The 95th Annual Meeting of the Japanese Pharmacological Society, March 7 to 9, 2022, Fukuoka, Japan

Effects of pemafibrate and bezafibrate on CDAHFD-induced murine nonalcoholic steatohepatitis (NASH) model

BILIS

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Introduction

Nonalcoholic steatohepatitis (NASH) is associated with fibrosis leading to cirrhosis, and occasionally hepatocellular carcinoma.

In this study, mice were fed with a choline-deficient methionine-reduced high-fat diet (CDAHFD) for 6 and 12 weeks to confirm the development of NASH pathology.

We also evaluated the effects of pemafibrate (PF), a selective PPARα modulator, on the progression of NASH pathology. Bezafibrate (BF), a PPAR-pan agonist, was also administered as a control.

Methods

Materials

- Animals
  Male C57BL/6J mice, 6 weeks old (Japan SLC, Inc.)
- Diets
  - CDAHFD (Research Diets, Inc.)
  - Normal diet (CLEA Japan, Inc.)
- Drug
  - PF (Parmodia, Kowa Company, Ltd.)
  - BF (Tokyo Chemical Industry Co., Ltd.)

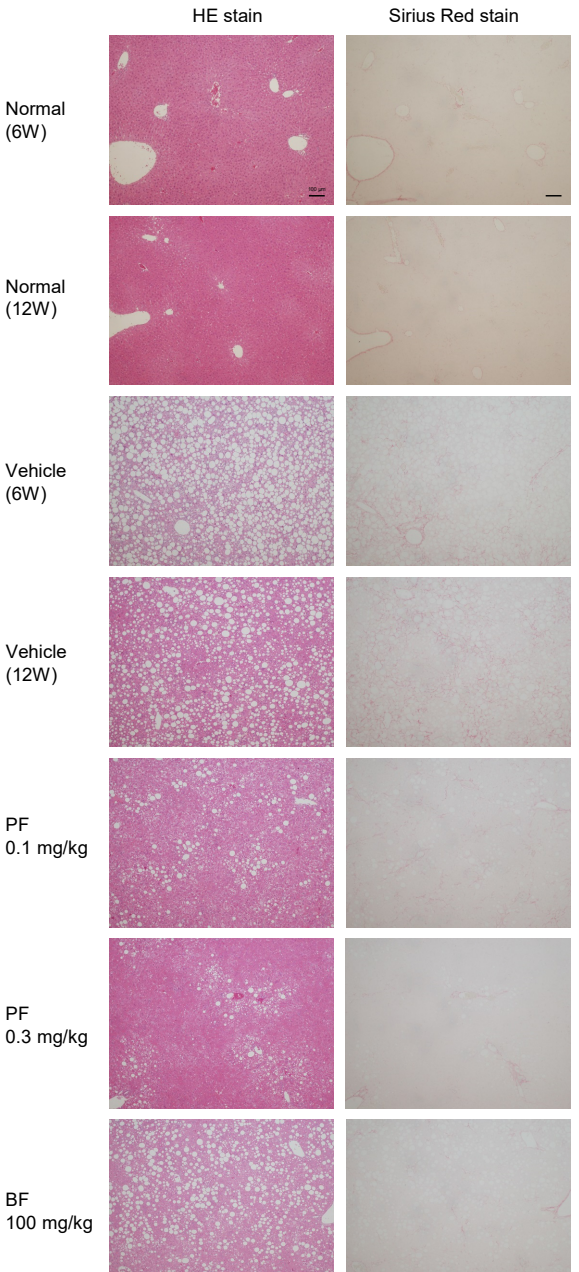
Group design and study schedule

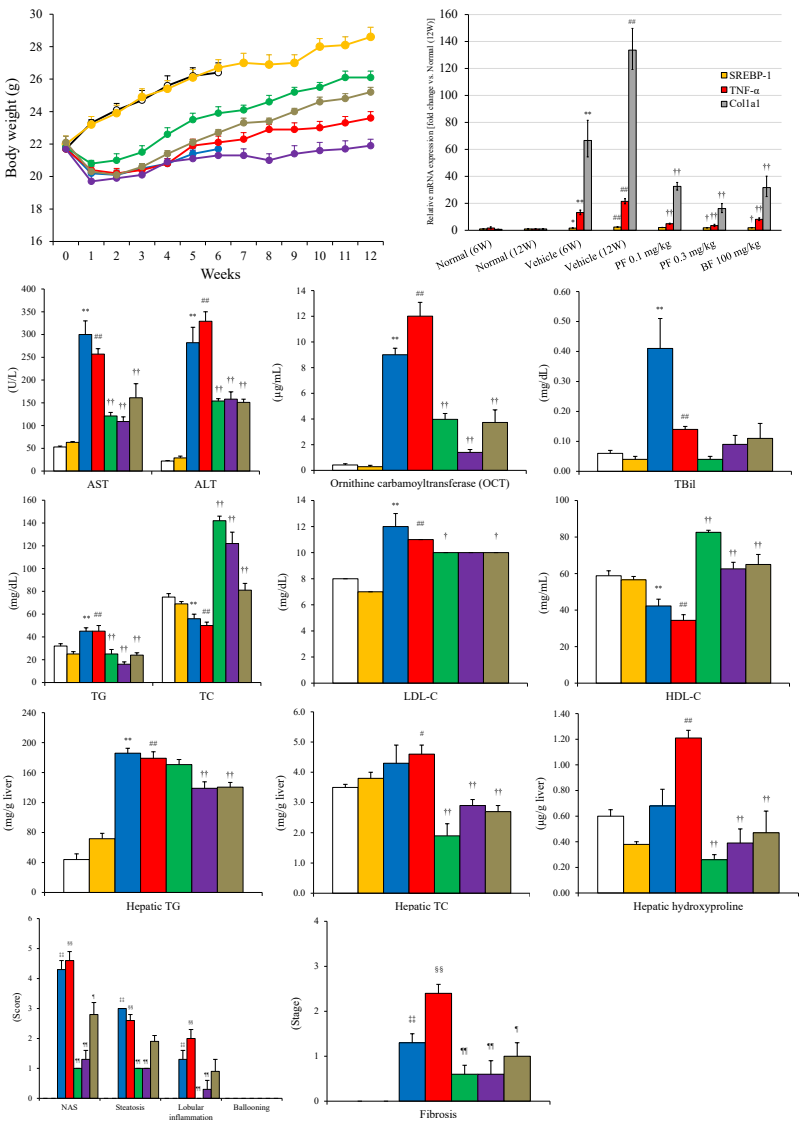
Food	Period (weeks)	Group	Administration	No. of animals
Normal diet	6	Normal (6W)	Vehicle, 10 mL/kg/day, p.o., 6 weeks	6
	12	Normal (12W)	Vehicle, 10 mL/kg/day, p.o., 12 weeks	6
CDAHFD	6	Vehicle (6W)	Vehicle, 10 mL/kg/day, p.o., 6 weeks	8
	12	Vehicle (12W)	Vehicle, 10 mL/kg/day, p.o., 12 weeks	8
		PF 0.1 mg/kg	PF, 0.1 mg/kg/day, p.o., 12 weeks	8
		PF 0.3 mg/kg	PF, 0.3 mg/kg/day, p.o., 12 weeks	8
		BF 100 mg/kg	PF, 0.3 mg/kg/day, p.o., 12 weeks	8

Vehicle: 0.5%MC solution, 5 mL/kg, q.d.

This study was conducted as approved by the Institutional Animal Experiment Committee of NISSEI BILIS Co., Ltd., Shiga Laboratory.

Results





Normal (6W) Normal (12W) Vehicle (6W) Vehicle (12W)
PF 0.1 mg/kg PF 0.3 mg/kg BF 100 mg/kg

Each value represents the mean ± S.E.
* and ** : p<0.05 and p<0.01 vs. Normal (6W) by Student's t-test
# and ## : p<0.05 and p<0.01 vs. Normal (12W) by Student's t-test
† and †† : p<0.05 and p<0.01 vs. Vehicle (12W) by Dunnett test
‡‡ : p<0.01 vs. Normal (6W) by Wilcoxon test
§§ : p<0.01 vs. Normal (12W) by Wilcoxon test
¶ and ¶¶ : p<0.05 and p<0.01 vs. Vehicle (12W) by Steel test

Conclusion

Serum and hepatic biomarkers (e.g., serum ALT, ornithine carbamoyltransferase (OCT), and hepatic TG) and hepatic mRNA expression of SREBP-1c, TNF-α, and Col1a1 were significantly increased in mice fed with CDAHFD for 6 weeks compared to control mice.

In addition, mice fed with CDAHFD for an additional 6 weeks (12 weeks total) showed higher serum ALT, OCT, hepatic TC, hydroxyproline (HP), and hepatic mRNA expressions than mice fed CDAHFD for 6 weeks, revealing the development of NASH pathology.

100 mg/kg of BF administered by gavage for 12 weeks almost suppressed the progression of NASH pathology in CDAHFD fed mice. Administration of 0.1 and 0.3 mg/kg of PF suppressed the progression of NASH pathology as much as or better than administration of BF.

These findings showed that PF might thus be effective in preventing NASH.

☑ The author has no conflict of interest to disclose with respect to this presentation.