Supplementary materials

Table S1: The list of primers used in RT-qPCR for rat

Gene	Primer sequences (Forward)	Primer sequences (Reverse)
Il6	GCAAGAGACTTCCAGCCAGT	GCAAGAGACTTCCAGCCAGT
Il1b	TGACTTCACCATGGAACCCG	TCCTGGGGAAGGCATTAGGA
Tnf	GGGCTCCCTCTCATCAGTTC	CCTTTCCTCCCAAACCAAAGC
Hcrtr1	GCTCTTGAACAGCAGAGGGT	ACCGAATCATGGCTCTTCGG
Pparg	TGCTGGTGATCAGAAGGCTG	TGGCATCTCTGTGTCAACCAT
Ppargc1a	TTCAGGAGCTGGATGGCTTG	GGGCAGCACACTCTATGTCA
Rela	TCCAGTGTGTGAAGAAGCGA	TTGTTGGTCTGGATGCGCTG
Tlr4	TGAGTTCTGAACGTCGAAAAGA	GGGGAAGTGGCAACTGATGA
Actb	TGGAGCAAACATCCCCCAAA	TGCCGTGGATACTTGGAGTG

Abbreviation：Il6, interleukin 6; Il1b, interleukin 1 beta; Tnf, tumor necrosis factor; Hcrtr, hypocretin receptor 1; Pparg, peroxisome proliferator-activated receptor gamma; Ppargc1a, PPARG coactivator 1 alpha; Rela, RELA proto-oncogene, NF-kB subunit; Tlr4, toll-like receptor 4; Actb ,actin, beta.

Table S2: The list of primers used in RT-qPCR for cells

Gene	Primer sequences (Forward)	Primer sequences (Reverse)
Srebf1	CAGCAGTGAGTCTGCCTTGA	CAGCAGTGAGTCTGCCTTGA
Cebpa	CTAGGAGATTCCGGTGTGGC	CCCGAGAGGAAGCAGGAATC
Pparg	GGCATTGTGAGACATCCCCA	GGCATTGTGAGACATCCCCA
Il6	ACCAGTGACTGAAAGACGCA	GGCGGCTTAGTTAGATCCCT
Il1b	TGCCACCTTTTGACAGTGATG	TGATGTGCTGCTGCGAGATT
Tnf	GGCAGTTAGGCATGGGATGA	TCCACTTGGTGGTTTGCTGA
Actb	GTACTCTGTGTGGATCGGTGG	AACGCAGCTCAGTAACAGTCC

Abbreviation：Srebf1, sterol regulatory element binding transcription factor 1; Cebpa, enhancer binding protein alpha; Pparg, peroxisome proliferator activated receptor gamma; Il6, interleukin 6; Il1b,interleukin 1 beta; Tnf, tumor necrosis factor; Actb, actin, beta.

Supplementary Table 3 Ingredient of TP23302 and TP23300

Ingredient g/kg	TP23302	TP23300
Casein	189	267
Maltodextrin	108	157
Sucrose	67	89
Corn Starch	497	0
Soybean Oil	21	33
Lard	21	301
Cellulose	48	67
Mineral Mix, M1020	36	66
Vitamin Mix, V1010	9	13
L-Cystine	2	4
Choline Bitartrate	2	3
TBHQ	0.067	0.067
Total	1000.067	1000.067

The purified diet TP 23,300 supplies energy as 20.6% carbohydrate (7% sucrose calories), 19.4% protein, 60% fat with total 5.0 kcal/g; and the purified diet TP23302 supplies energy as 70% carbohydrate (7% sucrose calories), 20% protein, 10% fat with total 3.8 kcal/g.

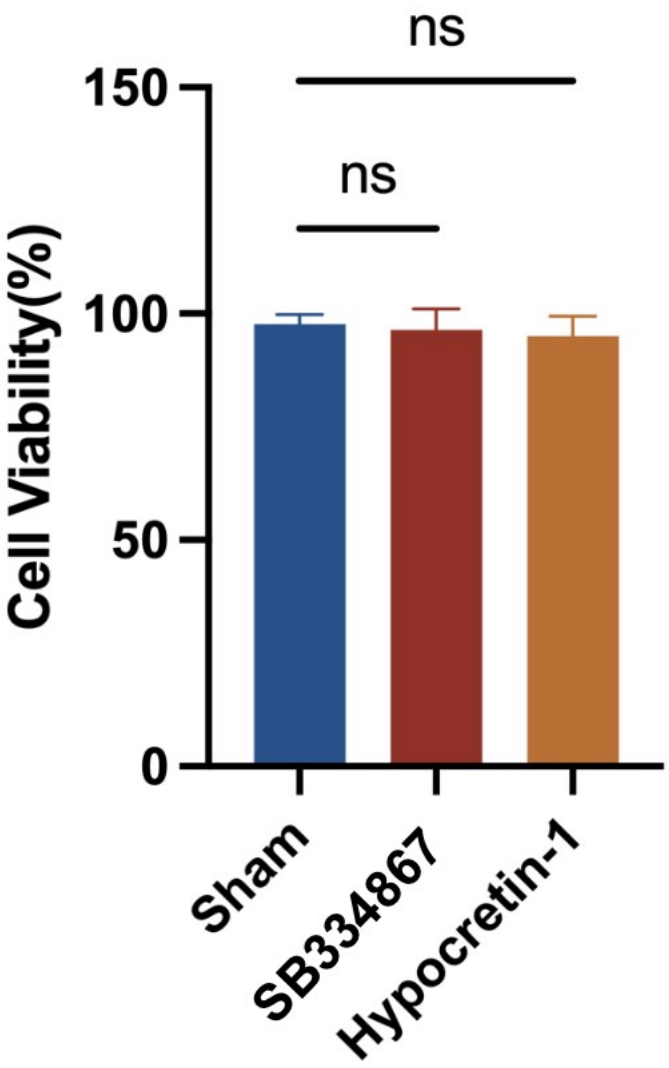


Figure S1 Cell viability assays in 3T3-L1 cells after dosing, hypocretin and antagonists had no significant effect on cell viability(n=5).

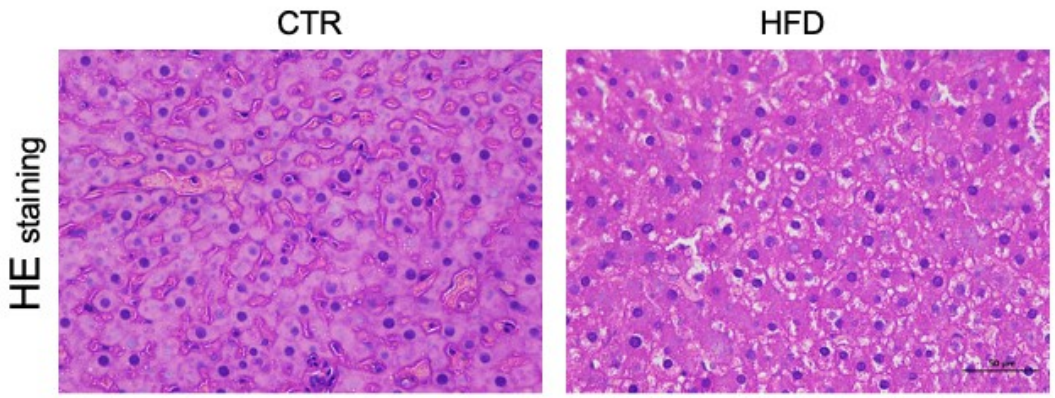
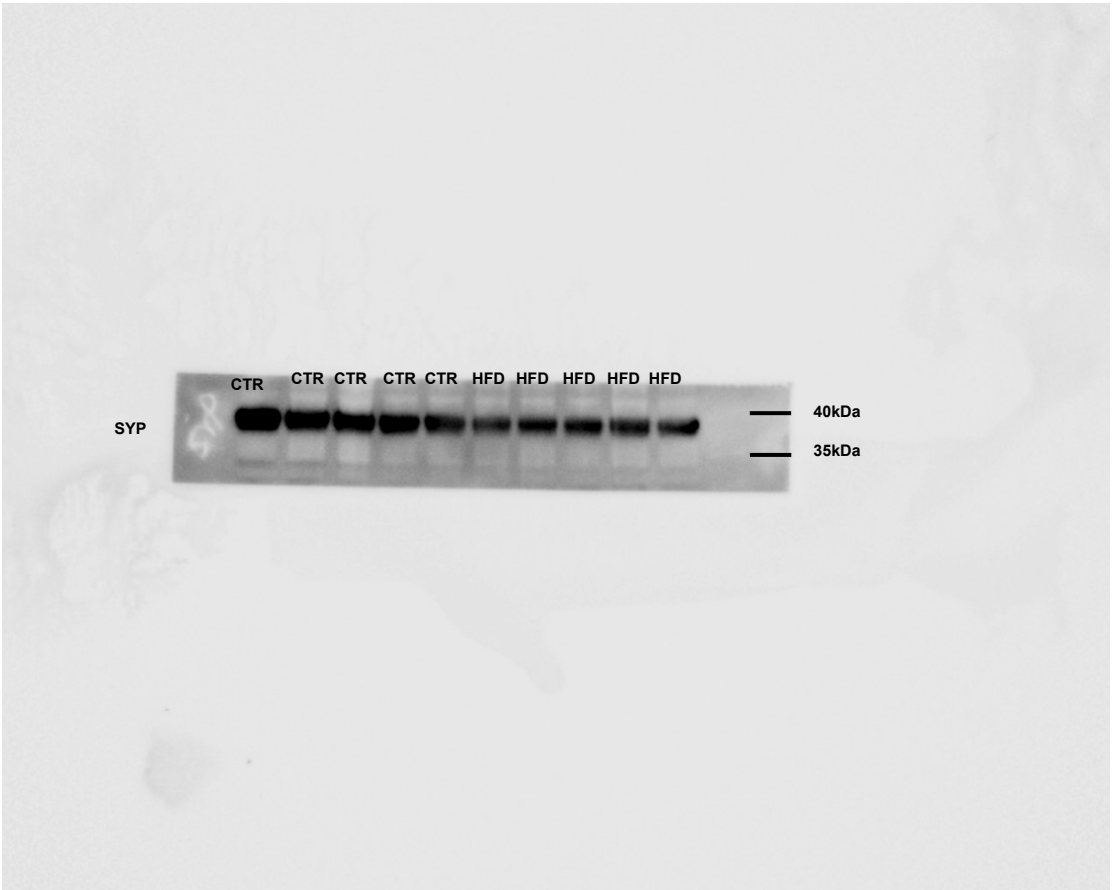


Figure S2 HE staining was performed on the liver of rats in HFD and CTR groups, and there was a gap caused by fat in the liver of HFD group.



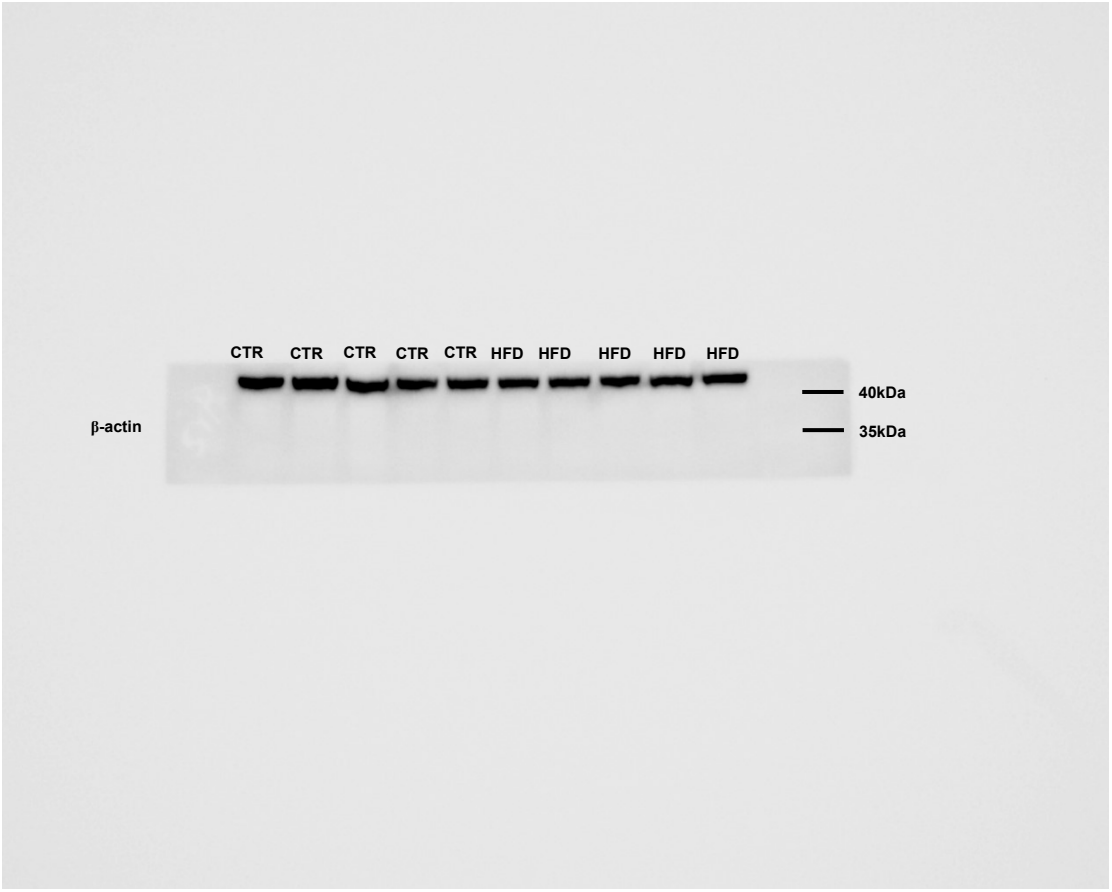


Figure S3：The full uncropped Gels and Blots images of SYP and β-actin(n=5). HFD resulted in decreased expression of SYP.

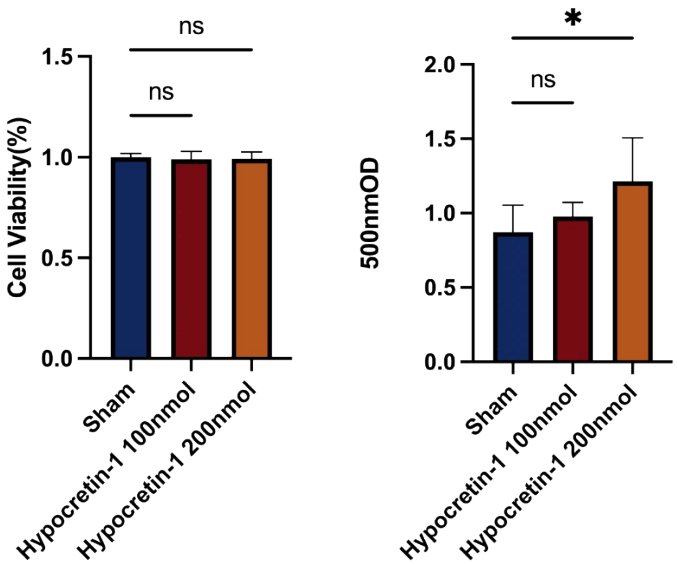


Figure S4: Cell viability assays in 3T3-L1 cells after dosing, hypocretin-1 100nmol and hypocretin-1 200nmol had no significant effect on cell viability. After oil red O staining, the cells were eluted with isopropanol, and the absorbed light intensity was

measured at 500nm using a microplate reader, following gradient experiments, it was determined that 200 nmol Hypocretin-1 was more effective than the control group without exhibiting any cytotoxic effects(n=5).

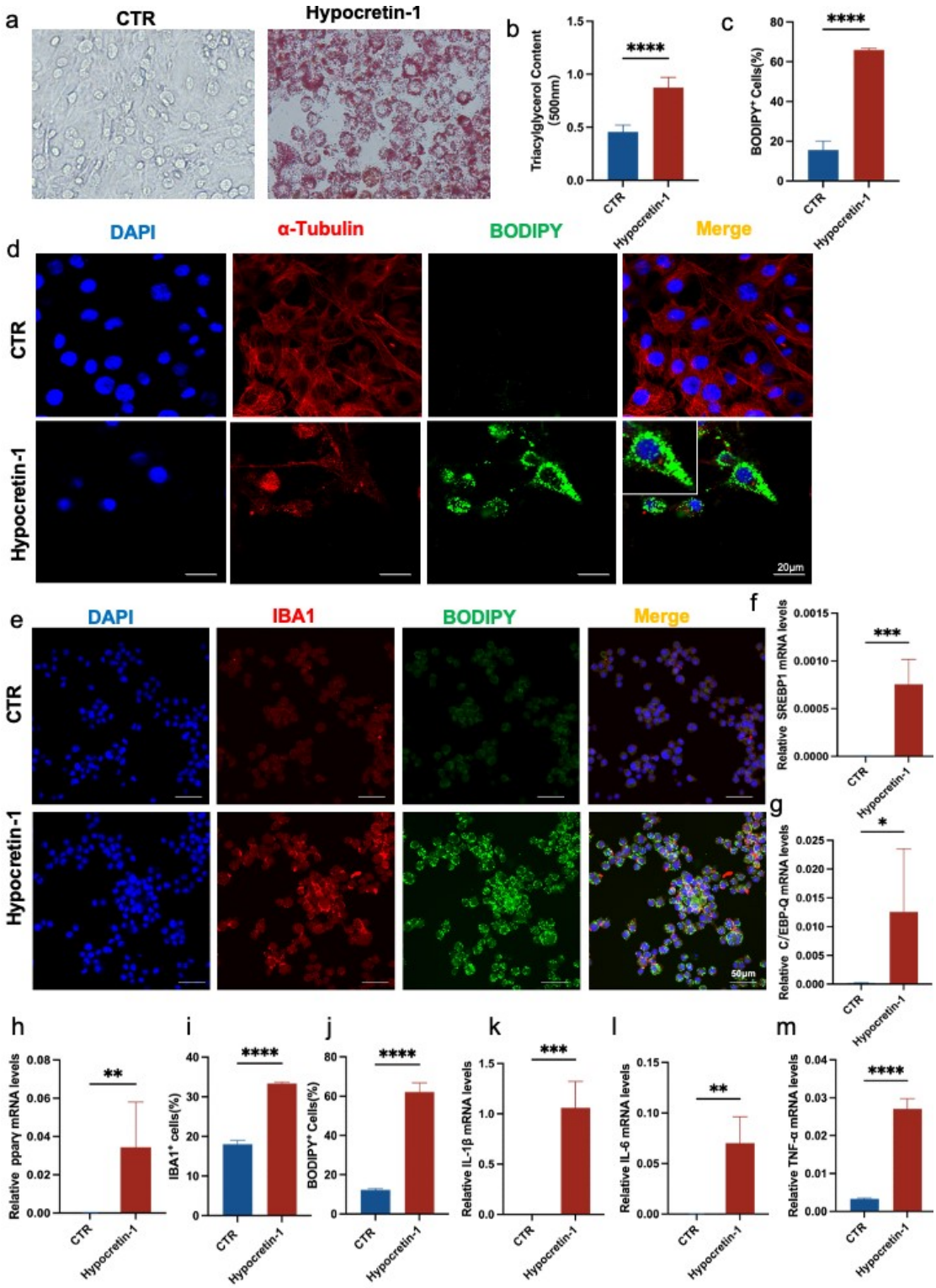


Figure S5:Effects of hypocretin-1 on lipid accumulation in 3T3-L1 cells. a. Oil red O

staining of 3T3-L1 cells. b. After oil red O staining, the cells were eluted with isopropanol, and the absorbed light intensity was measured at 500nm using a microplate reader (n=10). c. Quantification of relative fluorescence intensity for BODIPY (n=4) Immunofluorescence staining of 3T3-L1 cells showed that the hypocretin-1 increase lipid accumulation in 3T3-L1 cell. e. Immunofluorescence (IBA1 and BODIPY) showed that the conditioned medium increased lipid accumulation in BV2 cells; however, IBA1 intensity was altered. F-h. Adipogenic factor mRNA levels (SREBP1, C/EBP-Q, and pparγ) were measured following differentiation of 3T3-L1 cells. After treatment with a hypocretin-1, mRNA levels of adipogenic factors were significantly increased. I-j. While the BODIPY average fluorescence intensity of BV2 immunofluorescence staining increased between the treatment and CTR groups, the mean fluorescence intensity of IBA1 observed through BV2 immunofluorescence staining of the hypocretin-1 group was significantly higher than that of the model group (n=6). k-m. The mRNA levels of inflammatory factors (IL-6, IL-1β, and TNF-α) were analyzed. BV2 cells were altered following the introduction of the conditioned medium. Hypocretin-1 treatment notably increased the expression of inflammatory substances (n=5). One Way ANOVA analysis followed by Dunnett's test for post-hoc comparisons., no significant difference n.s.(*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$).