Supplemental Materials

Supplemental Table 1 Changes in brain lipid levels induced by IDFP, CPO and chlorpyrifos

	IDFP			CPO		Chlorpyrifos[a]			
	Swiss Webster			Swiss Webster		KIAA1363 +/+		KIAA1363 –/–	
Analyte	Control	10 mg kg^{-1}	30 mg kg^{-1}	Control	4 mg kg^{-1}	Control	100 mg kg^{-1}	Control	100 mg kg^{-1}
Brain lipid (nmol g^{-1}) (mean ± S.D.) (*n*=3-8)									
Anandamide **(2)**	0.004 ± 0.0002	0.051 ± 0.004	0.049 ± 0.003	0.016 ± 0.002	0.011 ± 0.002	0.0063 ± 0.0013	0.018 ± 0.0059	0.0077 ± 0.0033	0.019 ± 0.0055
2-AG **(1)**	3.7 ± 1.0	48 ± 6.4	71 ± 7.5	3.7 ± 1.0	40 ± 6.2	3.2 ± 0.5	19 ± 5	3.4 ± 0.4	54 ± 11
AA **(6)**	61 ± 7.5	14 ± 1.9	8.1 ± 0.25	61 ± 7.5	30 ± 5.5	56 ± 8	34 ± 6	51 ± 5	17 ± 3
N-Acylethanolamines (pmol g^{-1}) (mean ± S.D.) (*n*=3)									
C16:0 (*N*-palmitoyl-ethanolamine, **10**)	167 ± 6.0	1951 ± 57 ***	1869 ± 23 ***	151 ± 28	810 ± 33 ***	271 ± 138	1279 ± 322 **	180 ± 64	1507 ± 419 **
C18:0 **(29)**	333 ± 42	710 ± 56**	825 ± 53 **	229 ± 20	576 ± 32 ***	375 ± 120	651 ± 81 *	318 ± 95	779 ± 195 *
C18:1 (*N*-oleoyl-ethanolamine, **11**)	114 ± 3.0	1677 ± 29 ***	1491 ± 92 ***	81 ± 4	535± 25 ***	117 ± 25	651 ± 81 ***	95 ± 42	880 ± 209 **
C18:2 **(30)**	6.1 ± 1.6	95 ± 8.1 ***	80 ± 6.7 ***	ND	ND	ND	18 ± 4.5 ***	ND	26 ± 8.1 **
C20:0 **(31)**	24 ± 1.9	66 ± 5.0 **	82 ± 28	39 ± 9	58 ± 6	113 ± 25	145 ± 29	64 ± 14	154 ± 30 **
C20:4 (anandamide, **2**)	4.1 ± 0.2	51 ± 3.6 ***	49 ± 2.6 ***	16 ± 2	11 ± 2	6.3 ± 1.3	19 ± 5.6 **	7.7 ± 3.3	19 ± 5.5 *
C22:0 **(32)**	21 ± 4.0	43 ± 4.0 *	42 ± 8.3	21 ± 6	29 ± 2	116 ± 38	120 ± 32	90 ± 44	160 ± 60
C22:6 **(33)**	ND	44 ± 3.8 ***	58 ± 15 *	ND	ND	ND	ND	ND	ND
C24:0 **(34)**	ND	1.8 ± 0.1***	2.0 ± 0.1***	ND	ND	0.45 ± 0.90	1.9 ± 0.78	2.8 ± 4.9	2.8 ± 0.67
C24:1 **(35)**	29 ± 6.5	73 ± 7.6 *	71 ± 18	28 ± 2	47 ± 5	99 ± 26	142 ± 40	76 ± 14	191 ± 45 *
Monoacylglycerols (nmol g^{-1}) (mean ± S.D.) (*n=3*)									
2-C16:0 (2-palmitoylglycerol, **12**)	1 ± 0.1	5.6 ± 0.6 ***							

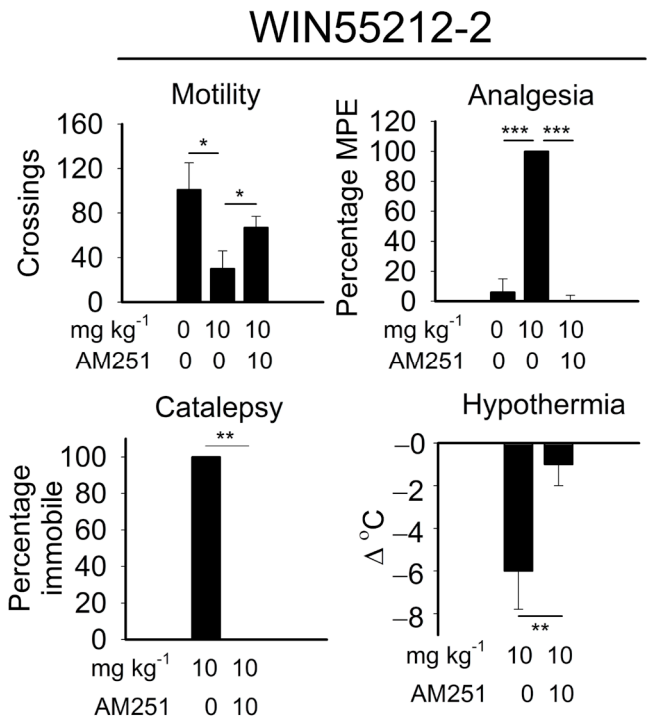
1-C16:0 (1-palmitoylglycerol, **13**)	0.03 ± 0.06	1.1 ± 0.1 ***
2-C18:1 (2-oleoylglycerol, **14**)	2.2 ± 0.6	13 ± 1 ***
1-C18:1 (1-oleoylglycerol, **15**)	ND	0.3 ± 0.2 *
2-C20:4 (2-arachidonoyl-glycerol, **1**)	3.7 ± 1.0	48 ± 6.4 ***

Asterisks indicate significance, *p<0.05, **p<0.01, ***p<0.001, ND: not detected

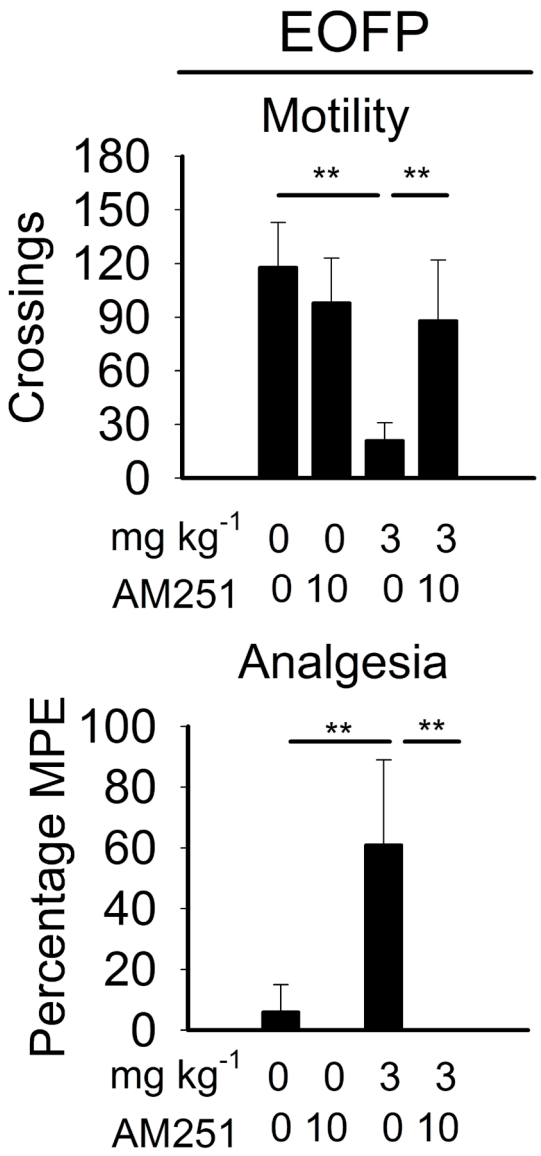
[a] KIAA1363 –/– mice are compromised in CPO detoxification in brain[S1] and therefore 2-AG and AA changes are more dramatic in –/– compared to +/+ mice.

Supplemental Table 2. Serine hydrolase inhibitory profiles for IDFP (10 mg kg^{-1}) and CPO (4 $mgkg^{-1}$) determined by ABPP-MudPIT.

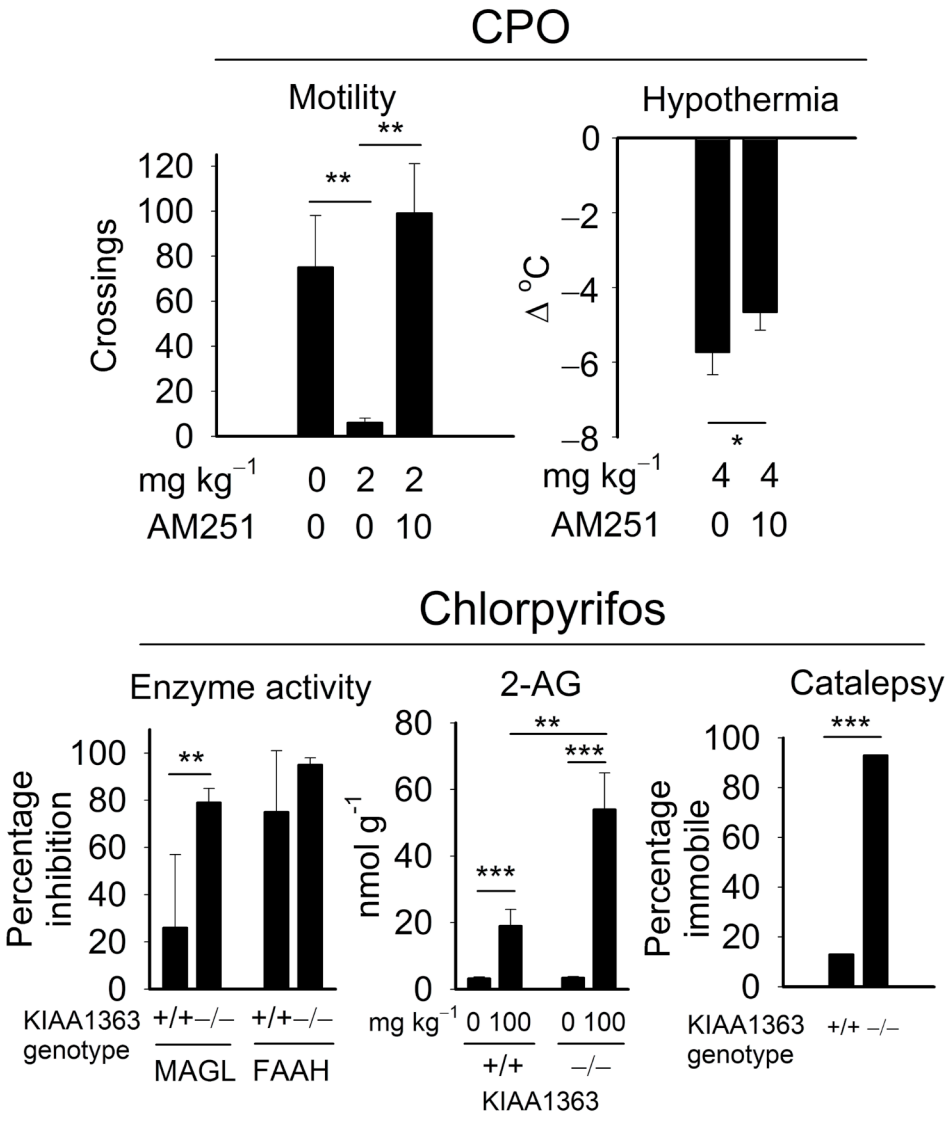
		control		IDFP			CPO		
Abbreviation	**Protein**	**av**	**SD**	**av**	**SD**	**p-value**	**av**	**SD**	**p-value**
KIAA1363	IPI00403586 - Adult male corpora quadrigemina cDNA, RIKEN full-length enriched library, clone:B230106I24 product	129.33	28.3608	11.33	0.57735	0.00197 **	90	1.73205	0.07454
PREPL	IPI00224078 - Prolyl oligopeptidase	112.67	14.1892	122.3	9.07377	0.37644	110.3	12.4231	0.8408
FAS	IPI00113223 - Fatty acid synthase	112.33	16.6533	133.3	11.8462	0.14972	109.7	28.5365	0.89558
ABHD6	IPI00321386 - Abhydrolase domain containing 6	97.667	20.5994	12	7.81025	0.00253 **	96.67	12.0968	0.94568
MAGL	IPI00132874 - monoglyceride lipase	91	23.6432	1	1.73205	0.00277 **	6.333	2.08167	0.00349 **
ABHD12	IPI00165731 - Abhydrolase domain-containing protein 12	67.333	16.563	58	12.7671	0.48265	72.33	10.116	0.67853
FAAH	IPI00117176 - Fatty-acid amide hydrolase	59.667	9.50438	1	1.73205	0.00046 ***	11.33	4.50925	0.00135 **
BAT5	IPI00130339 - Protein BAT5	49.333	11.9304	36.67	7.63763	0.19636	48.67	13.6504	0.95227
mAcoTE1	IPI00653566 - mitochondrial acyl-CoA thioesterase 1	36.667	9.2376	32	5.2915	0.48998	37.67	3.05505	0.86736
ABHD3	IPI00131173 - Lung alpha/beta hydrolase fold protein 3	34.667	8.73689	10.33	3.05505	0.01039 *	7.333	2.08167	0.00621 **
PEP	IPI00761930 - Prolyl endopeptidase	33	1	44	7	0.05441	41.67	3.21455	0.01117
iPLA2L	IPI00120080 - similar to CALCIUM-INDEPENDENT PHOSPHOLIPASE A2	32.333	2.51661	28.33	4.04145	0.21931	36.33	1.52753	0.07822
ACOT1	IPI00115871 - Acyl-coenzyme A thioesterase 1	31.667	6.65833	26.33	4.72582	0.32113	30.67	3.78594	0.83218
GPIDA	IPI00652417 - GPI deacylase	27.667	6.4291	33	3	0.26281	30	6.245	0.67542
AARE	IPI00387245 - Isoform 1 of Acylamino-acid-releasing enzyme	25.667	2.08167	6.333	3.78594	0.00149 **	9.333	1.52753	0.00039 ***
PLA2g7	IPI00755673 - Phospholipase A2, group VII	21.667	6.02771	23.33	5.85947	0.74859	16.33	4.04145	0.27201
Cgi67	IPI00108883 - Cgi67 serine protease precursor	20.667	4.16333	21.67	7.50555	0.84992	21	3.60555	0.92156
APT2	IPI00123518 - Acyl-protein thioesterase 2	19.333	3.51188	17.33	4.04145	0.55289	20.67	7.37111	0.79133
CE-N	IPI00138342 - Liver carboxylesterase N precursor	19.333	9.29157	0	0	0.02268 *	0.667	1.1547	0.02598 *
PPME1	IPI00415908 - Protein phosphatase methylesterase 1	19.333	4.93288	18.67	3.51188	0.85805	13.67	4.04145	0.19861
ABHD4	IPI00122628 - abhydrolase domain containing 4	16	3	15.33	3.51188	0.8149	13.33	5.50757	0.50231
ACPT1	IPI00130018 - Isoform 1 of Acyl-protein thioesterase 1	15.667	0.57735	13	1.73205	0.06468	14.67	4.72582	0.73442
AChE	IPI00128567 - Acetylcholinesterase precursor	15.667	2.51661	16.33	5.50757	0.85805	2.667	2.51661	0.00319 **
Chr10BWG	IPI00115549 - DNA segment, Chr 10, Brigham & Women's Genetics 1364 expressed	14	4.3589	14.67	2.88675	0.83601	12.33	4.50925	0.66922
ABHD11	IPI00170213 - Williams-Beuren syndrome critical region protein 21	14	4.58258	13	1.73205	0.74152	16	6.245	0.67787
NTE	IPI00128034 - Neuropathy target esterase homolog	14	6.08276	0	0	0.01631 *	15	8.7178	0.87847
RBBP9	IPI00135277 - Isoform 1 of Retinoblastoma-binding protein 9	13.333	1.52753	12	2.64575	0.49177	15.67	3.05505	0.30224
DPP9	IPI00462461 - Isoform 1 of Dipeptidyl peptidase 9	11	2.64575	11.67	3.05505	0.78928	10.33	6.1101	0.87074
HSL	IPI00228826 - lipase, hormone sensitive isoform 1	11	4.58258	0	0	0.01417 *	1.667	1.52753	0.02866 *
ACS	IPI00124428 - 1-O-acylceramide synthase precursor	10.333	2.08167	11.33	3.78594	0.70899	9	3.60555	0.60865
CPEP	IPI00132020 - Lysosomal Pro-X carboxypeptidase precursor	10.333	2.51661	9.333	3.05505	0.68427	7.333	2.51661	0.21807
DPP8	IPI00330837 - Dipeptidyl peptidase 8	9	3	9.333	3.05505	0.89925	10	5.19615	0.78717
LPL1	IPI00153133 - Lysophospholipase-like protein 1	6.3333	1.1547	5.667	5.1316	0.83699	11	3.4641	0.09126
PAFAH1Bg	IPI00118819 - Platelet-activating factor acetylhydrolase IB subunit gamma	5.6667	0.57735	8	0	0.00219	5	1	0.3739
LCTB	IPI00109293 - Serine beta-lactamase-like protein LACTB	5.3333	2.51661	5.667	2.51661	0.879	5	2	0.86619
NTE-R	IPI00331610 - weakly similar to NEUROPATHY TARGET ESTERASE	5.3333	2.08167	0	0	0.01135 *	7	5	0.62227
Tpp2	IPI00227843 - Tpp2 protein	5	1.73205	4.667	0.57735	0.76764	5.667	3.51188	0.78275
PARLP	IPI00124015 - Presenilins-associated rhomboid-like protein, mitochondrial precursor	4.6667	1.1547	6.333	2.3094	0.32616	3.667	1.52753	0.41687
ABHD13	IPI00133177 - Abhydrolase domain containing 13	3.6667	0.57735	4.333	0.57735	0.2302	3.667	1.52753	1
CD11c	IPI00318006 - NOD-derived CD11c +ve dendritic cells cDNA, RIKEN full-length enriched library, clone:F630106D23 product:serine hydrolase-like	3.6667	2.08167	0.667	1.1547	0.09445	0.667	1.1547	0.09445
LPP	IPI00137177 - Lysosomal protective protein precursor	3.3333	0.57735	3.333	1.52753	1	3	2.64575	0.8416
PAFAH2	IPI00123270 - Platelet-activating factor acetylhydrolase 2, cytoplasmic	3.3333	1.1547	2.667	0.57735	0.42165	3.333	1.52753	1
HTRA1	IPI00128040 - Serine protease HTRA1 precursor	3	1	4	1	0.28786	1.667	2.88675	0.49177
iPLA2	IPI00122327 - Isoform 2 of 85 kDa calcium-independent phospholipase A2	3	1	3.333	0.57735	0.64333	5.667	5.1316	0.42689



Supplemental Figure 1 CB_1-dependent effects of direct agonist WIN55212-2 in the tetrad tests for cannabinoid behavior with aversion by CB_1 receptor antagonist AM251 (10 mg kg^{-1} ip). Analgesia is scored as percentage maximum possible effect (MPE). *n*=3-5 mice/group. Asterisks indicate significance, *p<0.05, **p<0.01, ***p<0.001.



Supplemental Figure 2 CB_1-dependent effects of EOFP (3 mg kg^{-1} ip) on behavior. AM251 preadministered at 10 mg kg^{-1}. Analgesia is scored as percentage maximum possible effect (MPE). Data represent mean ± S.D. for n=5-10 mice/group. Asterisks indicate significance, **p<0.01.



Supplemental Figure 3 Cannabinoid-like effects of CPO and chlorpyrifos. Both CPO and chlorpyrifos elicit cannabinoid-like phenotypes during symptoms of cholinergic toxicity from AChE inhibition. CPO administered ip induces hypomotility at 2 mg kg^{-1} and hypothermia at 4 mg kg^{-1} averted fully and slightly by AM251 pretreatment (10 mg kg^{-1} i.p.), respectively. Hypothermia also occurs due to increased cholinergic signaling from AChE inhibition. CPO is acutely toxic with a steep dose-response whereas chlorpyrifos (which requires bioactivation to CPO**)** has a slower onset and shallower dose-response curve. Therefore, cannabinoid effects were determined with chlorpyrifos at the maximum sublethal dose comparing KIAA1363 +/+ versus –/– mice[S1] which are compromised in their ability to detoxify CPO in the brain. Chlorpyrifos elicits greater inhibition of MAGL activity and 2-AG elevation in the brain associated with increased cataleptic behavior in KIAA1363 –/– mice compared to their +/+ counterparts. Data for 2-AG levels are derived from **Supplemental Table 1.** n=3-4 mice/group for motility, hypothermia, enzyme activity and 2-AG levels and n=13-14 mice/group for catalepsy. Asterisks indicate significance, *p<0.05, **p<0.01, ***p<0.001.

Supplemental Reference

[S1] Nomura, D.K. *et al.* A brain detoxifying enzyme for organophosphorus nerve poisons. *Proc. Natl. Acad. Sci., U.S.A.* **102**, 6195-6200 (2005)**.**