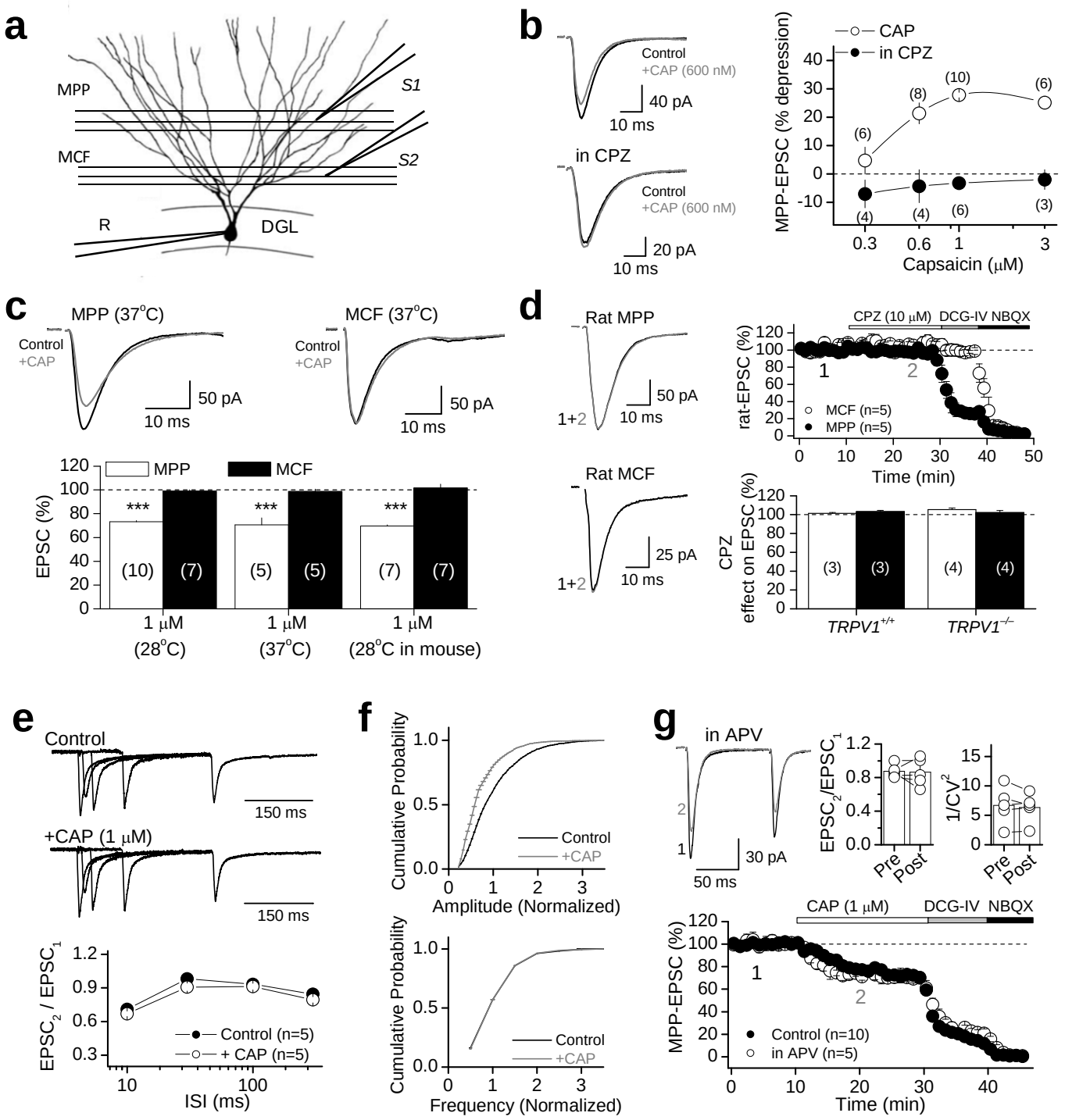
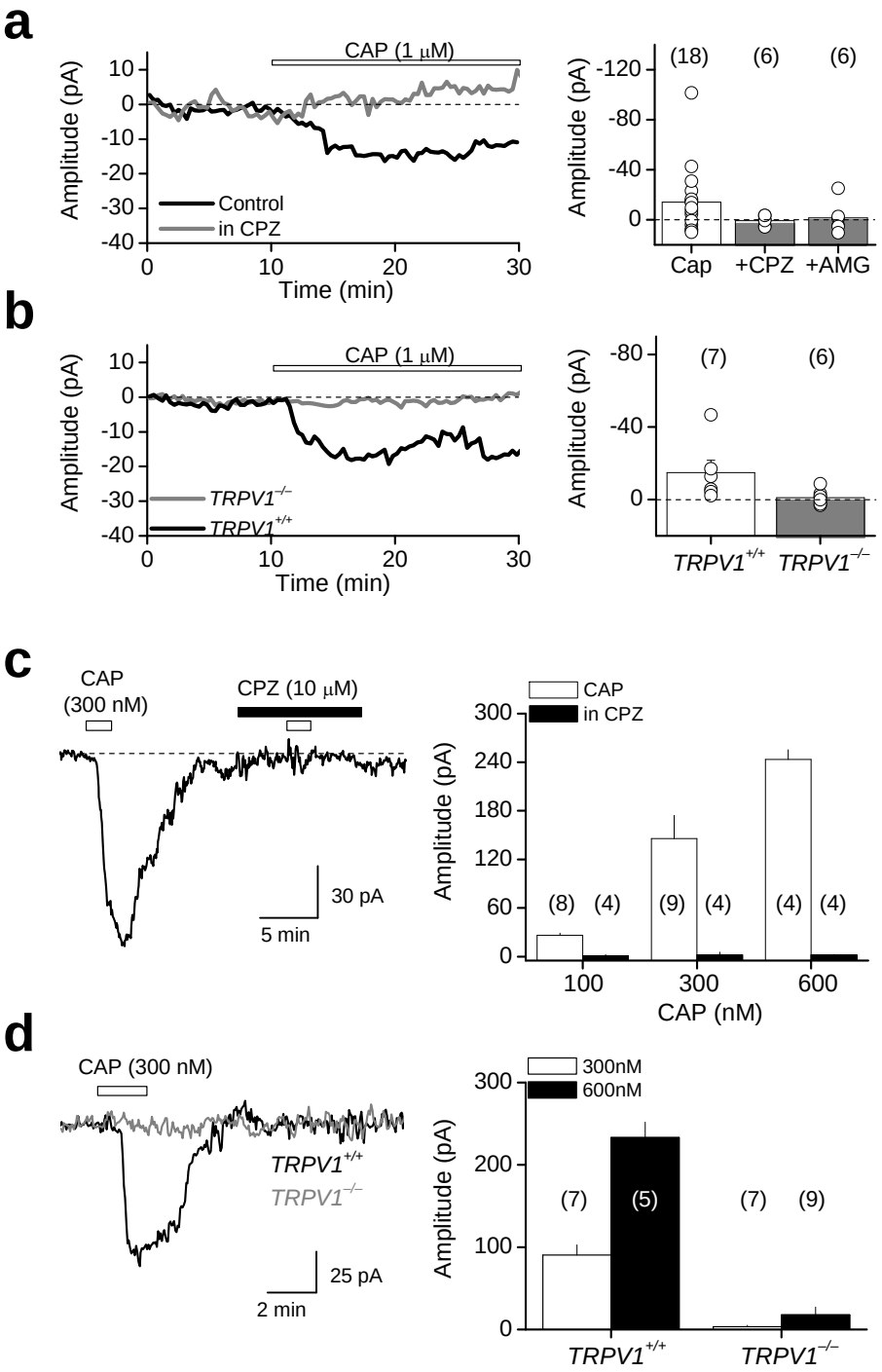
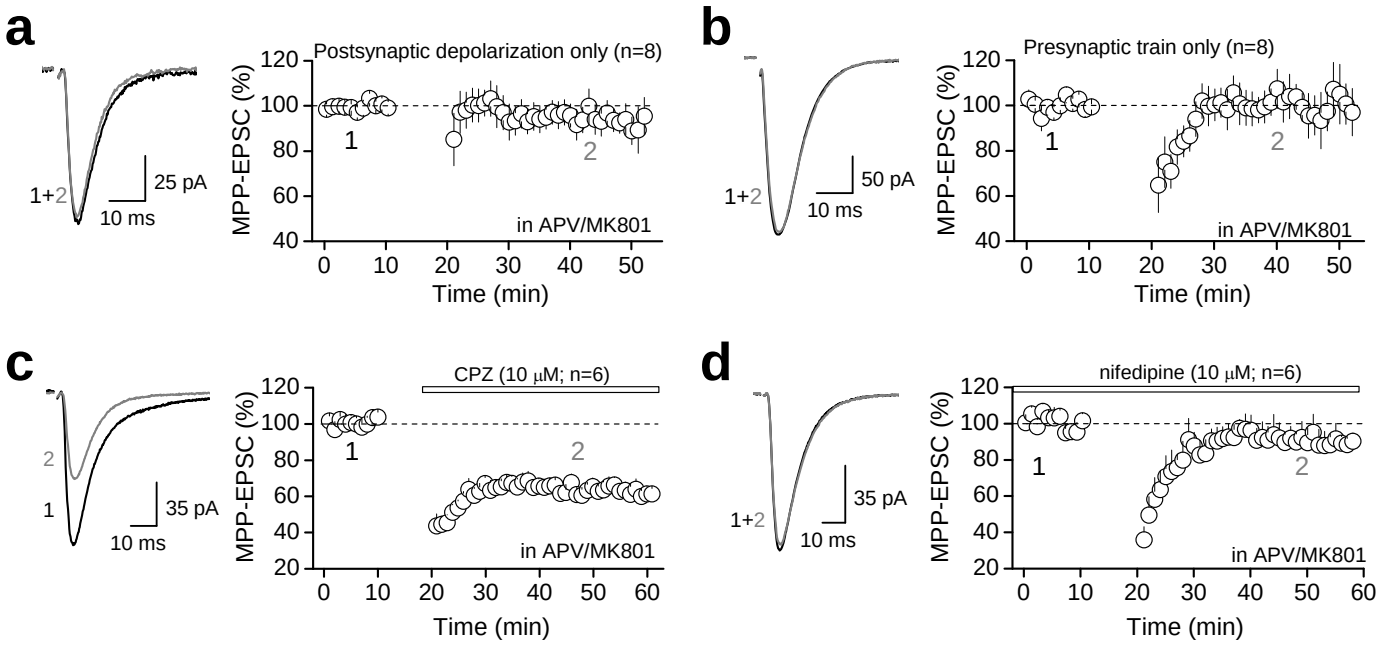


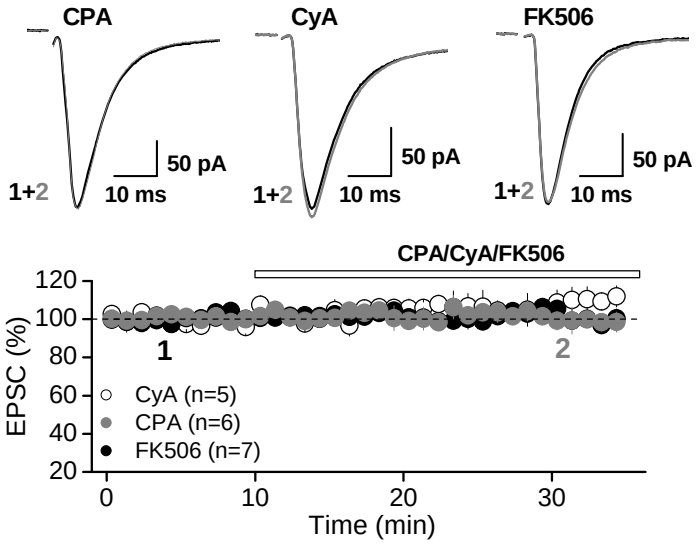
Supplementary Figure 1. **CAP-mediated depression of MPP synaptic inputs. a**, Diagram showing the recording configuration used in this study. Two stimulating pipettes, *S1* and *S2*, were placed in the molecular layer to activate medial perforant path (MPP) and mossy cell fibers (MCF), while synaptic evoked responses in dentate granule cell were monitored using a recording pipette (R) in the dentate granule cell layer (DGL). **b**, Capsaicin (CAP) suppresses MPP-EPSCs in a concentration-dependent manner (white circles) and the effects are blocked by capsazepine (CPZ, 10 μM, black circles). Representative averaged MPP-EPSCs before (*black*) and after (*gray*) 600 nM CAP are shown on the right. **c**, Summary data of CAP-induced effects on synaptic transmission in the dentate gyrus under 28 and 37°C (representative EPSCs recorded at 37°C are shown above). Increasing the recording temperature had no significant effect on CAP-mediated depression. Note that the input-specific nature of CAP-mediated suppression is also observed in mouse. **d**, CPZ had no effect on basal synaptic transmission in rat and mouse, strongly suggesting that TRPV1 receptors are not tonically activated. **e,** CAP-mediated depression did not significantly affect PPR measured at 10, 30, 100 and 300 ms interstimulus intervals (ISI). **f**, Cumulative probability plots of amplitude (*top*) and frequency (*bottom*) of asynchronous MPP-EPSCs evoked in the presence of extracellular strontium before (black) and after (gray) bath application of 1 μM CAP. **g**, CAP-mediated depression was similar in the presence or absence of the NMDAR blocker d-APV (50 μM). Number of cells is indicated in parenthesis. *** p<0,001. In panels d and g, averaged sample traces taken at times indicated by numbers are shown next to each summary plot.



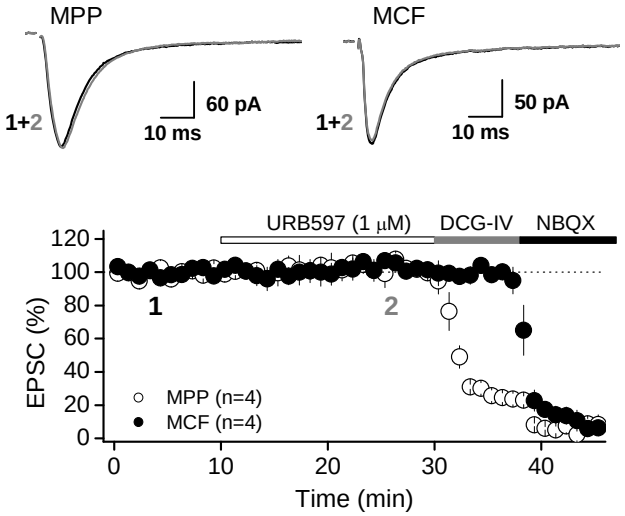
Supplementary Figure 2. CAP-induced inward current in dentate granule cells. a, Inward current induced in dentate granule cells (DGCs) by bath application of 1 μM CAP under control conditions (*black*, averaged traces from 18 cells) or in the presence of 10 μM CPZ (*gray*, averaged traces from 6 cells). Summary data are shown on the right. Open circles represent individual experiments. Experiments performed in the presence of 3 μM AMG9810 are also included in the bar graph. **b,** CAP-induced inward current in *TRPV1*$^{+/+}$ (black, averaged traces from 7 cells) but not in *TRPV1*$^{-/-}$ mice (gray, averaged traces from 6 cells). Summary data are shown on the right. **c**, Dose-dependent, CAP-induced inward currents in rat cultured DGCs. No inward currents were elicited in the presence of CPZ (10 μM). **d**, CAP also induced inward currents in cultured DGCs from *TRPV1*$^{+/+}$ but not in *TRPV1*$^{-/-}$ mice. **c-d,** Representative experiments using 300 nM CAP are shown on the left and summary data (mean ± s.e.m.) are shown on the right. Numbers in the summary plots represent number of cells.



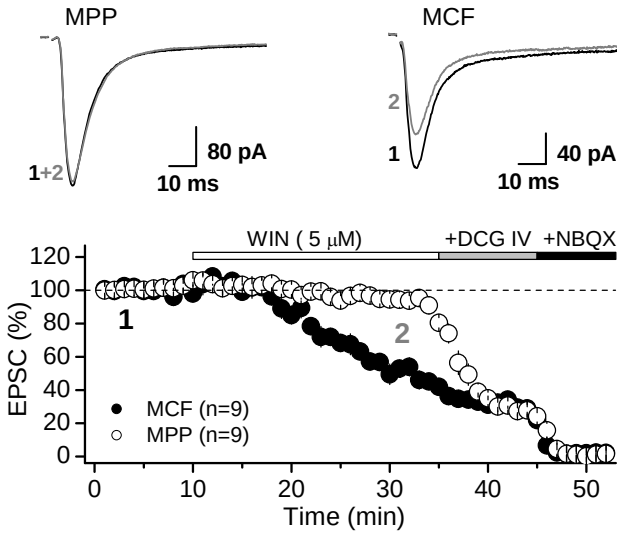
Supplementary Figure 3. TRPV1-LTD properties. a, Postsynaptic depolarization or **b**, presynaptic stimulation alone were insufficient to induce TRPV1-LTD. **c**, Bath application of CPZ (10 μM) immediately after TRPV1-LTD induction did not rescue MPP synaptic transmission. **d**, TRPV1-LTD could not be induced in the presence of the L-type voltage-gated calcium channel blocker nifedipine (10 μM). **a-d**, Averaged traces before (*black*) and after (*gray*) delivering a 1 Hz induction protocol are shown in the left panel; summary plots (mean ± s.e.m) are shown on the right. Number of cells is indicated in parenthesis. In all panels, averaged sample traces taken at times indicated by numbers are shown next to each summary plot.



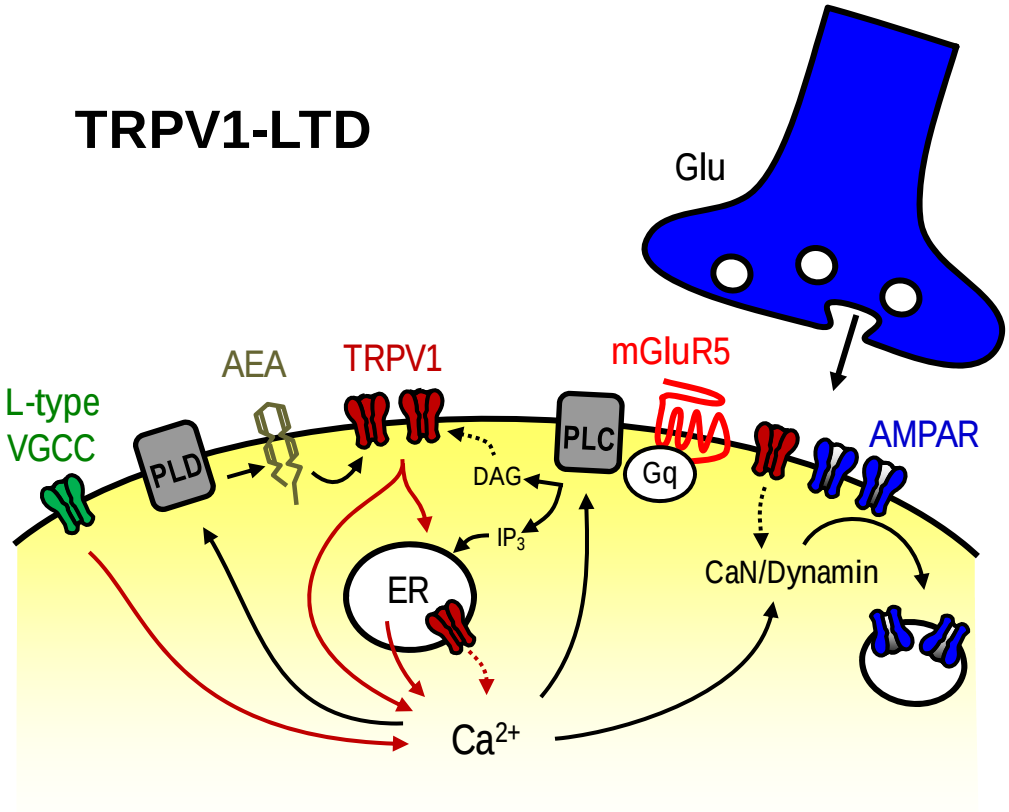
Supplementary Figure 4. Depletion of internal stores with CPA or blockade of calcineurin with cyclosporine A (CyA) or FK506 had no effect on basal synaptic transmission. Representative averaged traces before (*black*) and after 20-25 min (*gray*) bath application of 30 μM CPA, 25 μM CyA and 50 μM FK506 (*Top panel*). Summary plot (mean ± s.e.m.) showing the effects of CPA, CyA and FK506 on MPP synaptic transmission (*Bottom panel)*. Number of cells is indicated in parenthesis. Averaged sample traces taken at times indicated by numbers are shown next to each summary plot.



Supplementary Figure 5. Blocking anandamide degradation with URB597 had no effect on basal synaptic transmission. Representative averaged traces before (*black*) and after 15-20 min (*gray*) of bath application of 1 μM URB597 at both MPP- (*top left*) and MCF-mediated EPSCs (*top right*). Summary plot (mean ± s.e.m.) showing the effects of URB597, DCG-IV (1 μM) and NBQX (10 μM) on MPP and MCF synaptic transmission are shown in the bottom panel. Number of cells is indicated in parenthesis. Averaged sample traces taken at times indicated by numbers are shown next to each summary plot.



Supplementary Figure 6. CB1R activation selectively depressed MPP but not MCF synaptic transmission. Top panel shows representative averaged traces before (*black*) and after (*gray*) 20-25 min bath application of the specific CB1R agonist WIN 52,212 (5 μM) on MPP- and MCF-mediated EPSCs in rat dentate gyrus. Bottom panel shows summary data (mean ± s.e.m.). Note that in contrast to MCF synapses, MPP synapses are insensitive to bath application of the CB1R agonist WIN. Number of cells is indicated in parenthesis. Averaged sample traces taken at times indicated by numbers are shown next to each summary plot.



Supplementary Figure 7. Possible mechanism underlying TRPV1-LTD. Glutamate release during synaptic stimulation activates Gq-coupled mGluR5 receptors, leading to the activation of phospholipase C (PLC). Coincident activation of mGluR5/PLC and L-type voltage-gated Ca^{2+} channels (VGCC) via postsynaptic depolarization increases the activity of the Ca^{2+}-regulated enzyme phospholipase D (PLD), which likely triggers the biosynthesis of anandamide (AEA), an endocannabinoid/endovanilloid that activates TRPV1 receptors on the plasma membrane and/or intracellular compartments. In addition, PLC produces IP3, which increases Ca^{2+} release from the endoplasmic reticulum (ER), and diacylglycerol (DAG), which may directly modulate TRPV1 receptors. Stimulation of Ca^{2+}-sensitive phosphatase calcineurin (CaN) resulting from TRPV1 activation promotes a long-lasting, clathrin- and dynamin-dependent endocytosis of AMPA receptors. Solid red lines represent different Ca^{2+} sources and solid black lines denote established signal transduction pathways. Dotted lines represent putative pathways involved in TRPV1-LTD.

Supplementary Table 1: Effect of bath application of 1 μM capsaicin on synaptic currents in dentate granule cells

Parameter	Species	Value % (mean ± s.e.m.)		n	t-test* p-value	Figure
MPP-AMPA EPSC	Rat MPP	74.20 ± 1.27		10 c	<0.001 Paired	1a
	in APV	70.41 ± 3.51		5 c	<0.001 Paired	Suppl. 1g
	at 37°C	70.98 ± 3.16		5c	<0.001 Paired	Suppl. 1c
	TRPV1$^{+/+}$	70.02 ± 1.18		7 c/4 a	<0.001 Paired	1c
	TRPV1$^{-/-}$	103.14 ± 1.44		6 c/3 a	0.560 Paired	1c
MCF-AMPA EPSC	Rat	99.04 ± 2.56		7 c	0.269 Paired	1a
	at 37°C	98.72 ± 1.92		5 c	0.189 Paired	Suppl. 1c
	TRPV1$^{+/+}$	101.68 ± 3.21		7 c/4 a	0.214 Paired	Suppl. 1c
CAP-mediated depression in CPZ or AMG	Rat CPZ	104.12 ± 1.16		6 c	0.215 Paired	1b
	Rat AMG	103.37 ± 1.71		6 c	0.196 Paired	1b
MPP-NMDA EPSC	Rat –40 mV	100.88 ± 1.30		6 c	0.907 Paired	1d
	Rat +40 mV	100.21 ± 3.43		6 c	0.937 Paired	1d
Asynchronous release	Rat MPP	**Control**	**in CAP**			
	Amplitude	9.81 ± 0.91	7.54 ± 0.47	11c	0.004 Paired	1e
					<0.001 K-S	Suppl. 1f
	Frequency	4.76 ± 0.38	4.45 ± 0.44	11c	0.090 Paired	1e
					0.562 K-S	Suppl. 1f
Glutamate-evoked AMPA current	Rat MPP	57.81 ± 4.67		5 c	<0.001 Paired	1f
	Rat MCF	100.80 ± 2.96		5 c	0.615 Paired	1f
	TRPV1$^{+/+}$	63.28 ± 6.57		4 c/2 a	0.001 Paired	1g
	TRPV1$^{-/-}$	98.16 ± 3.37		4 c/2 a	0.637 Paired	1g
CPZ after capsaicin	Rat in Cap	78.85 ± 2.72			--------	
	+CPZ	82.35 ± 2.90		9 c	0.379 Paired	1h
MPP-AMPA EPSC in BAPTA	Rat	99.50 ± 4.85		6 c	<0.001 Unpaired	4a
MPP-AMPA EPSC in CPA	Rat	87.02 ± 1.85		10 c	<0.001 Unpaired	4a
MPP-AMPA EPSC in FK506	Rat	97.08 ± 3.29		7 c	<0.001 Unpaired	4c
MPP-AMPA EPSC in CyA	Rat	98.09 ± 1.74		6 c	<0.001 Unpaired	4c
MPP-AMPA EPSC in DIP	Rat	104.32 ± 1.68		10 c	<0.001 Unpaired	4e

The table includes quantitative analyses of experiments shown in Figs. 1, 4 and Supplementary Fig. 1; "n" represents number of cells (c) and animals (a) from *TRPV1*$^{+/+}$ and *TRPV1*$^{-/-}$ mice.
* t-test otherwise indicated

Supplementary Table 2: Paired pulse ratio (PPR) and coefficient of variation ($1/CV^2$) of MPP-EPSCs during both pharmacological and endogenous activation of TRPV1 receptors

Parameter	Species	Value % (mean ± s.e.m.) Pre	Post	n	Paired t-test p-value	Figure
Capsaicin 1 μM PPR 100 ms	Rat (28°C)	0.94 ± 0.03	0.94 ± 0.03	10 c	0.932	1a
	Rat (37°C)	0.92 ± 0.03	0.90 ± 0.04	5 c	0.264	Suppl.1c
	Rat in APV	0.88 ± 0.03	0.86 ± 0.07	5 c	0.846	Suppl. 1g
	TRPV1$^{+/+}$	0.99 ± 0.06	1.00 ± 0.06	7 c/4 a	0.626	1c
Capsaicin 1 μM	Rat					
PPR 300ms		0.84 ± 0.03	0.79 ± 0.03	5 c	0.399	Suppl. 1e
PPR 30 ms		0.98 ± 0.03	0.91 ± 0.04	5 c	0.262	Suppl. 1e
PPR 10 ms		0.71 ± 0.04	0.67 ± 0.02	5 c	0.306	Suppl. 1e
PPR in LTD	Rat	0.92 ± 0.03	0.87 ± 0.03	10 c	0.096	2a
	TRPV1$^{+/+}$	0.99 ± 0.07	0.92 ± 0.04	7 c/7a	0.108	2b
Bath application AEA PPR	Rat	0.80 ± 0.02	0.79 ± 0.04	6 c	0.856	5a
	CB1R$^{-/-}$	1.05 ± 0.13	1.05 ± 0.08	7c / 2a	0.974	5c
Loading AEA PPR	Rat Control	0.97 ± 0.07	0.96 ± 0.06	7 c	0.827	5b
	in AM251	0.95 ± 0.06	0.97 ± 0.07	5 c	0.860	5b
Capsaicin 1 μM $1/CV^2$	Rat (28°C)	10.91 ± 0.67	9.96 ± 0.56	10 c	0.056	1a
	Rat (37°C)	11.32 ± 0.96	8.47 ± 0.71	5 c	0.148	Suppl. 1c
	Rat in APV	6.70 ± 1.43	6.33 ± 1.11	5c	0.454	Suppl. 1g
	TRPV1$^{+/+}$	7.21 ± 0.66	7.19 ± 0.55	7 c/3 a	0.946	1c
AEA $1/CV^2$	Rat	11.44 ± 1.11	11.60 ± 1.47	6 c	0.821	5a
	CB1R$^{-/-}$	8.02 ± 1.34	7.53 ±1.14	7c / 2a	0.209	5c
LTD $1/CV^2$	Rat	8.08 ± 0.97	7.69 ± 1.14	10 c	0.579	2a
	TRPV1$^{+/+}$	6.96 ± 1.04	6.72 ± 0.92	7 c/7a	0.796	2b

The table includes quantitative analyses from experiments shown in Figs. 1, 2, 5 and Supplementary Fig. 1; "n" represents number of cells (c) and animals (a) from *TRPV1*$^{+/+}$ and *TRPV1*$^{-/-}$ mice.

Supplementary Table 3: TRPV1 activation and long-term synaptic plasticity

Parameter	Species	Value % (mean ± s.e.m.)	n	t-test p-value	Figure
MPP-LTD in APV/MK801	Rat 1Hz	70.19 ± 4.78	10 c	<0.001 Paired	2a
	in CPZ	106.22 ± 12.07	6 c	0.643 Paired	2a
	in AMG	100.08 ± 1.77	5 c	0.813 Paired	2a
	TRPV1$^{+/+}$	72.94 ± 4.33	7 c/7 a	<0.001 Paired	2b
	TRPV1$^{-/-}$	102.77 ± 2.77	10 c/8 a	0.521 Paired	2b
MPP-LTP without APV/MK801	Rat 1 Hz	184.99 ± 12.50	8 c	<0.001 Paired	2e
	in CPZ	263.21 ± 25.42	7 c	0.001 Unpaired	2e
	in AMG	267.02 ± 8.64	6 c	<0.001 Unpaired	2e
	TRPV1$^{+/+}$	149.46 ± 9.41	7 c/ 4 a	0.002 Paired	2f
	TRPV1$^{-/-}$	199.69 ± 8.15	8 c/4 a	0.001 Unpaired	2f
MCF-AMPA EPSC in APV/MK801	Rat 1 Hz	123.65 ± 6.06	10 c	0.004 Paired	2c
MPP-LTD in APVMK801	Rat 1 HZ				
	Paired	64.87 ± 2.59	8 c	<0.001 Paired	2c
	Unpaired	96.95 ± 3.90	7 c	<0.001 Unpaired	2c
	Presynaptic Burst	96.53 ± 6.71	8 c	0.520 Paired	Suppl. 3b
	Depolarization	99.31 ± 5.74	8 c	0.979 Paired	Suppl. 3a
MPP-LTD in APV/MK801	Rat 1 Hz				
	Incubated in CAP	99.28 ± 3.74	6 c	0.658 Paired	2d
	CAP after induction	63.78 ± 2.99	6 c	0.103 Paired	2d
	CPZ after induction	63.83 ± 3.70	6 c	<0.001 Paired	Suppl. 3c

The table includes quantitative analyses from experiments shown in Figs. 2 and Supplementary Fig. 3; "n" represents number of cells (c) and animals (a) from *TRPV1*$^{+/+}$ and *TRPV1*$^{-/-}$ mice.

Supplementary Table 4: Role of group I mGluR and calcium in TRPV1-LTD

Parameter	Species	Value % (mean ± s.e.m.)	n	t-test p-value	Figure
LTD in mGluR antagonists	Rat 1 Hz				
	MPEP	103.99 ± 5.06	10 c	<0.001 Unpaired	3a
	LY367385	68.87 ± 1.59	6 c	0.204 Unpaired	3a
LTD in U73122	Rat 1 Hz	99.46 ± 4.23	7 c	<0.001 Unpaired	3b
LTD in GDPβS	Rat 1 Hz	100.08 ± 2.17	7 c	<0.001 Unpaired	3b
LTD in BAPTA	Rat 1 Hz	106.85 ± 7.29	6 c	<0.001 Unpaired	4b
LTD in CPA	Rat 1 Hz	98.77 ± 1.35	7 c	<0.001 Unpaired	4b
LTD in FK506	Rat 1 Hz	98.37 ± 3.32	7 c	<0.001 Unpaired	4d
LTD in CyA	Rat 1 Hz	103.05 ± 2.40	7 c	<0.001 Unpaired	4d
LTD in DIP	Rat DIP	107.46 ± 4.73	10 c	<0.001 Unpaired	4f
	Rat DIP scrambled	70.92 ± 3.66	5c	0.632 Unpaired	4f
LTD in THL	Rat 1 Hz	65.36 ± 5.26	6 c	0.002 Unpaired	5f
	Rat CA1-iLTD	97.04 ± 3.33	6c	0.428 Unpaired	5f
MPP-AMPA EPSC	Rat				
	DHPG	92.11 ± 4.76	6 c	0.089 Paired	3c
	DHPG in MK801	94.80 ± 3.54	5 c	0.144 Paired	3c
MPP-AMPA EPSC in APV/MK801	Rat 1 Hz				
	DHPG+Dep	63.80 ± 2.63	6 c	<0.001 Paired	3d
	DHPG+Dep+CPZ	101.83 ± 2.87	8 c	<0.001 Unpaired	3d
MPP-EPSC Nifedipine baseline	Rat	101.16 ± 2.35	4 c	0.893 Paired	-----
LTD in Nifedipine	Rat 1 Hz	91.75 ± 7.29	6 c	0.331 Paired	Suppl. 3d

The table includes quantitative analyses from experiments shown in Figs. 3-5 and Supplementary Fig. 3.

Supplementary Table 5: Effect of anandamide on MPP AMPAR-EPSCs

Parameter	Species	Value % (mean ± s.e.m.)	n*	t-test p-value	Figure
AMPA EPSC (Bath application)	Rat MPP	69.06 ± 3.09	6 c	<0.001 Paired	5a
	Rat MCF	102.82 ± 1.19	6 c	0.433 Paired	5a
	TRPV1$^{-/-}$	96.47 ± 3.72	7 c / 3 a	0.323 Paired	5c
	CB1R$^{-/-}$	74.11 ± 1.43	8 c / 2 a	<0.001 Paired	5c
AMPA EPSC (URB597 effect on baseline)	Rat URB MPP	102.60 ± 1.96	4 c	0.279 Paired	Suppl. 5
	Rat URB MCF	102.51 ± 2.30	4 c	0.361 Paired	Suppl. 5
AMPA EPSC (Loading DGCs)	Rat MPP	73.56 ± 3.50	7 c	<0.001 Paired	5b
	in AM251	68.76 ± 3.38	5 c	0.207 Unpaired	5b
	in CPZ	102.81 ± 2.47	7 c	<0.001 Unpaired	5b
Sub-threshold 1Hz pairing protocol	Rat Control	96.41 ± 3.21	7 c	------	5d
	Rat URB	69.11 ± 5.11	8 c	<0.001 Paired	5d
	Rat URB+CPZ	100.04 ± 1.22	7 c	0.321 Paired	5d
	TRPV1$^{+/+}$ Control	97.52 ± 2.01	7 c / 3a	---------	5e
	TRPV1$^{+/+}$ in URB	56.43 ± 7.44	5 c / 2a	<0.001 Unpaired	5e
	TRPV1$^{-/-}$ in URB	97.06 ± 3.33	7 c / 2a	0.404 Unpaired	5e

The table includes quantitative analyses from experiments shown in Fig. 5 and Supplementary Fig. 5; "n" represents number of cells (c) and animals (a) from *TRPV1*$^{+/+}$ and *TRPV1*$^{-/-}$ mice.