

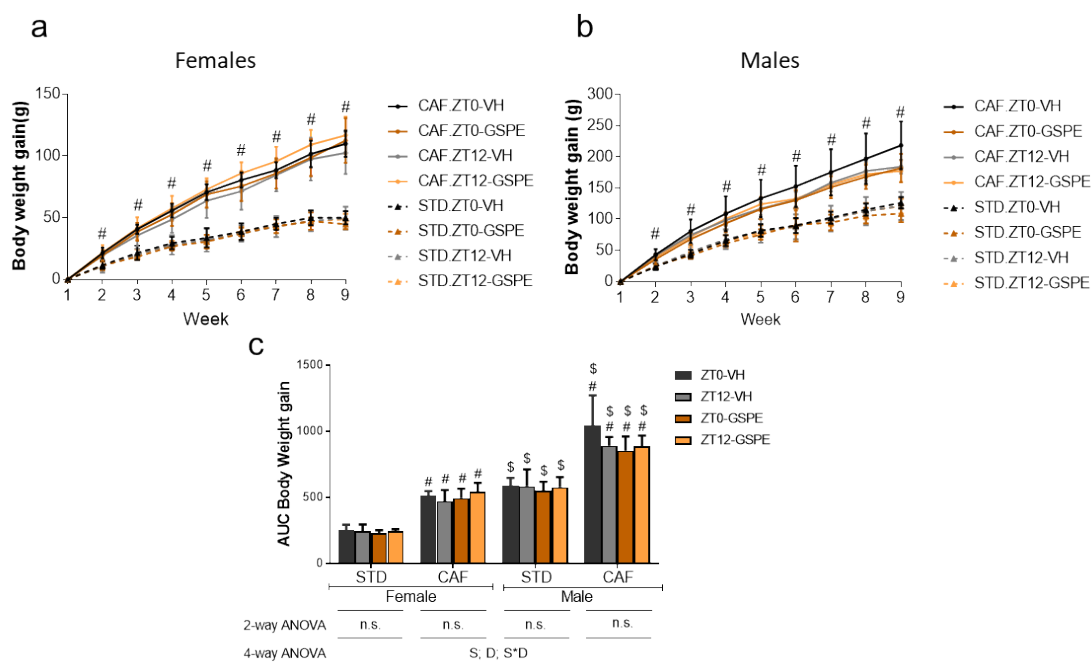


Figure S1. Body weight gain throughout the experiment. (a): Body weight gain in females rats-fed with either STD or CAF and treated with VH or GSPE at ZT0 or ZT12 for the last 4 weeks. (b): Body weight gain in males rats-fed with either STD or CAF and treated with VH or GSPE at ZT0 or ZT12 for the last four weeks. # indicates significant diet effect, analyzed by repeated-measures ANOVA followed by LSD post hoc test ($p < 0.05$); (c): Area under the curve (AUC) of body weight gain. Table below the graph indicates effects and interactions among the different factors (D: diet; GSPE; ZT; S: sex) analyzed by 2-way or 4-way ANOVA followed by LSD post hoc test: # and \$ indicate significant diet and sex effect respectively ($p < 0.05$). Data are showed as mean $\pm$ SD ($n = 8$). STD: standard diet; CAF: cafeteria diet; GSPE: grape seed proanthocyanidin extract; ZT: time of the day; ZT0: VH or GSPE time administration (when light was turned on); ZT12: VH or GSPE time administration (when light was turned off); n.s: no significant differences ($p > 0.05$).

Table S1. Overall effects in serum metabolites.

	Female								Male								4-way ANOVA effects ^b
	STD				CAF				STD				CAF				
	VH-ZT0	GSPE-ZT0	VH-ZT12	GSPE-ZT12	VH-ZT0	GSPE-ZT0	VH-ZT12	GSPE-ZT12	VH-ZT0	GSPE-ZT0	VH-ZT12	GSPE-ZT12	VH-ZT0	GSPE-ZT0	VH-ZT12	GSPE-ZT12	
	2-way ANOVA effects ^a				2-way ANOVA effects ^a				2-way ANOVA effects ^a				2-way ANOVA effects ^a				
Aminoacids metabolism																	
Leucine	n.s				GSPE, ZT				ZT				ZT				D, GSPE, ZT, S*D, S*ZT, D*ZT, S*D*GSPE
Tyrosine	n.s				GSPE, ZT				ZT				ZT				D, S, GSPE, ZT, S*D, S*ZT, S*D,GSPE
Lysine	ZT				ZT				ZT, GSPE*ZT				ZT				D, ZT, S*D
Phenylalanine	ZT				GSPE, ZT				ZT				ZT				D, GSPE, ZT, S*ZT, D*ZT, S*D*GSPE
Isoleucine	n.s				n.s.				GSPE, ZT				ZT				D, S, ZT, S*D, S*GSPE, S*ZT
Alanine	ZT				ZT				ZT				ZT				D, S, ZT
Valine	n.s				n.s.				ZT, GSPE*ZT				ZT				D, ZT, S*ZT, D*S*GSPE*ZT
Tryptophan	n.s				n.s.				GSPE				ZT				D, S, GSPE, ZT, S*ZT, GSPE*ZT, S*D*GSPE
Glycine	ZT				ZT				ZT				GSPE, ZT				S, ZT, GSPE*ZT, S*D*GSPE
Histidine	ZT				ZT				n.s.				GSPE				S, ZT, S*GSPE
Glutamine	n.s				ZT				ZT				n.s.				D, ZT, S*D, S*D*ZT
Glutamate	n.s				n.s.				ZT				n.s.				D, S
Glucose	n.s				n.s.				n.s.				ZT, GSPE*ZT				S, ZT, S*D
Pyruvate	n.s				n.s.				n.s.				n.s.				S, S*GSPE*ZT
Lactate	n.s				n.s.				n.s.				n.s.				n.s.
ARA+EPA	n.s				GSPE*ZT				n.s.				n.s.				D, S, ZT, S*D, S*GSPE*ZT, D*S*GSPE*ZT
Triglycerides	n.s				n.s.				ZT				ZT				D, S, ZT,S*D
Free Cholesterol	GSPE				n.s.				GSPE, GSPE*ZT				n.s.				D, S*D, S*GSPE, S*D*GSPE, D*S*GSPE*ZT
Oleic Acid	n.s				n.s.				ZT				ZT				D, S, ZT, S*D
MUFAs	n.s				ZT				ZT				ZT				D, S, ZT, S*D, D*ZT
Linoleic Acid	n.s				ZT				ZT				ZT				D, S, ZT, S*D, D*ZT
Total Fatty Acids	GSPE				n.s.				GSPE, GSPE*ZT				ZT				D, S, ZT, S*D, S*GSPE, D*ZT, S*D*ZT
Diglycerides	n.s				n.s.				n.s.				n.s.				D, S, S*D
DHA	n.s				n.s.				GSPE, ZT				n.s.				S, ZT, S*D, S*D*GSPE

PUFAs	n.s	n.s.	n.s.	n.s.	D, S*D, S*GSPE*ZT
Glycerol	n.s	n.s.	n.s.	n.s.	D, S, GSPE, S*D
Total Phospholipids	n.s	n.s.	n.s.	ZT	D, S*D, D*ZT, S*GSPE*ZT
Esterified Cholesterol	n.s	GSPE*ZT	n.s.	n.s.	D, S, GSPE, S*D, S*GSPE*ZT
Cholesterol	n.s	GSPE*ZT	GSPE	n.s.	D, S, GSPE, S*D, S*GSPE*ZT
Acetate	n.s	ZT	ZT, GSPE*ZT	n.s.	D, S, S*ZT, GSPE*ZT, D*GSPE*ZT, D*S*GSPE*ZT
Choline	ZT	n.s.	GSPE, ZT	ZT	D, S, ZT, S*D*GSPE
Betaine	n.s	n.s.	n.s.	n.s.	D, S*D, S*GSPE*ZT
N,N-Dimethylglycine	n.s	n.s.	n.s.	n.s.	D, GSPE*ZT
Formate	n.s	ZT, GSPE*ZT	GSPE, ZT, GSPE*ZT	n.s.	D, S, GSPE, ZT, S*D, S*GSPE, S*ZT, D*GSPE, D*ZT, S*D*GSPE, D*GSPE*ZT
Cholate	n.s	n.s.	ZT, GSPE*ZT	n.s.	S*D, D*ZT, D*GSPE*ZT

^aGSPE and ZT effects and its interaction analyzed by 2-way ANOVA (p<0.05).

^bSexo, diet, GSPE and ZT effects and its interaction analyzed by 4-way ANOVA (p<0.05).

STD: standard diet; CAF: cafeteria diet; GSPE: grape seed proanthocyanidin; time of day; ZT0: VH or GSPE time administration (when light was turned on); ZT12:

VH or GSPE time administration (when light was turned off).

Table S2. Correlation between hypothalamus clock genes and serum melatonin hormone.

Serum hormone	Hypothalamus Clock genes	R Pearson	<i>p</i> value ^a
Melatonin	<i>Per2</i>	0.449	0.003
Melatonin	<i>Per1</i>	0.281	0.068
Melatonin	<i>Clock</i>	0.278	0.071
Melatonin	<i>Cry</i>	0.147	0.345
Melatonin	<i>RORα</i>	0.064	0.684
Melatonin	<i>Bmal1</i>	0.017	0.913

^aPearson's rank-order correlation coefficient (R).

^bThe correlations were significant when the P-value ($n = 8$).

Table S3. Correlation between hypothalamus clock genes and serum metabolites.

Serum Metabolites	Hypothalamus Clock genes	R Pearson	<i>p</i> value ^a
Tyrosine	<i>Per2</i>	-0.439	0.000
Alanine	<i>Per2</i>	-0.429	0.000
Leucine	<i>Per2</i>	-0.407	0.000
Alanine	<i>Per1</i>	-0.403	0.000
Isoleucine	<i>Per2</i>	-0.376	0.001
Glutamate	<i>Bmal1</i>	0.350	0.001
Valine	<i>Per2</i>	-0.347	0.002
Lysine	<i>Per1</i>	-0.329	0.003
Betaine	<i>Cry</i>	0.329	0.003
Tryptophan	<i>Per2</i>	-0.323	0.003
Tyrosine	<i>Per1</i>	-0.320	0.004
Tyrosine	<i>Bmal1</i>	0.313	0.005
Histidine	<i>Per2</i>	-0.312	0.005
Glycerol	<i>RORα</i>	-0.305	0.006
Lysine	<i>Per2</i>	-0.298	0.007
Choline	<i>Cry</i>	0.295	0.008
Glycine	<i>Cry</i>	0.295	0.008
Glucose	<i>Cry</i>	0.293	0.008
Choline	<i>Per2</i>	0.279	0.012
Histidine	<i>RORα</i>	0.266	0.017
Alanine	<i>Bmal1</i>	0.263	0.018
Betaine	<i>Bmal1</i>	0.260	0.020
Glycine	<i>RORα</i>	0.260	0.020
Phenylalanine	<i>RORα</i>	0.258	0.021
Phenylalanine	<i>Cry</i>	0.257	0.022
Free Cholesterol	<i>Bmal1</i>	-0.256	0.022
Phenylalanine	<i>Bmal1</i>	0.248	0.026

Phenylalanine	<i>Clock</i>	0.247	0.027
Diglycerides	<i>Bmal1</i>	-0.247	0.027
Glycerol	<i>Cry</i>	-0.246	0.028
Isoleucine	<i>Per1</i>	-0.243	0.030
Glutamate	<i>Per1</i>	-0.240	0.032
ARA+EPA	<i>Bmal1</i>	-0.240	0.032
Linoleic Acid	<i>Per2</i>	-0.240	0.032
Free Cholesterol	<i>Per1</i>	0.229	0.041
Leucine	<i>Per1</i>	-0.228	0.042
Free Cholesterol	<i>RORα</i>	0.228	0.042
Leucine	<i>RORα</i>	0.225	0.045
Isoleucine	<i>Bmal1</i>	0.217	0.053
Linoleic Acid	<i>Per1</i>	-0.217	0.053
DHA	<i>Per2</i>	-0.216	0.054
Choline	<i>Bmal1</i>	0.215	0.055
Acetate	<i>Clock</i>	0.214	0.056
Leucine	<i>Bmal1</i>	0.214	0.057
Glutamate	<i>Per2</i>	-0.214	0.057
Histidine	<i>Cry</i>	0.213	0.057
Betaine	<i>RORα</i>	0.213	0.058
Triglycerides	<i>Per1</i>	-0.211	0.060
Choline	<i>Per1</i>	0.211	0.060
Formate	<i>Per2</i>	-0.211	0.061
Glycine	<i>Clock</i>	0.207	0.065
Diglycerides	<i>Cry</i>	-0.205	0.069
Oleic Acid	<i>Cry</i>	-0.202	0.072
Histidine	<i>Bmal1</i>	0.200	0.075
Valine	<i>RORα</i>	0.199	0.077
Tyrosine	<i>RORα</i>	0.197	0.080
MUFAs	<i>Cry</i>	-0.197	0.081
Triglycerides	<i>Cry</i>	-0.196	0.082
Glycine	<i>Bmal1</i>	0.195	0.083
MUFAs	<i>Per1</i>	-0.194	0.085
MUFAs	<i>Per2</i>	-0.194	0.085
Glutamine	<i>Cry</i>	0.194	0.085
Total Phospholipids	<i>Bmal1</i>	-0.193	0.087
Oleic Acid	<i>Per1</i>	-0.192	0.088
Tyrosine	<i>Clock</i>	0.192	0.088
Pyruvate	<i>Clock</i>	-0.191	0.090
Triglycerides	<i>Per2</i>	-0.189	0.094
Lysine	<i>Cry</i>	-0.188	0.095
PUFAs	<i>Bmal1</i>	-0.185	0.100
Betaine	<i>Clock</i>	0.181	0.108
Formate	<i>Bmal1</i>	-0.180	0.110
Acetate	<i>Per2</i>	0.180	0.110
Glutamine	<i>Per2</i>	0.179	0.113

Creatine	<i>Cry</i>	0.178	0.114
Esterified Cholesterol	<i>RORα</i>	0.176	0.118
Cholesterol	<i>Bmal1</i>	-0.173	0.125
Valine	<i>Per1</i>	-0.171	0.130
Histidine	<i>Clock</i>	0.170	0.132
Formate	<i>Cry</i>	-0.168	0.136
Choline	<i>RORα</i>	0.168	0.136
Oleic Acid	<i>Per2</i>	-0.168	0.136
Linoleic Acid	<i>Cry</i>	-0.165	0.143
Valine	<i>Bmal1</i>	0.161	0.152
Glucose	<i>Clock</i>	0.159	0.158
Diglycerides	<i>Clock</i>	-0.157	0.165
Isoleucine	<i>RORα</i>	0.154	0.173
Creatine	<i>RORα</i>	0.154	0.174
Lactate	<i>Clock</i>	-0.149	0.188
Total Fatty Acids	<i>Per2</i>	-0.149	0.188
Total Phospholipids	<i>Cry</i>	-0.147	0.193
Cholesterol	<i>RORα</i>	0.147	0.194
N,N-Dimethylglycine	<i>Clock</i>	0.145	0.198
Glycerol	<i>Per1</i>	-0.145	0.201
Tryptophan	<i>RORα</i>	0.144	0.203
Lysine	<i>Bmal1</i>	0.143	0.204
DHA	<i>Per1</i>	-0.139	0.219
Glycerol	<i>Clock</i>	-0.138	0.221
ARA+EPA	<i>Clock</i>	-0.138	0.222
PUFAs	<i>Cry</i>	-0.135	0.231
Total Fatty Acids	<i>Cry</i>	-0.134	0.237
Esterified Cholesterol	<i>Per1</i>	0.133	0.238
Formate	<i>Clock</i>	-0.132	0.242
Cholesterol	<i>Per1</i>	0.130	0.251
Glutamine	<i>Bmal1</i>	0.128	0.256
ARA+EPA	<i>Per1</i>	0.125	0.269
Creatine	<i>Bmal1</i>	0.124	0.275
Cholesterol	<i>Per2</i>	-0.122	0.281
Phenylalanine	<i>Per2</i>	-0.122	0.283
Total Phospholipids	<i>Per2</i>	-0.121	0.284
Lysine	<i>RORα</i>	-0.121	0.286
ARA+EPA	<i>Cry</i>	-0.119	0.294
N,N-Dimethylglycine	<i>RORα</i>	0.114	0.314
Cholate	<i>Clock</i>	-0.113	0.317
Total Phospholipids	<i>Clock</i>	-0.109	0.334
Histidine	<i>Per1</i>	-0.106	0.350
Acetate	<i>Bmal1</i>	0.106	0.351
Glutamate	<i>Cry</i>	0.105	0.354
Acetate	<i>Per1</i>	0.103	0.361
Glutamine	<i>Per1</i>	0.103	0.365

Glucose	<i>RORα</i>	0.103	0.365
Total Fatty Acids	<i>Bmal1</i>	-0.101	0.374
Cholate	<i>Per1</i>	-0.100	0.379
Esterified Cholesterol	<i>Cry</i>	0.099	0.385
Glycine	<i>Per1</i>	0.098	0.388
Cholesterol	<i>Clock</i>	-0.096	0.395
PUFAs	<i>Clock</i>	-0.096	0.398
Lactate	<i>Cry</i>	-0.096	0.398
Glutamate	<i>Clock</i>	-0.095	0.404
Total Fatty Acids	<i>Per1</i>	-0.095	0.404
Tryptophan	<i>Cry</i>	0.094	0.407
Cholate	<i>Bmal1</i>	-0.093	0.411
Pyruvate	<i>Cry</i>	-0.092	0.417
Lactate	<i>Bmal1</i>	-0.091	0.422
Diglycerides	<i>RORα</i>	-0.090	0.430
Glutamine	<i>Clock</i>	0.088	0.436
Pyruvate	<i>Bmal1</i>	0.088	0.438
DHA	<i>Cry</i>	-0.085	0.453
DHA	<i>Bmal1</i>	-0.084	0.457
Diglycerides	<i>Per2</i>	-0.084	0.458
Esterified Cholesterol	<i>Clock</i>	-0.084	0.461
Creatine	<i>Per1</i>	0.083	0.462
Esterified Cholesterol	<i>Bmal1</i>	-0.082	0.472
Esterified Cholesterol	<i>Per2</i>	-0.082	0.472
Phenylalanine	<i>Per1</i>	0.081	0.475
Formate	<i>Per1</i>	-0.080	0.478
Cholate	<i>Cry</i>	-0.076	0.501
Pyruvate	<i>RORα</i>	-0.076	0.501
Alanine	<i>Cry</i>	-0.074	0.514
Diglycerides	<i>Per1</i>	-0.073	0.518
Oleic Acid	<i>RORα</i>	-0.073	0.522
N,N-Dimethylglycine	<i>Cry</i>	0.069	0.540
Free Cholesterol	<i>Cry</i>	0.067	0.553
Pyruvate	<i>Per1</i>	-0.067	0.556
Betaine	<i>Per1</i>	0.067	0.557
Formate	<i>RORα</i>	0.065	0.566
Glycerol	<i>Per2</i>	0.063	0.579
Triglycerides	<i>RORα</i>	-0.062	0.585
Lactate	<i>Per2</i>	0.062	0.587
Cholate	<i>Per2</i>	-0.060	0.598
Valine	<i>Clock</i>	0.059	0.601
PUFAs	<i>RORα</i>	-0.058	0.608
Tryptophan	<i>Bmal1</i>	-0.057	0.613
ARA+EPA	<i>RORα</i>	-0.055	0.627
MUFAs	<i>Clock</i>	-0.055	0.629
Acetate	<i>RORα</i>	-0.055	0.631

Leucine	<i>Clock</i>	0.054	0.635
Glucose	<i>Per1</i>	0.054	0.636
Glutamate	<i>RORα</i>	0.053	0.639
MUFAs	<i>RORα</i>	-0.052	0.647
MUFAs	<i>Bmal1</i>	-0.050	0.657
PUFAs	<i>Per2</i>	-0.049	0.666
N,N-Dimethylglycine	<i>Per2</i>	0.046	0.688
Valine	<i>Cry</i>	0.045	0.691
Glucose	<i>Bmal1</i>	-0.045	0.693
Free Cholesterol	<i>Clock</i>	-0.045	0.694
Linoleic Acid	<i>Clock</i>	-0.044	0.699
Cholesterol	<i>Cry</i>	0.043	0.706
Tryptophan	<i>Per1</i>	0.041	0.715
Lactate	<i>Per1</i>	0.041	0.718
Glucose	<i>Per2</i>	0.040	0.723
Oleic Acid	<i>Clock</i>	-0.039	0.728
Isoleucine	<i>Clock</i>	0.039	0.730
Pyruvate	<i>Per2</i>	-0.039	0.734
Tyrosine	<i>Cry</i>	0.038	0.735
Oleic Acid	<i>Bmal1</i>	-0.037	0.744
Leucine	<i>Cry</i>	0.036	0.752
DHA	<i>Clock</i>	0.034	0.761
Total Fatty Acids	<i>Clock</i>	-0.034	0.764
Betaine	<i>Per2</i>	-0.034	0.765
Choline	<i>Clock</i>	0.032	0.776
Triglycerides	<i>Clock</i>	-0.030	0.794
Lysine	<i>Clock</i>	-0.028	0.805
Glutamine	<i>RORα</i>	0.027	0.810
Total Phospholipids	<i>RORα</i>	-0.025	0.829
Alanine	<i>Clock</i>	0.023	0.839
Creatine	<i>Per2</i>	-0.023	0.839
Triglycerides	<i>Bmal1</i>	-0.023	0.842
ARA+EPA	<i>Per2</i>	0.021	0.854
Total Fatty Acids	<i>RORα</i>	0.021	0.856
Linoleic Acid	<i>Bmal1</i>	-0.020	0.860
Glycerol	<i>Bmal1</i>	-0.018	0.876
Free Cholesterol	<i>Per2</i>	-0.015	0.896
Creatine	<i>Clock</i>	0.014	0.905
Isoleucine	<i>Cry</i>	0.013	0.909
Linoleic Acid	<i>RORα</i>	-0.012	0.915
Glycine	<i>Per2</i>	0.012	0.915
Total Phospholipids	<i>Per1</i>	0.011	0.920
Tryptophan	<i>Clock</i>	0.009	0.933
Alanine	<i>RORα</i>	0.009	0.939
Acetate	<i>Cry</i>	-0.006	0.960
Lactate	<i>RORα</i>	0.005	0.967

N,N-Dimethylglycine	<i>Bmall</i>	-0.005	0.968
PUFAs	<i>Perl</i>	0.003	0.978
N,N-Dimethylglycine	<i>Perl</i>	-0.003	0.980
DHA	<i>RORα</i>	0.001	0.990
Cholate	<i>RORα</i>	0.001	0.992

^aPearson's rank-order correlation coefficient (R).

^bThe correlations were significant when the P-value was < 0.05. (*n* = 8)