



Supplementary Figure S1. Different eCbome tone in the jejunum and the ileum of ob/ob and db/db mice. **(A)** Concentrations of the eCbome-related mediators in the jejunum and ileum, respectively (fmol/mg wet tissue weight), measured by HPLC-MS/MS. **(B)** mRNA expression of receptors and metabolic enzymes for 2-monoacylglycerols and N-acylethanolamines in the jejunum and the ileum, respectively, measured by qPCR-based TaqMan Open Array. Data are presented as the mean \pm S.E.M of n=7-10. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.005$, **** $P \leq 0.001$. For mRNA expression, relative units were calculated versus the mean of the CT ob mice values set at 1. Data were analyzed by one-way ANOVA followed by Tukey's post hoc test. Abbreviations: see supplementary Table S1 and Table S2.

Supplementary Table S1. Endocannabinoid and related lipid mediator abbreviations.

Symbol	Endocannabinoids name
2-AG	1(3)- and 2-arachidonoyl-glycerol
AEA	<i>N</i> -arachidonoyl-ethanolamine
DHEA	<i>N</i> -docosahexanoyl-ethanolamine
2-DHG	1(3)- and 2-docosahexaenoyl-glycerol
DPA	docosapentaenoic acid (n-3)
2-DPG	1(3)- and 2-docospentaenoyl-glycerol (n-3)
EPEA	<i>N</i> -eicosapentanoyl-ethanolamine
EPA	eicosapentaenoic acid
2-EPG	2-eicosapentaenoyl-glycerol
15-HEPE	15-hydroxyeicosapentaenoic acid
18-HEPE	18-hydroxyeicosapentaenoic acid
13-HODE	13-hydroxyoctadecadienoic acid
13-HODE-G	13-hydroxyoctadecadienoyl-glycerol
11-HETE	11-hydroxyeicosatetraenoic acid
13(S)-HOTre	13S-hydroxy-9Z,11E,15Z-octadecatrienoic acid
12-HEPE	12-hydroxyeicosapentaenoic acid
15-HEPE	15-hydroxyeicosapentaenoic acid
14-HDHA	14-hydroxydocosahexaenoic acid
17-HDHA	14-hydroxydocosahexaenoic acid
LA	Linoleic acid
LEA	<i>N</i> -linoleoyl-ethanolamine
2-LG	1(3)- and 2-linoleoyl-glycerol
SEA	<i>N</i> -stearoyl-ethanolamine
OEA	<i>N</i> -oleoyl-ethanolamine
2-OG	1(3)- and 2-oleoyl-glycerol
PEA	<i>N</i> -palmitoyl-ethanolamine
2-PG	2-palmitoyl-glycerol
NAGly	<i>N</i> -arachidonoyl glycine
PGD₂	Prostaglandin D ₂
PGE₂	Prostaglandin E ₂

Supplementary Table S2. List of the genes analyzed by qPCR based TaqMan Open Array and their function.

Gene symbol	Gene name	Function
<i>Cacna1b</i>	calcium channel, voltage-dependent, T type, alpha 1B subunit	receptor
<i>Cacna1h</i>	calcium channel, voltage-dependent, T type, alpha 1H subunit	receptor
<i>Cnr1</i>	cannabinoid receptor 1	receptor
<i>Cnr2</i>	cannabinoid receptor 2	receptor
<i>Gpr119</i>	G protein-coupled receptor 119	receptor
<i>Gpr18</i>	G protein-coupled receptor 18	receptor
<i>Gpr55</i>	G protein-coupled receptor 55	receptor
<i>Ppara</i>	peroxisome proliferator activated receptor alpha	receptor
<i>Pparg</i>	peroxisome proliferator activated receptor gamma	receptor
<i>Ptgfr</i>	prostaglandin F receptor	receptor
<i>Trpv1</i>	transient receptor potential cation channel, subfamily V, member 1	ligand-activated channel
<i>Trpv2</i>	transient receptor potential cation channel, subfamily V, member 2	ligand-activated channel
<i>Trpv4</i>	transient receptor potential cation channel, subfamily V, member 4	ligand-activated channel
<i>Abhd4</i>	abhydrolase domain containing 4	anabolic enzyme for NAEs
<i>Akr1b3</i>	aldo-keto reductase family 1, member B3 (aldose reductase)	anabolic enzyme for prostamides, catabolic enzyme for AEA and 2-AG
<i>Fam213b</i>	family with sequence similarity 213, member B	anabolic enzyme for prostamides, catabolic enzyme for AEA and 2-AG
<i>Gde1</i>	glycerophosphodiester phosphodiesterase 1	anabolic enzyme for NAEs
<i>Gdgd1</i>	glycerophosphodiester phosphodiesterase domain containing 1	anabolic enzyme for NAEs
<i>Hrasls5</i>	HRAS-like suppressor family, member 5	anabolic enzyme for NAEs
<i>Inpp5d</i>	inositol polyphosphate-5-phosphatase D	anabolic enzyme for NAEs
<i>Napepld</i>	N-acyl phosphatidylethanolamine-specific phospholipase D-like enzyme	anabolic enzyme for NAEs
<i>Pla2g5</i>	phospholipase A2, group V	AA-releasing enzyme possibly involved in phospholipid remodeling and hence biosynthesis of eCB precursors
<i>Ptgs2</i>	prostaglandin-endoperoxide synthase 2	anabolic enzyme for prostamides, catabolic enzyme for AEA and 2-AG
<i>Ptpn22</i>	protein tyrosine phosphatase, non-receptor type 22 (lymphoid)	anabolic enzyme for AEA
<i>Ptges</i>	prostaglandin E synthase	anabolic enzyme for prostamides, catabolic enzyme for AEA and 2-AG
<i>Comt</i>	catechol-O-methyltransferase	catabolic enzyme for N-acyl-dopamines
<i>Faah</i>	fatty acid amide hydrolase	catabolic enzyme for NAEs, primary fatty acid amides, N-acyl-taurines and N-acyl-glycines
<i>Naaa</i>	N-acylethanolamine acid amidase	catabolic enzyme for saturated NAEs
<i>Pam</i>	peptidylglycine alpha-amidating monooxygenase	anabolic enzyme for primary fatty acid amides, catabolic enzyme for N-acyl-glycines
<i>Dagla</i>	diacylglycerol lipase, alpha	anabolic enzyme for 2-acylglycerols

<i>Daglb</i>	diacylglycerol lipase, beta	anabolic enzyme for 2-acylglycerols
<i>Dgke</i>	diacylglycerol kinase, epsilon	anabolic/catabolic enzyme for 2-acylglycerols
<i>Enpp2</i>	ectonucleotide pyrophosphatase/phosphodiesterase 2	autotaxin- a LysoPLD: produces LPA.
<i>Pla1a</i>	phospholipase A1 member A	anabolic enzyme for 2-acylglycerols
<i>Plcb1</i>	phospholipase C, beta 1	anabolic enzyme for 2-acylglycerols
<i>Abhd12</i>	abhydrolase domain containing 12	catabolic enzyme for monoacylglycerols
<i>Abhd16a</i>	abhydrolase domain containing 16	catabolic enzyme for monoacylglycerols
<i>Abhd6</i>	abhydrolase domain containing 6	catabolic enzyme for monoacylglycerols
<i>Agk</i>	acylglycerol kinase	catabolic enzyme for monoacylglycerols
<i>Alox12</i>	arachidonate 12-lipoxygenase	catabolic enzyme for AEA and 2-AG
<i>Alox15</i>	arachidonate 15-lipoxygenase	catabolic enzyme for AEA and 2-AG
<i>Ces1d</i>	carboxylesterase 1D	catabolic enzyme for monoacylglycerols
<i>Ces2h</i>	carboxylesterase 2H	catabolic enzyme for monoacylglycerols
<i>Mgl1 (Magl)</i>	monoglyceride lipase	catabolic enzyme for monoacylglycerols
<i>Mogat1</i>	monoacylglycerol O-acyltransferase 1	catabolic enzyme for monoacylglycerols
<i>Ppt1</i>	palmitoyl-protein thioesterase 1	catabolic enzyme for 2-AG
<i>Gapdh</i>	glyceraldehyde-3-phosphate dehydrogenase	reference gene
<i>Hprt</i>	hypoxanthine guanine phosphoribosyl transferase	reference gene
<i>Rps13</i>	ribosomal protein S13	reference gene
<i>Tbp</i>	TATA box binding protein	reference gene

Supplementary Table S3. qPCR primer sequences for the targeted mouse genes.

Gene symbol	Gene name	Forward Primer sequence (5'-3')	Reverse Primer sequence (5'-3')
<i>Rorgt2</i>	Retinoid orphan receptor gamma t	GAAATGTTGTTGACCCCTCT	TCATACCCAAACCCCATAAAAC
<i>Il17a</i>	Interleukin 17a	AAGGCCCTCAGACTACCTCAA	TTCCAGATCACAGAGGGATATCTA
<i>Rpl19</i>	Ribosomal Protein L19	GAAGGTCAAAGGAATGTGTTCA	CCTTGTCTGCCTTCAGCTTGT