the liver.

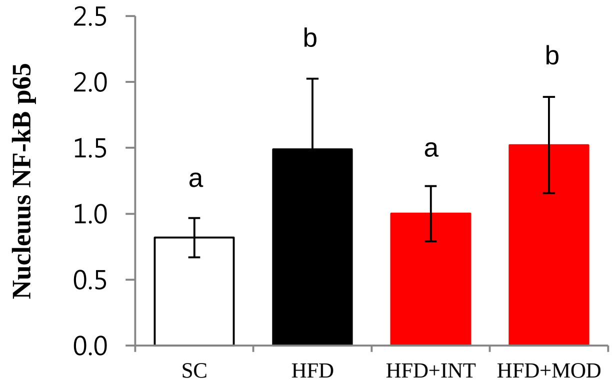
A. TNF-α levels



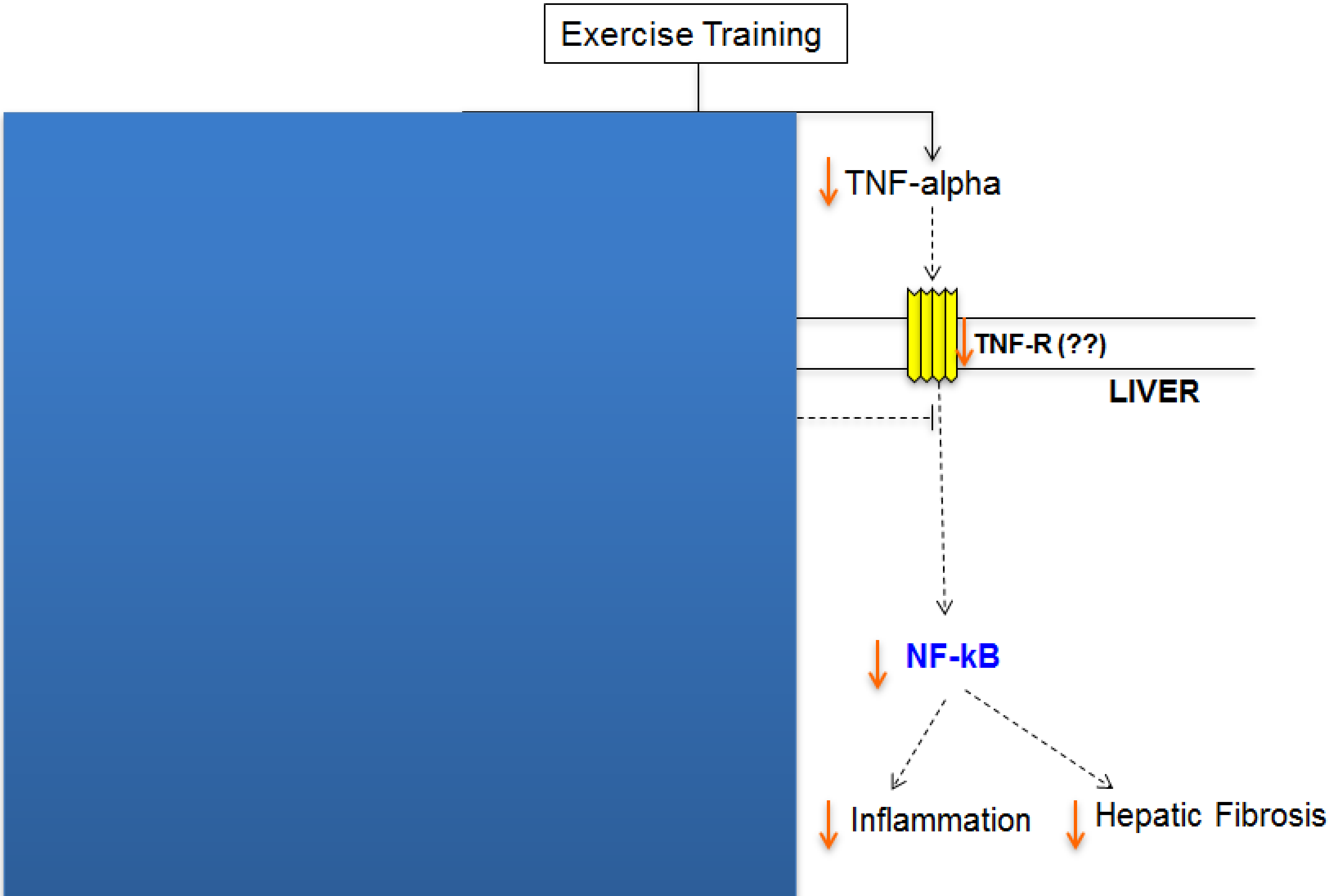


B. Nucleus NF-kB p65





Exercise training suppresses TNF-α-mediated activation of the NF-kB pathway secondary to a HFD in the liver.

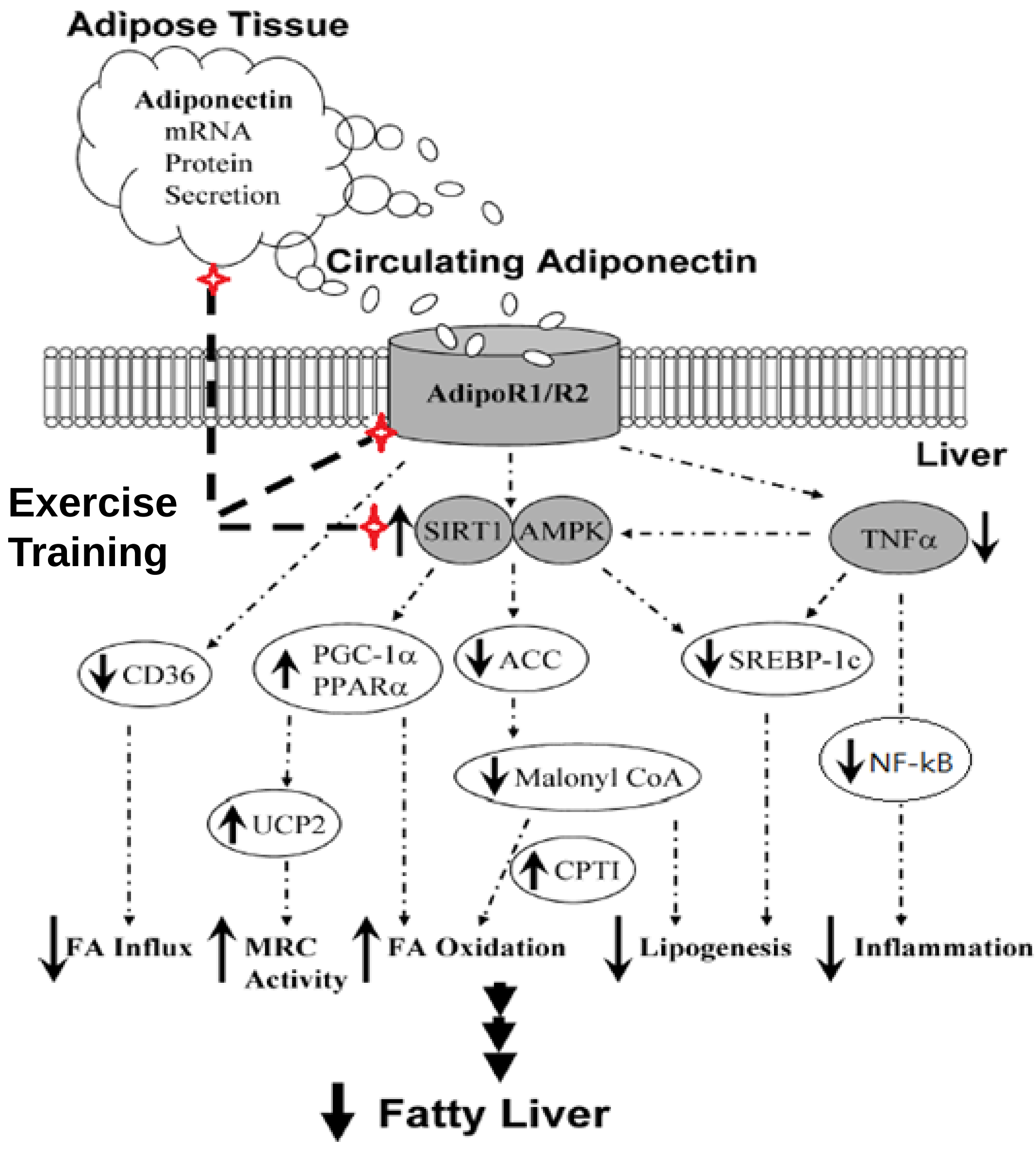


CONCLUSIONS

- **Exercise training intervened at the second half of a 16-HFD regimen alleviates hepatic steatosis and metabolic complications associated with obesity.**

- **Compared to moderate intensity, high-intensity training induces greater benefits against obesity-induced NAFLD.**

- **Hepatic benefits of exercise training against HFD-induced NAFLD are associated with adiponectin/AdipoR2-mediated activation of the AMPK/SIRT1 pathway (i.e., fatty acid oxidation, MRC activity, ipogenesis) as well as suppression of TNF-α-mediated activation of the NF-kB pathway (i.e., inflammation, fibrosis).**



(Modified from Exp Biol Med 234:850–859, 2009)

ACKNOWLEDGEMENT

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