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Miglitol upregulates uncoupling protein 1 (UCP1) by enhancing β3-adrenergic signaling in mature brown adipocytes of rat.

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Background

We previously reported that miglitol, an alpha-glucosidase inhibitor (α-GI), increases energy expenditure by enhancing β3-adrenergic signaling of brown adipose tissue (BAT) and reduces obesity in high fat diet-induced obese mice (Figure1-6, Table1) (Nutrition & Metaboliasm 2014 Mar 26;11(1):14. doi: 10.1186/1743-7075-11-14). However, this report did not describe the mechanism by which miglitol enhances β3-adrenergic signaling. Miglitol, unlike other α-GIs, enters the circulation. We hypothesized that miglitol directly enhances β3-adrenergic signaling.

Objective

To determine whether miglitol has a direct effect on β3-adrenergic signaling in rat mature brown adipocytes (rBAC).

Materials and Methods

We cultured rat brown adipocytes with a culture kit (Takara, Japan). After the cells finished maturing, we added medium containing miglitol with or without a β3-adrenergic agonist (CL316,243). After 24 h, the cells were harvested. We used quantitative real-time PCR to determine the expressions of two genes involved in BAT thermogenesis: peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) and uncoupling of protein 1 (UCP1).

Results

Figure1. Miglitol decreased body weight gain in high fat diet-induced obese mice.

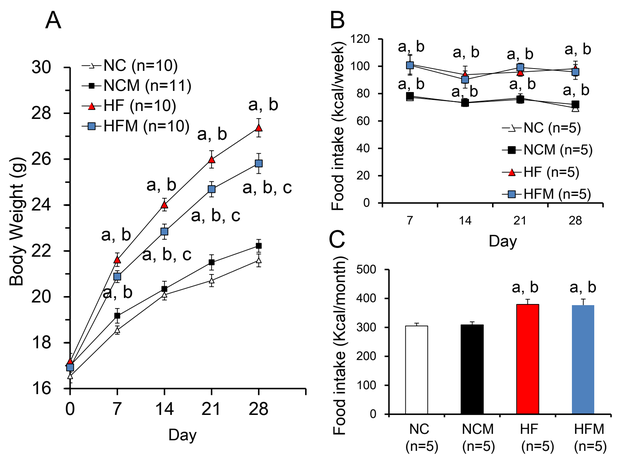


Table 1. Miglitol ameliorated insulin resistance in high fat diet-induced obese mice.

	n	NC	NCM	HF	HFM
Body weight (g)	10-11	21.5 ± 0.2	22.2 ± 0.2	27.3 ± 0.4 [a, b]	25.8 ± 0.4 [a, b, c]
Glucose (mg/dl)	5	118 ± 6.6	129 ± 15.4	282 ± 4.1 [a, b]	240 ± 9.1 [a, b, c]
Total cholesterol (mg/dl)	5-7	62 ± 4.7	68 ± 4.9	150 ± 7.2 [a, b]	141 ± 4.2 [a, b]
Triglyceride (mg/dl)	6	42 ± 8.4	45 ± 5.7	42 ± 4.9	46 ± 5.2
Insulin (μU/ml)	5	5.3 ± 1.2	3.4 ± 0.5	12.3 ± 1.9 [a, b]	6.7 ± 1.2
HOMA-R	5	1.4 ± 0.3	1.1 ± 0.3	8.4 ± 1.3 [a, b]	4.0 ± 0.7 [a, b, c]
Weight of epididymal white adipose tissue (g)	9-14	0.27 ± 0.02	0.28 ± 0.01	1.1 ± 0.08 [a, b]	0.85 ± 0.04 [a, b, c]
Weight of subcutaneous white adipose tissue (g)	6	0.3 ± 0.03	Not measured	1.5 ± 0.15 [a]	0.98 ± 0.12 [a, c]
Active glucagon-like peptide1 (pg/ml)	8-9	54.8 ± 7.9	61.1 ± 4.9	66 ± 7.5	76.9 ± 14.4
Concentration of miglitol (μmol/L)	3-4	Not measured	0.06 ± 0.02	Not measured	0.26 ± 0.13

Values are means ± SE for 3–14 mice. Blood samples were collected under fasting conditions. [a]P < 0.05, vs mice fed normal chow diet (NC). [b]P < 0.05, vs mice fed normal chow diet plus miglitol (NCM). [c]P < 0.05, vs mice fed high-fat diet alone (HF).

Figure2. Miglitol increased oxygen consumption in high fat diet-induced obese mice.

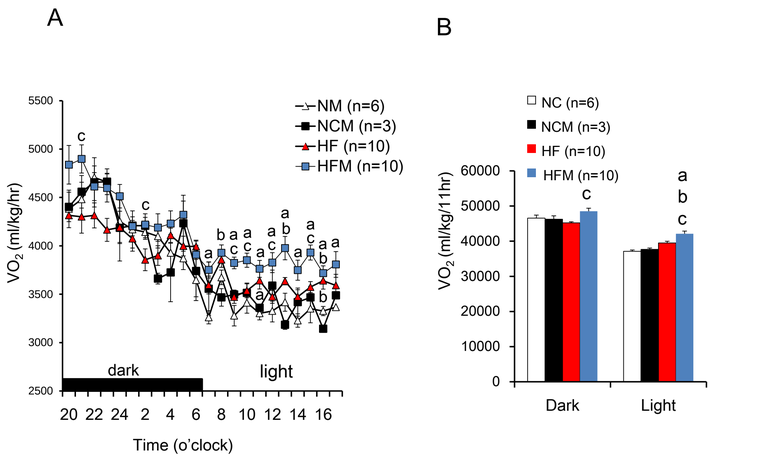


Figure3. Interscapular BAT temperature in HFM mice was significantly higher than in HF mice.

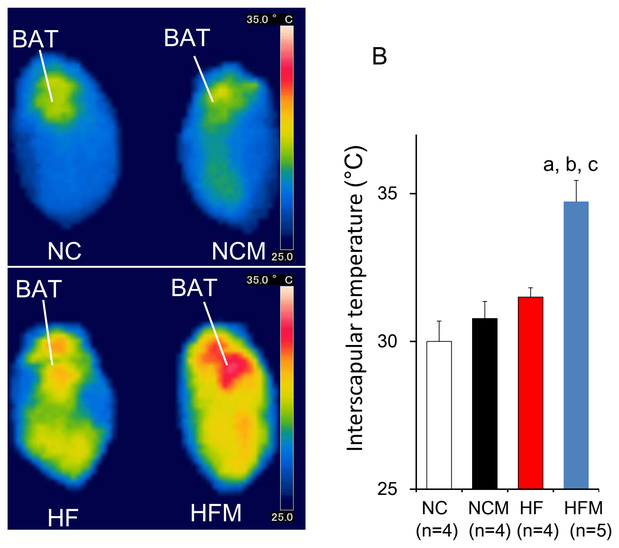


Figure 4. Miglitol enhanced the gene and protein expressions of UCP1 in HFM mice.

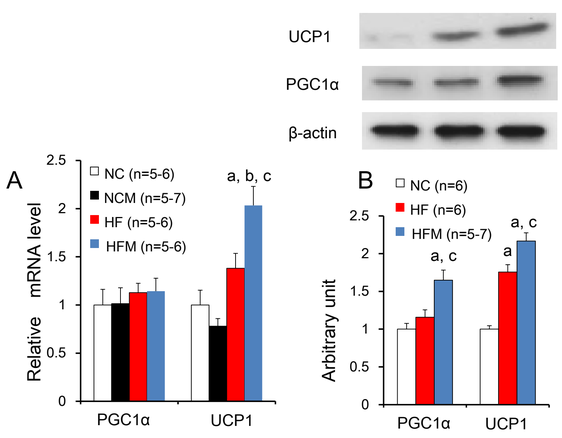


Figure 5. Miglitol enhanced β3-adrenergic signaling in BAT of HFM mice.

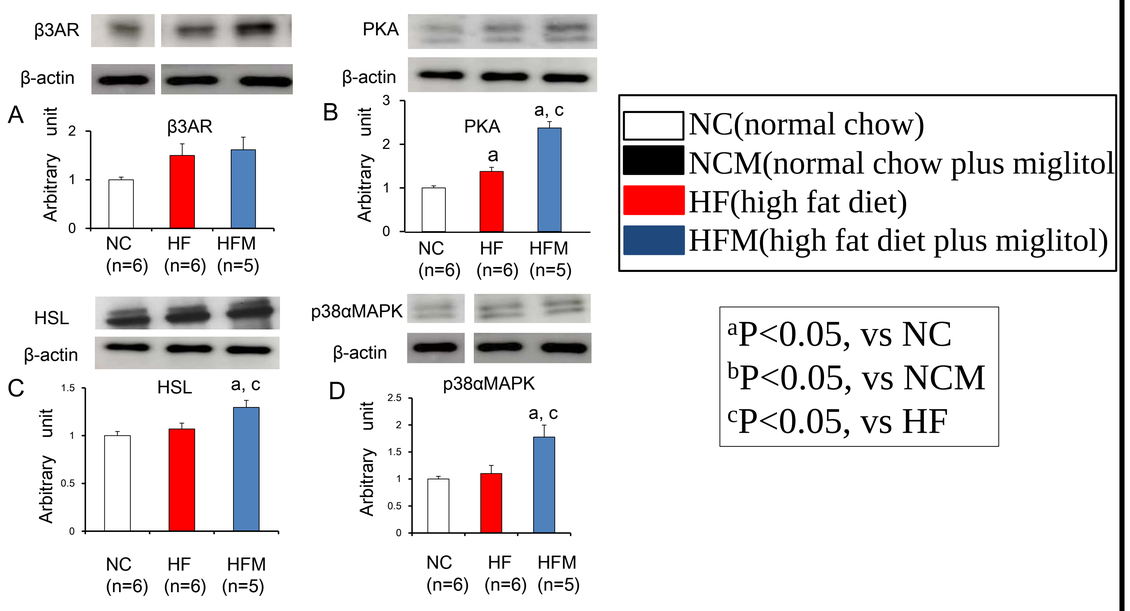


Figure 6. β3-adrenergic agonist induced greater amount of cAMP and PKA protein in HFM mice than HF mice.

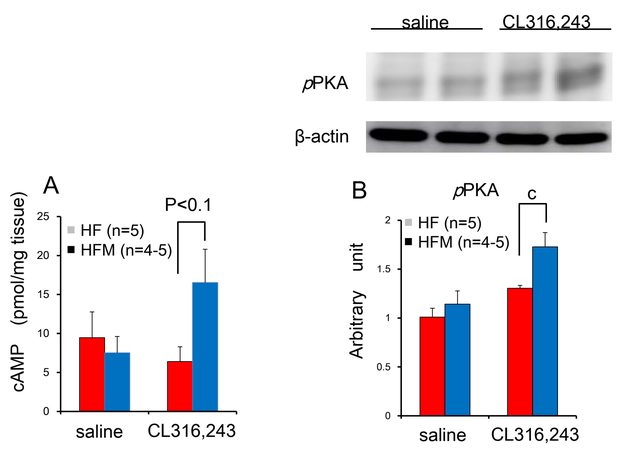
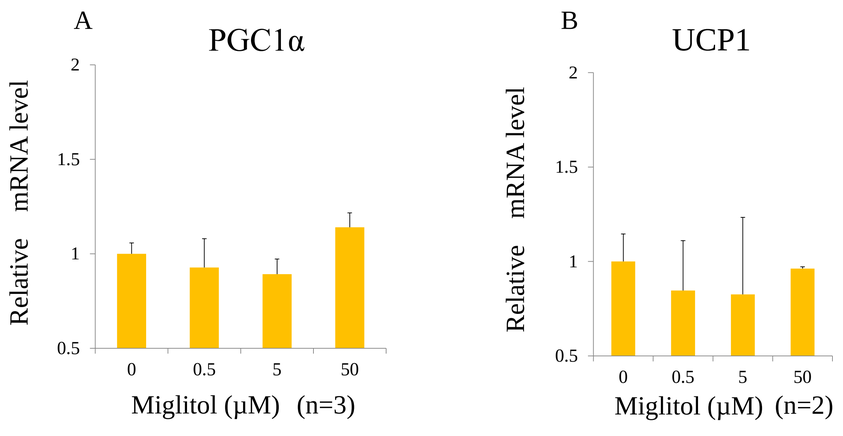
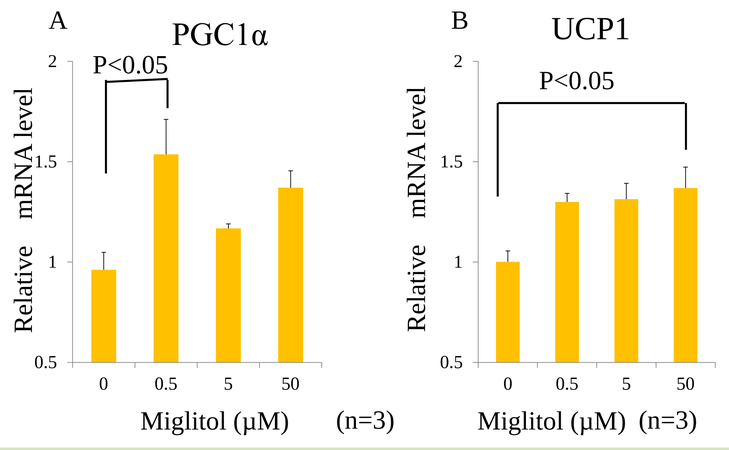


Figure 7. Effect of miglitol alone on the expressions of PGC1α and UCP1 in rBAC.



Miglitol alone did not affect gene expressions of PGC1α and UCP1.

Figure 8. Effect of miglitol plus β3-adrenergic agonist on the expressions of PGC1α and UCP1 in rBAC.



Miglitol enhanced the gene expressions of PGC1α and UCP1 in the presence of a β3-adrenergic agonist.

Conclusion

Miglitol increased the sensitivity of β3-adrenergic receptor in rat mature brown adipocytes. This suggests that miglitol entered the circulation and directly enhanced β3-adrenergic signaling of BAT in rodents.

We have nothing to disclose.