Supplemental Information
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Calorie Restriction-like Effects of 30 Days of Resveratrol Supplementation on Energy Metabolism and Metabolic Profile in Obese Humans

Silvie Timmers, Ellen Konings, Lena Bilet, Riekelt H. Houtkooper, Tineke van de Weijer, Gijs H. Goossens, Joris Hoeks, Sophie van der Krieken, Dongryeol Ryu, Sander Kersten, Esther Moonen-Kornips, Matthijs K.C. Hesselink, Iris Kunz, Vera B. Schrauwen-Hinderling, Ellen Blaak, Johan Auwerx, and Patrick Schrauwen

Inventory

Figure S1 corresponds to figure 3

Table S1 corresponds to table 2

Table S2 corresponds to table 3

Table S3 corresponds to figure 2

Table S4 does not correspond to a figure/table but is a summary of our findings and adds to the comprehension of the conclusion of the manuscript.

FIGURE S1

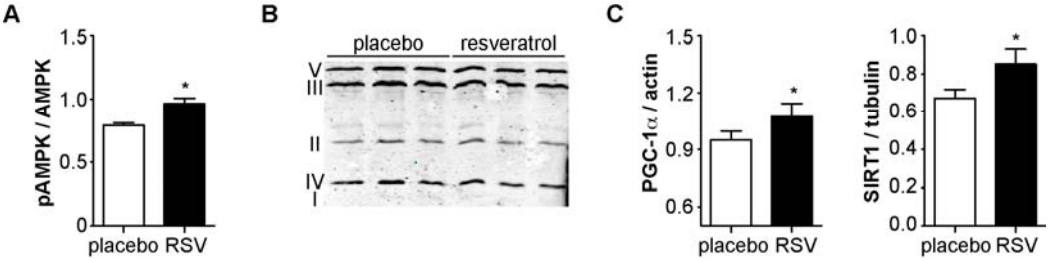

Figure S1. Western Blot Analysis

(A) Quantitative analysis of the effect of resveratrol (RSV) on the phosphorylation of AMPK on Thr^{172} of the α-subunit in vastus lateralis muscle. Data are presented as the ratio of pAMPK/AMPK (n=9).

(B) Representative western blot for the individual complexes of the electron transport chain (n=11, a subset of 3 subjects is shown).

(C) Quantitative analysis of the western blots of PGC-1α and SIRT1. Data are normalized for the loading control, actin for PGC-1α and tubulin for SIRT1. Values are given as means ± SEM (n=11 for PGC-1α, n=8 for SIRT1), * $p<0.05$.

Table S1. Blood Safety Parameters

	Placebo	Resveratrol	p-value
Erythrocytes (10^{12}/l)	4.85 ± 0.09	4.81 ± 0.09	0.52
Hemoglobin (mmol/l)	9.07 ± 0.17	8.95 ± 0.15	0.17
Hematocrit (%)	44.00 ± 1.00	43.00 ± 1.00	0.35
MCV (fl)	90.18 ± 1.73	89.73 ± 1.72	0.10
MCHC (mmol/l)	20.77 ± 0.10	20.81 ± 0.11	0.79
Trombocytes (10^9/l)	237.55 ± 11.88	228.90 ± 10.60	0.10
RDW (%)	13.25 ± 0.15	13.48 ± 0.26	0.40
Leucocytes (10^9/l)	7.03 ± 0.44	6.48 ± 0.39	0.03
PT (sec)	10.62 ± 0.06	10.58 ± 0.09	0.65
aPTT (sec)	29.00 ± 0.83	30.63 ± 1.88	0.48
INR	1.00 ± 0.01	1.00 ± 0.01	0.90
Sodium (mmol/l)	140.18 ± 0.35	139.64 ± 0.58	0.40
Potassium (mmol/l)	4.26 ± 0.07	4.18 ± 0.07	0.57
Phosphate (mmol/l)	0.88 ± 0.03	0.92 ± 0.04	0.08
Chloride (mmol/l)	106.36 ± 0.94	106.18 ± 0.60	0.83
Urea (mmol/l)	4.50 ± 0.24	4.37 ± 0.21	0.15
Creatinine (µmol/l)	76.10 ± 3.83	75.82 ± 3.28	0.83
Alkaline phosphatase (U/l)	79.00 ± 4.11	76.55 ± 3.81	0.30
Gamma GT (U/l)	29.60 ± 3.71	28.00 ± 2.61	0.44
ASAT (U/l)	19.00 ± 1.46	18.91 ± 1.11	0.93
ALAT (U/l)	31.91 ± 2.21	28.09 ± 1.54	0.02
Bilirubin (µmol/l)	14.25 ± 1.00	13.86 ± 1.07	0.42
Total protein (g/l)	66.55 ± 1.24	65.39 ± 0.80	0.14
Albumin (g/l)	38.02 ± 0.79	37.33 ± 0.55	0.18

On day 30, blood of the subjects was analyzed for several clinical chemistry, hematology and coagulation markers in order to confirm that resveratrol supplementation did not cause adverse effects. Values are given as means ± SEM (n=11).

Table S2. Time Course RQ and EE

		Placebo	Resveratrol		Placebo	Resveratrol	
Time (h:min)	**Activity**	**RQ**		**p-value**	**EE (MJ/d)**		**p-value**
-	**Sleeping metabolic rate**	0.87 ± 0.01	0.89 ± 0.01	0.09	8.09 ± 0.24	7.75 ± 0.23	0.007
9.00-10.00	**breakfast**	0.87 ± 0.01	0.89 ± 0.01	0.17	11.86 ± 0.57	11.11 ± 0.46	0.05
10.00-13.00	**stepping + snack**	0.91 ± 0.01	0.94 ± 0.01	0.02	14.40 ± 0.32	13.86 ± 0.32	0.07
13.00-15.30	**lunch**	0.89 ± 0.01	0.89 ± 0.01	0.44	11.75 ± 0.44	11.65 ± 0.47	0.44
15.30-18.00	**stepping + snack**	0.90 ± 0.01	0.93 ± 0.01	0.01	14.85 ± 0.31	14.55 ± 0.25	0.24
18.00-20.00	**diner**	0.89 ± 0.01	0.90 ± 0.01	0.35	12.62 ± 0.39	12.26 ± 0.43	0.16
20.00-24.00	**stepping + snack**	0.91 ± 0.01	0.92 ± 0.01	0.33	13.16 ± 0.21	13.49 ± 0.23	0.27
-	**Sleeping metabolic rate**	0.88 ± 0.01	0.90 ± 0.01	0.21	8.06 ± 0.22	7.90 ± 0.18	0.06

Detailed time course of RQ and energy expenditure (EE) over the last 24h of resveratrol or placebo supplementation. Values are given as means ± SEM (n=10).

Table S3. Gene Set Enrichment Analysis

Gene Sets that Are Upregulated by Resveratrol

NAME	SIZE	NES	FDR q-val
KEGG_DRUG METABOLISM - CYTOCHROME P450	65	1.9769608	0.055391833
REACT_OLFACTORY SIGNALING PATHWAY	326	1.883034	0.09561254
REACT_RESPIRATORY ELECTRON TRANSPORT, ATP SYNTHESIS BY CHEMIOSMOTIC COUPLING, AND HEAT PRODUCTION BY UNCOUPLING PROTEINS.	80	1.8434185	0.10389777
WIP_HS_ELECTRON_TRANSPORT_CHAIN	88	1.8122538	0.11256053
KEGG_OLFACTORY TRANSDUCTION	362	1.8074874	0.09481991
KEGG_NEUROACTIVE LIGAND-RECEPTOR INTERACTION	272	1.77137	0.11674452
KEGG_METABOLISM OF XENOBIOTICS BY CYTOCHROME P450	74	1.7553229	0.12136926
REACT_RESPIRATORY ELECTRON TRANSPORT	64	1.7295214	0.14394456
WIP_HS_METAPATHWAY_BIOTRANSFORMATION	168	1.7112943	0.15443122
KEGG_STEROID HORMONE BIOSYNTHESIS	49	1.6833845	0.18774375

Gene Sets that Are Downregulated by Resveratrol

NAME	SIZE	NES	FDR q-val
WIP_HS_T_CELL_RECEPTOR_SIGNALING_PATHWAY	133	-3.1916971	0
REACT_TCR SIGNALING	64	-3.005096	0
REACT_COSTIMULATION BY THE CD28 FAMILY	66	-2.9632292	0
REACT_GENERATION OF SECOND MESSENGER MOLECULES	33	-2.9366267	0
REACT_INTERFERON GAMMA SIGNALING	69	-2.915365	0
NCI_TCR_PATHWAY	63	-2.9115481	0
NCI_CXCR4_PATHWAY	100	-2.8939204	0
NCI_CD8TCRPATHWAY	52	-2.8382792	0
REACT_CYTOKINE SIGNALING IN IMMUNE SYSTEM	201	-2.8212645	0

NCI_PDGFRBPATHWAY	124	-2.8036184	0
REACT_PD-1 SIGNALING	25	-2.7586458	0
KEGG_LEISHMANIASIS	66	-2.6811383	0
NCI_TXA2PATHWAY	54	-2.6645982	0
REACT_PHOSPHORYLATION OF CD3 AND TCR ZETA CHAINS	22	-2.6398609	0
REACT_DOWNSTREAM TCR SIGNALING	47	-2.639546	0
KEGG_ANTIGEN PROCESSING AND PRESENTATION	67	-2.6350987	0
REACT_SIGNALING BY INTERLEUKINS	102	-2.6347778	0
REACT_INTERLEUKIN-3, 5 AND GM-CSF SIGNALING	48	-2.6297154	0
REACT_TRANSLOCATION OF ZAP-70 TO IMMUNOLOGICAL SYNAPSE	20	-2.615988	0
REACT_INTERFERON SIGNALING	106	-2.6144912	0
KEGG_VIRAL MYOCARDITIS	68	-2.610482	0
KEGG_OSTEOCLAST DIFFERENTIATION	124	-2.5870695	0
REACT_IMMUNOREGULATORY INTERACTIONS BETWEEN A LYMPHOID AND A NON-LYMPHOID CELL	67	-2.5784707	0
NCI_FCER1PATHWAY	58	-2.5762885	0
WIP_HS_IL-3_SIGNALING_PATHWAY	44	-2.5416484	0
BIOC_CTLA4PATHWAY	17	-2.5320008	0
REACT_INTERLEUKIN-2 SIGNALING	37	-2.5155833	0
REACT_GPVI-MEDIATED ACTIVATION CASCADE	32	-2.5145288	0
REACT_CELL SURFACE INTERACTIONS AT THE VASCULAR WALL	90	-2.504863	0
WIP_HS_IL-2_SIGNALING_PATHWAY	36	-2.501475	0
BIOC_HIVNEFPATHWAY	52	-2.4811022	0
NCI_IL8CXCR2_PATHWAY	33	-2.4680712	0
REACT_FORMATION OF PLATELET PLUG	256	-2.4612563	0
WIP_HS_B_CELL_RECEPTOR_SIGNALING_PATHWAY	93	-2.457269	0
KEGG_INFLUENZA A	165	-2.4498298	0
KEGG_FC GAMMA R-MEDIATED PHAGOCYTOSIS	90	-2.441085	0
KEGG_GRAFT-VERSUS-HOST DISEASE	38	-2.436977	0

NCI_IL12_2PATHWAY	62	-2.4258018	0
WIP_HS_TYPE_II_INTERFERON_SIGNALING_(IFNG)	36	-2.4174535	0
REACT_SIGNAL REGULATORY PROTEIN (SIRP) FAMILY INTERACTIONS	16	-2.4125907	0
WIP_HS_IL-4_SIGNALING_PATHWAY	46	-2.3988845	0
REACT_ADAPTIVE IMMUNITY SIGNALING	406	-2.3978803	0
NCI_TCPTP_PATHWAY	40	-2.3929656	0
KEGG_PHAGOSOME	142	-2.3906705	0
KEGG_ALLOGRAFT REJECTION	35	-2.390225	0
REACT_REGULATION OF SIGNALING BY CBL	22	-2.3880403	0
NCI_IL8CXCR1_PATHWAY	27	-2.3865337	0
REACT_INTERACTIONS OF THE IMMUNOGLOBULIN SUPERFAMILY (IGSF) MEMBER PROTEINS	49	-2.3851216	0
NCI_PI3KCIPATHWAY	47	-2.3776176	0
REACT_ANTIGEN PRESENTATION_ FOLDING, ASSEMBLY AND PEPTIDE LOADING OF CLASS I MHC	25	-2.3743033	0
WIP_HS_IL-7_SIGNALING_PATHWAY	26	-2.370715	0
WIP_HS_REGULATION_OF_TOLL-LIKE_RECEPTOR_SIGNALING_PATHWAY	141	-2.367435	0
KEGG_CHEMOKINE SIGNALING PATHWAY	182	-2.3660667	0
REACT_PLATELET ACTIVATION	238	-2.3499827	3.52E-05
KEGG_SHIGELLOSIS	61	-2.3481314	3.46E-05
KEGG_NATURAL KILLER CELL MEDIATED CYTOTOXICITY	127	-2.3426235	3.40E-05
KEGG_TUBERCULOSIS	170	-2.3404236	3.34E-05
BIOC_TCRPATHWAY	42	-2.3288894	3.28E-05
KEGG_SALMONELLA INFECTION	81	-2.3285587	3.22E-05
NCI_IFNGPATHWAY	42	-2.3255553	6.49E-05
NCI_GMCSF_PATHWAY	35	-2.323727	9.61E-05
WIP_HS_LEUKOCYTE_TARBASE	124	-2.3193054	9.46E-05
KEGG_CELL ADHESION MOLECULES (CAMS)	129	-2.3113422	1.25E-04
NCI_TNFPATHWAY	46	-2.3104668	1.23E-04
WIP_HS_IL-6_SIGNALING_PATHWAY	44	-2.3059502	1.21E-04

KEGG_APOPTOSIS	82	-2.304132	1.50E-04
REACT_RESPONSE TO ELEVATED PLATELET CYTOSOLIC CA2+	81	-2.3031735	1.47E-04
REACT_PLATELET ACTIVATION TRIGGERS	81	-2.3018825	1.45E-04
REACT_HEMOSTASIS	471	-2.3016825	1.43E-04
NCI_IL12_STAT4PATHWAY	32	-2.299623	1.41E-04
WIP_HS_IL-5_SIGNALING_PATHWAY	34	-2.2968433	1.39E-04
KEGG_T CELL RECEPTOR SIGNALING PATHWAY	106	-2.289124	1.37E-04
WIP_HS_TOLL-LIKE_RECEPTOR_SIGNALING_PATHWAY	100	-2.2786198	1.65E-04
WIP_HS_TCR_SIGNALING	22	-2.2754219	1.63E-04
NCI_INTEGRIN_A4B1_PATHWAY	32	-2.2745643	1.61E-04
KEGG_LEUKOCYTE TRANSENDOTHELIAL MIGRATION	112	-2.2721574	1.59E-04
NCI_IL2_STAT5PATHWAY	30	-2.2624764	1.57E-04
BIOC_RHOPATHWAY	30	-2.2533038	1.55E-04
BIOC_NKCELLSPATHWAY	20	-2.2500315	1.77E-04
NCI_NECTIN_PATHWAY	28	-2.2460837	1.75E-04
REACT_INTERLEUKIN RECEPTOR SHC SIGNALING	27	-2.2445626	1.73E-04
NCI_AVB3_OPN_PATHWAY	31	-2.2435489	1.96E-04
REACT_INTEGRIN CELL SURFACE INTERACTIONS	83	-2.2385252	1.94E-04
NCI_RAC1_PATHWAY	52	-2.2383287	1.92E-04
KEGG_PROTEIN PROCESSING IN ENDOPLASMIC RETICULUM	165	-2.2322483	1.89E-04
KEGG_TOXOPLASMOSIS	127	-2.224728	2.34E-04
NCI_THROMBIN_PAR1_PATHWAY	42	-2.22046	2.31E-04
NCI_VEGFR1_2_PATHWAY	68	-2.2173662	2.29E-04
KEGG_HERPES SIMPLEX INFECTION	176	-2.2170615	2.49E-04
BIOC_IL7PATHWAY	16	-2.2165563	2.46E-04
NCI_FASPATHWAY	38	-2.2125952	2.66E-04
BIOC_AMIPATHWAY	21	-2.2095914	2.63E-04
KEGG_NOD-LIKE RECEPTOR SIGNALING PATHWAY	58	-2.206224	2.82E-04
BIOC_ECMPATHWAY	22	-2.2058637	3.00E-04

BIOC_NFKBPATHWAY	22	-2.1963716	4.02E-04
REACT_CTLA4 INHIBITORY SIGNALING	21	-2.1920862	4.84E-04
KEGG_STAPHYLOCOCCUS AUREUS INFECTION	47	-2.1917832	4.79E-04
REACT_ACTIVATION OF CHAPERONES BY IRE1ALPHA	45	-2.1906514	4.74E-04
NCI_PTP1BPATHWAY	51	-2.186575	4.89E-04
KEGG_INTESTINAL IMMUNE NETWORK FOR IGA PRODUCTION	46	-2.1859972	4.85E-04
KEGG_TOLL-LIKE RECEPTOR SIGNALING PATHWAY	100	-2.1823518	5.00E-04
KEGG_TYPE I DIABETES MELLITUS	41	-2.1822712	4.95E-04
REACT_PLATELET DEGRANULATION	76	-2.1792736	4.90E-04
BIOC_CSKPATHWAY	21	-2.1780436	4.86E-04
WIP_HS_ADIPOCYTE_TARBASE	17	-2.1777108	4.81E-04
KEGG_B CELL RECEPTOR SIGNALING PATHWAY	73	-2.1770425	4.76E-04
BIOC_TNFR2PATHWAY	18	-2.1720812	5.47E-04
KEGG_PATHOGENIC ESCHERICHIA COLI INFECTION	53	-2.1687157	5.42E-04
NCI_IL2_1PATHWAY	55	-2.1679046	5.37E-04
KEGG_MEASLES	133	-2.163485	5.69E-04
KEGG_HEMATOPOIETIC CELL LINEAGE	80	-2.1606114	5.64E-04
WIP_HS_INTEGRIN_CELL_SURFACE_INTERACTIONS	15	-2.1601222	5.59E-04
NCI_AMB2_NEUTROPHILS_PATHWAY	41	-2.1547117	5.89E-04
BIOC_GLEEVECPATHWAY	22	-2.1534536	5.84E-04
NCI_IL27PATHWAY	26	-2.1517205	5.79E-04
REACT_INFLAMMASOMES	17	-2.1466086	6.25E-04
KEGG_MALARIA	49	-2.1440923	6.37E-04
KEGG_HTLV-I INFECTION	258	-2.143463	6.32E-04
NCI_INTEGRIN5_PATHWAY	17	-2.141736	6.27E-04
NCI_IL6_7PATHWAY	45	-2.1412413	6.21E-04
REACT_CD28 CO-STIMULATION	29	-2.1404538	6.33E-04
KEGG_REGULATION OF ACTIN CYTOSKELETON	208	-2.1323092	6.93E-04
BIOC_LAIRPATHWAY	16	-2.1301816	7.36E-04

NCI_HIVNEFPATHWAY	35	-2.1283083	7.47E-04
NCI_TOLL_ENDOGENOUS_PATHWAY	26	-2.1151865	8.21E-04
KEGG_PRIMARY IMMUNODEFICIENCY	35	-2.106903	9.41E-04
REACT_THE ROLE OF NEF IN HIV-1 REPLICATION AND DISEASE PATHOGENESIS	28	-2.100416	9.97E-04
REACT_ASSOCIATION OF TRIC_CCT WITH TARGET PROTEINS DURING BIOSYNTHESIS	29	-2.098923	9.89E-04
WIP_HS_KIT_RECEPTOR_SIGNALING_PATHWAY	56	-2.0973399	0.001026911
KEGG_ACUTE MYELOID LEUKEMIA	57	-2.0968208	0.001034313
WIP_HS_MAPK_SIGNALING_PATHWAY	160	-2.093754	0.001071812
BIOC_FASPATHWAY	27	-2.087879	0.001092478
BIOC_NO2IL12PATHWAY	15	-2.0841186	0.001129477
BIOC_CASPASEPATHWAY	21	-2.082723	0.001121049
BIOC_KERATINOCYTEPATHWAY	43	-2.07871	0.00117042
WIP_HS_INTERLEUKIN-3,_5_AND_GM-CSF_SIGNALING	16	-2.0713346	0.001339471
NCI_INTEGRIN2_PATHWAY	28	-2.0658157	0.001404977
WIP_HS_TNF-ALPHA-NF-KB_SIGNALING_PATHWAY	185	-2.0609932	0.001466814
KEGG_RHEUMATOID ARTHRITIS	87	-2.0600512	0.001470178
WIP_HS_INTERFERON_TYPE_I	28	-2.0600033	0.001459677
NCI_BCR_5PATHWAY	66	-2.0594187	0.001477417
NCI_IL4_2PATHWAY	60	-2.059172	0.001467013
REACT_SEMAPHORIN INTERACTIONS	65	-2.0533848	0.001567565
BIOC_IL2RBPATHWAY	34	-2.0504084	0.001611794
REACT_SIGNALING BY RHO GTPASES	121	-2.0455878	0.00165782
REACT_INTEGRIN ALPHAIIB BETA3 SIGNALING	27	-2.0452664	0.001646465
KEGG_BIOSYNTHESIS OF UNSATURATED FATTY ACIDS	21	-2.037153	0.001758598
REACT_CELL-EXTRACELLULAR MATRIX INTERACTIONS	18	-2.0304053	0.001896827
KEGG_OTHER GLYCAN DEGRADATION	17	-2.0297048	0.001897774
NCI_ANGIOPOIETINRECEPTOR_PATHWAY	48	-2.0268133	0.001965854
WIP_HS_RANKL-RANK_SIGNALING_PATHWAY	55	-2.0247173	0.001966095
NCI_IL1PATHWAY	32	-2.0234203	0.002030815

NCI_MYC_REPRESSPATHWAY	62	-2.0197527	0.002136653
REACT_RHO GTPASE CYCLE	121	-2.0185149	0.002162162
WIP_HS_CELL_SURFACE_INTERACTIONS_AT_THE_VASCULAR_WALL	36	-2.0149705	0.002214421
BIOC_EGFPATHWAY	26	-2.012483	0.002250164
BIOC_PTENPATHWAY	16	-2.0056415	0.002337149
NCI_ERBB1_RECEPTOR_PROXIMAL_PATHWAY	33	-2.0043683	0.002335085
REACT_PROTEIN FOLDING	54	-2.00279	0.002369915
BIOC_GSK3PATHWAY	26	-2.0026329	0.00238005
NCI_IL2_PI3KPATHWAY	37	-1.9945135	0.002588744
BIOC_P53HYPOXIAPATHWAY	20	-1.9921327	0.002634367
KEGG_CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)	101	-1.9900556	0.002702796
KEGG_BACTERIAL INVASION OF EPITHELIAL CELLS	70	-1.9867301	0.002746774
NCI_CMYB_PATHWAY	82	-1.9857032	0.002730127
REACT_P75NTR SIGNALS VIA NF-KB	16	-1.9785255	0.002988969
NCI_ECADHERIN_STABILIZATION_PATHWAY	40	-1.9779519	0.002983994
WIP_HS_EBV_LMP1_SIGNALING	22	-1.9777207	0.002978202
NCI_EPHA2_FWDPATHWAY	16	-1.977513	0.002960579
KEGG_SYSTEMIC LUPUS ERYTHEMATOSUS	116	-1.9758341	0.002966265
REACT_UNFOLDED PROTEIN RESPONSE	60	-1.9718972	0.003079111
REACT_NUCLEOTIDE-BINDING DOMAIN, LEUCINE RICH REPEAT CONTAINING RECEPTOR (NLR) SIGNALING PATHWAYS	51	-1.9718379	0.003061209
REACT_CHAPERONIN-MEDIATED PROTEIN FOLDING	49	-1.9717852	0.003054488
REACT_VIRAL DSRNA_TLR3_TRIF COMPLEX ACTIVATES RIP1	25	-1.9706969	0.003047578
NCI_GLYPICAN_1PATHWAY	27	-1.9691544	0.003063144
NCI_ENDOTHELINPATHWAY	62	-1.9676932	0.003090687
NCI_CASPASE_PATHWAY	49	-1.9672807	0.003084248
NCI_SYNDECAN_4_PATHWAY	31	-1.9656968	0.00310095
NCI_FAK_PATHWAY	57	-1.9642185	0.003172604
WIP_HS_FOCAL_ADHESION	184	-1.9635513	0.003199586

KEGG_ADHERENS JUNCTION	73	-1.9560665	0.00335038
NCI_ECADHERIN_NASCENTAJ_PATHWAY	38	-1.9552695	0.003376116
NCI_LYSOPHOSPHOLIPID_PATHWAY	65	-1.9501927	0.003631476
KEGG_LYSOSOME	122	-1.9470923	0.003708638
WIP_HS_APOPTOSIS_MODULATION_BY_HSP70	18	-1.9468039	0.003699987
BIOC_PDGFPATHWAY	26	-1.9449476	0.003809317
NCI_IL3_PATHWAY	24	-1.9431885	0.00386226
REACT_INTERFERON ALPHA_BETA SIGNALING	64	-1.9402235	0.003949524
KEGG_CHRONIC MYELOID LEUKEMIA	73	-1.9374653	0.004023213
NCI_LYMPHANGIOGENESIS_PATHWAY	24	-1.9281691	0.004251898
REACT_G ALPHA (12_13) SIGNALLING EVENTS	77	-1.9246988	0.004405566
REACT_FORMATION OF TUBULIN FOLDING INTERMEDIATES BY CCT_TRIC	21	-1.9246123	0.00438262
KEGG_PERTUSSIS	71	-1.9242588	0.004390685
BIOC_IL6PATHWAY	21	-1.9214544	0.004440921
WIP_HS_INTERFERON_ALPHA-BETA_SIGNALING	24	-1.9210826	0.004418148
BIOC_IL2PATHWAY	22	-1.917379	0.004557698
REACT_NEF-MEDIATES DOWN MODULATION OF CELL SURFACE RECEPTORS BY RECRUITING THEM TO CLATHRIN ADAPTERS	21	-1.9168459	0.004575906
KEGG_FC EPSILON RI SIGNALING PATHWAY	77	-1.9162374	0.004592581
BIOC_FCER1PATHWAY	37	-1.9153317	0.004579675
REACT_NEPHRIN INTERACTIONS	22	-1.9141845	0.004586953
WIP_HS_INFLAMMATORY_RESPONSE_PATHWAY	32	-1.9090894	0.00481389
NCI_CD40_PATHWAY	30	-1.9033732	0.005008108
NCI_EPHRINBREVPATHWAY	30	-1.9024303	0.005031189
NCI_P38ALPHABETAPATHWAY	30	-1.9004377	0.005113904
WIP_HS_EGF_RECEPTOR_SIGNALING_PATHWAY	143	-1.8966523	0.005195555
REACT_DOWN-STREAM SIGNAL TRANSDUCTION	36	-1.8949499	0.005247768
REACT_TRAF6 MEDIATED INDUCTION OF NFKB AND MAP KINASES UPON TLR7_8 OR 9 ACTIVATION	73	-1.8872705	0.005669379
REACT_PLATELET SENSITIZATION BY LDL	15	-1.8831625	0.00586245

BIOC_TIDPATHWAY	19	-1.8829594	0.00585268
REACT_P75 NTR RECEPTOR-MEDIATED SIGNALLING	86	-1.8829311	0.00582481
WIP_HS_MUSCLE_CELL_TARBASE	328	-1.8811718	0.005936944
NCI_EPOPATHWAY	33	-1.8811679	0.00590894
NCI_TRAIL_PATHWAY	28	-1.8807642	0.005890639
NCI_CERAMIDE_PATHWAY	45	-1.8801349	0.005880735
REACT_CD28 DEPENDENT PI3K_AKT SIGNALING	19	-1.8781047	0.005975447
WIP_HS_APOPTOSIS	83	-1.8780979	0.005947783
NCI_CD8TCRDOWNSTREAMPATHWAY	67	-1.8759261	0.006069485
WIP_HS_G13_SIGNALING_PATHWAY	37	-1.8706902	0.006389288
REACT_PREFOLDIN MEDIATED TRANSFER OF SUBSTRATE TO CCT_TRIC	27	-1.8702604	0.006377927
WIP_HS_INTEGRIN-MEDIATED_CELL_ADHESION	99	-1.8698312	0.006375916
NCI_FGF_PATHWAY	54	-1.8683932	0.006410027
WIP_HS_NOD_PATHWAY	39	-1.866042	0.006499623
NCI_IL23PATHWAY	37	-1.8649479	0.006569438
WIP_HS_SQUAMOUS_CELL_TARBASE	117	-1.8642224	0.006576047
REACT_TAK1 ACTIVATES NFKB BY PHOSPHORYLATION AND ACTIVATION OF IKKS COMPLEX	22	-1.8636843	0.006573375
KEGG_FOCAL ADHESION	198	-1.8626368	0.006642122
NCI_AP1_PATHWAY	69	-1.8617864	0.006683086
WIP_HS_IL-1_PATHWAY	53	-1.8615816	0.006653774
REACT_TOLL LIKE RECEPTOR 3 (TLR3) CASCADE	67	-1.860271	0.006728928
KEGG_RENAL CELL CARCINOMA	70	-1.8601748	0.006699672
NCI_INTEGRIN_CS_PATHWAY	26	-1.8574877	0.006853806
REACT_SEMA4D IN SEMAPHORIN SIGNALING	28	-1.8569036	0.006858972
BIOC_GCRPATHWAY	17	-1.8511567	0.007214225
NCI_HDAC_CLASSI_PATHWAY	65	-1.8505273	0.007251964
WIP_HS_SIGNALING_OF_HEPATOCYTE_GROWTH_FACTOR_RECEPTOR	33	-1.8479131	0.007381756
REACT_MYD88 DEPENDENT CASCADE INITIATED ON ENDOSOME	74	-1.8473257	0.007400869

NCI_ERBB2ERBB3PATHWAY	43	-1.8446246	0.007595204
REACT_CLATHRIN DERIVED VESICLE BUDDING	60	-1.8427671	0.007696442
REACT_TOLL LIKE RECEPTOR 7_8 (TLR7_8) CASCADE	74	-1.8420358	0.007755715
KEGG_AUTOIMMUNE THYROID DISEASE	49	-1.8403913	0.007855522
WIP_HS_FAS_PATHWAY_AND_STRESS_INDUCTION_OF_HSP_REGULATION	38	-1.8394657	0.007904647
NCI_CXCR3PATHWAY	43	-1.8386271	0.007897158
BIOC_CERAMIDEPATHWAY	21	-1.8383093	0.007881178
BIOC_CHEMICALPATHWAY	20	-1.8375019	0.007938497
REACT_SIGNALING BY EGFR	51	-1.8334502	0.008200912
BIOC_TOLLPATHWAY	32	-1.831022	0.00837821
BIOC_METPATHWAY	35	-1.8293363	0.008481098
NCI_NFKAPPABATYPICALPATHWAY	17	-1.8291018	0.008487571
BIOC_CCR5PATHWAY	17	-1.8283324	0.008485848
NCI_ILK_PATHWAY	44	-1.8273059	0.008522934
KEGG_NON-SMALL CELL LUNG CANCER	54	-1.8256892	0.008672221
REACT_TRANS-GOLGI NETWORK VESICLE BUDDING	60	-1.825211	0.008662016
BIOC_CXCR4PATHWAY	23	-1.8247247	0.008659306
NCI_P75NTRPATHWAY	66	-1.823523	0.008752542
KEGG_NEUROTROPHIN SIGNALING PATHWAY	126	-1.8230648	0.008764952
WIP_HS_INSULIN_SIGNALING	160	-1.8215282	0.008853972
BIOC_NKTPATHWAY	28	-1.8185842	0.009043474
REACT_COOPERATION OF PREFOLDIN AND TRIC_CCT IN ACTIN AND TUBULIN FOLDING	28	-1.8184261	0.009008421
REACT_SIGNALLING BY NGF	222	-1.8174424	0.009035066
BIOC_ACTINYPATHWAY	18	-1.8167003	0.009054083
REACT_TOLL LIKE RECEPTOR 9 (TLR9) CASCADE	76	-1.8165551	0.009019394
WIP_HS_EICOSANOID_SYNTHESIS	19	-1.8153262	0.009083658
KEGG_PANCREATIC CANCER	70	-1.814876	0.009079379
NCI_HDAC_CLASSIII_PATHWAY	36	-1.8122996	0.009247158
BIOC_CALCINEURINPATHWAY	18	-1.8103873	0.009341

KEGG_AFRICAN TRYPANOSOMIASIS	34	-1.8101227	0.009374057
WIP_HS_EPO_RECEPTOR_SIGNALING	26	-1.808065	0.009520139
REACT_TRIGLYCERIDE BIOSYNTHESIS	33	-1.7988191	0.010253353
KEGG_COLORECTAL CANCER	62	-1.7947834	0.010588672
NCI_NFAT_TFPATHWAY	48	-1.7945398	0.010556559
BIOC_MAPKPATHWAY	84	-1.792605	0.010657342
REACT_MEMBRANE TRAFFICKING	145	-1.7906474	0.010846768
NCI_RHOA_REG_PATHWAY	43	-1.7895484	0.010865686
REACT_PLATELET AGGREGATION (PLUG FORMATION)	34	-1.786117	0.011204754
BIOC_TPOPATHWAY	22	-1.7855176	0.011221645
BIOC_DEATHPATHWAY	32	-1.7779057	0.011974087
KEGG_CARBOHYDRATE DIGESTION AND ABSORPTION	38	-1.7734265	0.012349037
NCI_ERBB1_DOWNSTREAM_PATHWAY	106	-1.7707475	0.012598489
WIP_HS_LYMPHOCYTE_TARBASE	407	-1.770456	0.012567803
WIP_HS_TGF_BETA_SIGNALING_PATHWAY_NETPATH	117	-1.7638924	0.013362426
NCI_PDGFRAPATHWAY	21	-1.7587968	0.013894224
NCI_HIF1APATHWAY	18	-1.7581452	0.013917537
NCI_ER_NONGENOMIC_PATHWAY	39	-1.7579918	0.01388214
REACT_SMOOTH MUSCLE CONTRACTION	24	-1.7574564	0.013904452
KEGG_SPHINGOLIPID METABOLISM	40	-1.7570717	0.013904913
NCI_AVB3_INTEGRIN_PATHWAY	73	-1.7557452	0.013980775
NCI_ALPHASYNUCLEIN_PATHWAY	32	-1.7547078	0.014057365
REACT_TRAF6 MEDIATED INDUCTION OF PROINFLAMMATORY CYTOKINES	62	-1.7539696	0.014121322
NCI_THROMBIN_PAR4_PATHWAY	15	-1.7533691	0.014135659
BIOC_TNFR1PATHWAY	28	-1.7531135	0.014128104
BIOC_TH1TH2PATHWAY	17	-1.7511908	0.014305572
REACT_SEMA4D INDUCED CELL MIGRATION AND GROWTH-CONE COLLAPSE	24	-1.7510194	0.014284329
WIP_HS_HYPERTROPHY_MODEL	20	-1.7497274	0.014500368
NCI_KITPATHWAY	52	-1.7475505	0.014736447

NCI_RAC1_REG_PATHWAY	38	-1.7463287	0.014809483
NCI_VEGFR1_PATHWAY	28	-1.745497	0.014873933
KEGG_PHOSPHATIDYLINOSITOL SIGNALING SYSTEM	78	-1.7431507	0.015185053
BIOC_MTORPATHWAY	21	-1.7401983	0.015515841
WIP_HS_RIG-I-MDA5_MEDIATED_INDUCTION_OF_IFN-ALPHA-BETA_PATHWAYS	21	-1.7354453	0.016160844
WIP_HS_EPITHELIUM_TARBASE	269	-1.7301913	0.016720043
BIOC_PAR1PATHWAY	19	-1.7265502	0.017169883
REACT_GOLGI ASSOCIATED VESICLE BIOGENESIS	53	-1.7227432	0.017502205
BIOC_IL12PATHWAY	20	-1.7191168	0.01811797
KEGG_PATHWAYS IN CANCER	324	-1.716018	0.018533086
BIOC_BIOPEPTIDESPATHWAY	37	-1.7141166	0.018775648
BIOC_TALL1PATHWAY	15	-1.7121788	0.019059075
REACT_SPHINGOLIPID METABOLISM	25	-1.7065523	0.019786797

Table S4. Comparison of Calorie Restriction with Resveratrol

	Calorie restriction		Resveratrol	
	Rodents	Humans	Rodents	Humans
Body weight	↓	↓	≠↓	≠
Insulin	↓	↓	↓	↓
Energy expenditure				
Total	≠↓	↓	↑	≠
Postprandial	↓	↓	?	↓
Sendentary/Sleep	↓	↓	?	↓
Fat mass and fat-free mass	↓	↓	↓	?
Liver fat	↓	↓	↓	↓
Intramyocellular lipids	↓	↓	↓	↑
Insulin sensitivity	↑	↑	↑	↑
Inflammation markers	↓	↓	↓	↓
Mitochondrial efficiency	↑	↑	↑	↑

Comparison of chronic calorie restriction in rodents and overweight humans to the effects of 30 days of resveratrol supplementation in obese humans on markers of ageing. To make the comparison complete, we also included the effects of resveratrol in rodents. The measured effects of calorie restriction and resveratrol on the above markers of aging were obtained from references that are included in the supplemental references.

↓ decrease, ↑ increase, ≠ similar, ? currently unknown

Supplemental Experimental Procedures

Analysis of resveratrol and dihydroresveratrol

To check compliance, the analytics of resveratrol (original and metabolites) were processed in a blinded fashion by a liquid chromatography mass spectrometry (LC-MS) system in both the resveratrol- and placebo-supplemented period by DSM Nutritional Products, Ltd. Kaiseraugst, Switzerland. Plasma collected on day 0, 7, 14, 21, 30 and during the stay in the respiration chamber (day 29) was processed for the determination of "free" trans-resveratrol and dihydroresveratrol (aglycone) and "total" trans-resveratrol and dihydroresveratrol (aglycone + glucuronide conjugates). After addition of an internal standard and liquid-liquid extraction ("free" analyte) or pre-digesting by β-glucuronidase followed by liquid-liquid extraction ("total" analyte), the samples were injected in a C18 column. Detection was performed using MS in the SIM mode.

Plasma biochemistry

In the morning of day 30 -after a standardized overnight fast for 12 hours- and during the postprandial microdialysis test, blood samples were withdrawn for the determination of plasma glucose, insulin, non-esterified fatty acids (NEFA) and triglycerides (TG) levels as described (Phielix et al., 2008). Glycerol and lactate levels during the microdialysis test were analyzed enzymatically on a Cobas Mira automated spectrophotometer. The concentration of leptin and adiponectin in plasma were analyzed by radioimmunoassay using commercial kits (Millipore Corporation, Billerica, MA, USA) in accordance with the manufacturer's instructions. High-sensitivity C-reactive protein was measured

with a commercially available kit (Horiba ABX, Montpellier, France). Plasma inflammatory markers (IL-1b, IL-6, IL-8 and TNF-α) were measured with a commercially available Multi Spot ELISA kit (Meso Scale Discovery, Gaithersburg, MD, USA).

Molecular and protein expression

Mitochondrial DNA (mtDNA) copy number, the ratio of NADH dehydrogenase subunit one (ND1) to lipoprotein lipase (LPL) (mtDNA/nuclear DNA) was determined as described (Phielix et al., 2008).

Oxidative phosphorylation (OXPHOS), SIRT1, and PGC-1α protein levels were measured in whole muscle by western blotting as an additional reflection of mitochondrial density, as described (Timmers et al., 2011). OXPHOS proteins were detected using a monoclonal antibody cocktail of five monoclonal antibodies directed against the different OXPHOS complexes (MS601, MitoSciences, Eugene, OR). SIRT1 was detected using a polyclonal antibody (#2493 Cell Signaling, Technology, Inc., Beverly MA, USA). PGC1α was measured using a polyclonal antibody (Santa Cruz, Heidelberg, Germany). Total and the phosphorylated subunit α of AMPK (#2531 and #2532 Cell Signalling Technology, Inc., Beverly MA, USA) were detected as described (Feige et al., 2008).

Postprandial substrate utilization and tissue lipolysis

In 10 subjects, the lipolytic effects of resveratrol in adipose tissue and skeletal muscle were successfully determined by microdialysis, essentially according to (Goossens et al., 2004).

To study the response of tissue lipolysis on a mixed meal, subjects were instructed to consume a liquid meal within 5 minutes. The total energy content of the shake was 2.6 MJ and consisted of 32.6 En% carbohydrates, 61.2 En% fat and 6.3 En% protein. Blood samples were taken before ingestion of the liquid test meal (t= -30 and 0 min) and for 6h after meal ingestion at t= 30, 60, 90, 120, 180, 240, 300 and 360 min to determine glycerol, glucose, pyruvate and lactate in the plasma. Microdialysate was collected from the probes in 30 min fractions during the baseline period and during the early postprandial period (0-120 min) and at 1h fractions during the last 4h postprandially (120-360 min) to determine glycerol, glucose, pyruvate and lactate levels. Microdialysates were measured by Pronexus Analytical AB (Stockholm, Sweden) on a CMA 600 Microdialysis Analyzer (CMA Microdialysis AB, Solna, Sweden). Energy expenditure and substrate utilization were measured, before and for 6h after ingestion of the liquid test meal, using a ventilated hood system that analyses gasses every 15 seconds (Omnical, Maastricht University, The Netherlands) (Schoffelen et al., 1997). Metabolic rate was calculated from VO_2 (L/min) and VCO_2 (L/min) according to the equations of Frayn (Frayn, 1983). Nitrogen excretion was calculated based on the assumption that protein oxidation represents ~15% of total energy expenditure. Energy expenditure was calculated using the formula of Weir (Weir, 1949).

Microarray

Total RNA was prepared from human muscle using Trizol reagent (Invitrogen, Breda, The Netherlands), treated with DNase and purified on columns using

the RNeasy Mini Kit (Qiagen, Venlo, The Netherlands). RNA quantity and quality was assessed spectrophotometrically (ND-1000, NanoDrop Technologies, Wilmington, USA) and with 6000 Nano chips (Bioanalyzer 2100; Agilent, Amstelveen, The Netherlands), respectively.

The Ambion WT Expression kit (Life Technologies, P/N 4411974) and the Affymetrix GeneChip WT Terminal Labeling kit (Affymetrix, Santa Clara, CA; P/N 900671) were used for the preparation of labeled cDNA from 100ng of total RNA. Labeled samples were hybridized on Affymetrix GeneChip human Gene 1.1 ST arrays, provided in plate format. Hybridization, washing and scanning of the array plates was performed on an Affymetrix GeneTitan Instrument, according to the manufacturer's recommendations. Detailed protocols can be found in the Affymetrix WT Terminal Labeling and Hybridization User Manual (P/N 702808 revision 4), and are also available upon request.

Quality control of the datasets obtained from the scanned Affymetrix arrays was performed using Bioconductor (Gentleman et al., 2004) packages integrated in an on-line pipeline (Lin et al., 2011). Various advanced quality metrics, diagnostic plots, pseudo-images and classification methods were applied for selection of ascertain only excellent quality arrays were used in the subsequent analyses (Heber and Sick, 2006). An extensive description of the applied criteria is available upon request.

The more than 803000 probes on the Human Gene 1.1 ST array were redefined according to Dai et al. (Dai et al., 2005) utilizing current genome information, yielding 19738 unique genes. Probes were reorganized based on the Entrez Gene database, build 37, version 2 (remapped CDF v14).

Normalized expression estimates were obtained from the raw intensity values using the robust multiarray analysis (RMA) preprocessing algorithm (Irizarry et al., 2003). All genes represented on the array were considered for the unbiased Gene Set Enrichment Analysis (GSEA) (Subramanian et al., 2005). GSEA was run using 1000 permutations per gene set.

Unsupervised hierarchical clustering was performed using complete linkage and Pearson rank correlation distance on the normalized transcripts using software implemented in Genepattern (http://www.broadinstitute.org/cancer/software/genepattern/) (de Hoon et al., 2004; Reich et al., 2006). The z-score was calculated by subtracting the mean expression value for each transcript from each of the values and then dividing the resulting values by the standard deviation. Color in the heat-maps reflects the relative transcript abundance level with red being higher and blue lower than the mean transcript abundance value. Transcript ordering is determined as in hierarchical clustering using the distance function 1-correlation. Mouse microarray data (Lagouge et al., 2006) were reanalysed using KEGG pathway gene sets in the GSEA software (Broad institute) (Subramanian et al., 2005).

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