Table S1: Genes upregulated with Quis treatment

Affymetrix Probeset	*Accession Number*	*Unigene Gene Name*	*Fold Change*	*95% CI*
1387316_at	NM_030845	Chemokine (C-X-C motif) ligand 1; Cxcl1	13.0	7.3 to 18.7
1369191_at	NM_012589	Interleukin 6; Il6	11.7	4.2 to 17.2
1389402_at	AI178746	Csrnp1; AXUD1	4.6	1.7 to 7.7
1382351_at	AI069972	Ras-related GTPase; Kir/Gem	4.4	1.0 to 8.2
1378032_at	AI176265	NFkappaBiz; IκBz	4.0	0.1 to 8.2
*1398266_a_at	D83508	Early growth response 2; egr2	3.9	3.1 to 4.6
1393728_at	AA964541	Leukemia inhibitory factor; Lif	3.6	1.1 to 6.3
*1386995_at	BI288701	B-cell translocation gene 2; Btg2	3.5	0.4 to 7.0
*1387306_a_at	NM_053633	Early growth response 2; egr2	3.4	2.3 to 4.4
1387260_at	NM_053713	Kruppel-like factor 4; KLF4	3.3	1.7 to 5.0
*1387410_at	U72345	Nuclear receptor subfamily 4, group A, member 2; Nr4a2; Nurr1	3.1	2.3 to 3.9
1387068_at	NM_019361	Activity regulated cytoskeletal-associated protein; Arc	2.9	2.5 to 3.4
1372389_at	BF420059	immediate early response 2; Ier2	2.9	1.4 to 4.5
*1386994_at	NM_017259	B-cell translocation gene 2; Btg2	2.8	1.8 to 3.8
*1369007_at	L08595	Nuclear receptor subfamily 4, group A, member 2; Nr4a2	2.8	2.4 to 3.2
1394451_at	AI236455	Annexin A1	2.7	1.3 to 4.1
1380229_at	AW530004	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F; Maff	2.6	1.6 to 3.5
*1368147_at	BE110108	Dual specificity phosphatase 1; Dusp1	2.5	0.8 to 4.2
1373866_at	AI228596	Coq10b	2.4	1.2 to 3.8
1369217_at	NM_017352	Nuclear receptor subfamily 4, group A, member 3; Nr4a3; Nor1	2.4	1.2 to 3.6
1369268_at	NM_012912	Activating transcription factor 3; Atf3	2.4	1.5 to 3.3
1386935_at	NM_024388	Nuclear receptor subfamily 4, group A, member 1; Nr4a1; Nur77	2.4	1.7 to 3.1
1394925_at	AI578037	Similar to RIKEN cDNA 2310035C23	2.3	-0.2 to 5.2
*1368146_at	U02553	Dual specificity phosphatase 1; Dusp1	2.3	2.0 to 2.5
1368124_at	NM_133578	Dual specificity phosphatase 5; Dusp5	2.2	0.2 to 4.3
1368596_at	NM_021693	SNF1-like kinase; SIK1	2.2	1.4 to 3.0
1368050_at	NM_053662	Cyclin L1; Ccnl1; Ania-6	2.1	0.4 to 4.0
*1371019_at	BM387324	Tribbles homolog 1; Trib1	2.1	1.4 to 2.9
*1391643_at	BI290758	Tribbles-1; Trib1	2.1	1.2 to 3.0
1369737_at	NM_017334	CAMP responsive element modulator; Cren	2.1	-0.3 to 4.7
1387870_at	AB025017	TIS11	2.1	0.8 to 3.4
1396849_at	AW534332	Ser/Thr kinase 35; STK35	2.0	1.1 to 3.1
1387788_at	NM_021836	Junb	2.0	1.4 to 2.6
1380772_at	BE105726	AT rich interactive domain 5A ; Arida; MRF1	2.0	0.2 to 4.0

*, more that one probe set identified for a given gene.
Genes highlighted in red are unique to Quis treatment.

Table S2: Genes upregulated with DHPG treatment

Affymetrix Probeset	*Accession Number*	*Unigene Gene Name*	*Fold Change*	*95% CI*
1387316_at	NM_030845	Chemokine (C-X-C motif) ligand 1: Cxcl1	13.3	8.7 to 17.9
1369191_at	NM_012589	Interleukin 6; IL6	7.5	-0.9 to 15.8
1378032_at	AI176265	NFkappaBiz; IκBz	3.8	1.4 to 6.5
1389402_at	AI178746	Csrnp1	3.7	2.2 to 5.3
1393728_at	AA964541	Leukemia inhibitory factor; Lif	3.2	2.6 to 3.8
*1386995_at	BI288701	B-cell translocation gene 2; Btg2	3.2	1.1 to 5.3
1382351_at	AI069972	Ras-related GTPase; Kir/Gem	3.1	1.7 to 4.5
*1387306_a_at	NM_053633	Early growth response 2; egr2	2.9	0.9 to 5.0
*1398266_a_at	D83508	Early growth response 2; egr2	2.8	1.9 to 3.8
*1386994_at	NM_017259	B-cell translocation gene 2; Btg2	2.6	0.6 to 4.7
1377340_at	AI179507	Tissue factor pathway inhibitor 2; TFPI2	2.5	-0.9 to 6.4
1372389_at	BF420059	immediate early response 2; Ier2	2.5	1.3 to 3.8
1394451_at	AI236455	Annexin A1	2.5	0.5 to 4.7
1387260_at	NM_053713	Kruppel-like factor 4; KLF4	2.5	1.3 to 3.8
1372025_at	BI296467	Paternally expressed 3; PEG3/PW1	2.4	-0.9 to 6.2
1382138_at	BG380221	Notch-regulated ankyrin repeat protein	2.3	0.4 to 4.4
1387870_at	AB025017	TIS11	2.3	0.8 to 3.9
1379228_at	BF418531	Fms-like tyrosine kinase ligand 3; Flt3l	2.1	-0.5 to 5.2
*1368147_at	BE110108	Dual specificity phosphatase 1; Dusp1	2.1	0.8 to 3.5
1387410_at	U72345	Nuclear receptor subfamily 4, group A, member 2; Nr4a2; Nurr1	2.1	0.5 to 3.8
1369217_at	NM_017352	Nuclear receptor subfamily 4, group A, member 3; Nr4A3; Nor1	2.0	0.9 to 3.2
1380229_at	AW530004	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F; Maff	2.0	1.0 to 3.1
*1368146_at	U02553	Dual specificity phosphatase 1; Dusp1	2.0	1.6 to 2.4

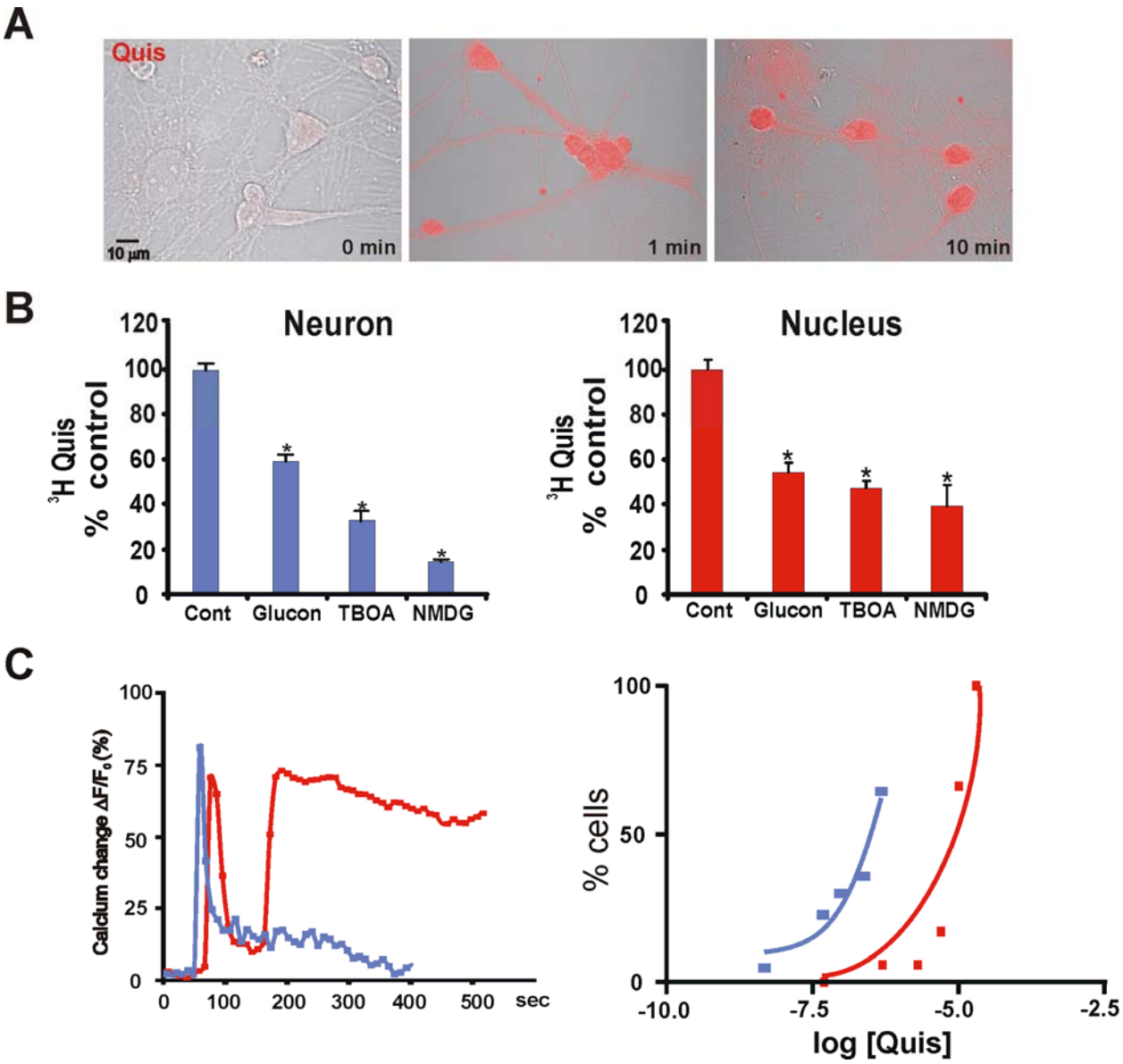
*, more that one probe set identified for a given gene.
Genes highlighted in blue are unique to DHPG treatment.

Table S3: Gene-specific primers used for QRT-PCR

Gene	***5′ - 3′ Forward Primer***	***5′ - 3′ Reverse Primer***
Arc	TCCTGCAGATTGGTAAGTGC	GTGCAACCCTTTCAGCTCTC
Atf3	TGCCAAGTGTCGAAACAAGA	CGGTGCAGGTTGAGCATGTA
Ccnl1	GGGCAGGTGTTGTTTCATC	CATGGCAACAATCTCGAAAC
Crem	ATGAGGAGACTGACCTTGCC	GGAGCTCGGATCTGGTAAGT
Dusp5	TTCACAAGAGAAGCTCGAAGG	GCCACCCTGGTCATAAGC
Egr2	GGAGATGGCATGATCAACAT	TTGCCCATGTAAGTGAAGGT
Gapdh	TGCCCCCATGTTTGTGATG	TGTGGTCATGAGCCCTTCC
Junb	CAGTTACTCCCCAGCCTCTG	GCATGTGGGAGGTAGCTGAT
Nr4a1	AGGAGACCAAGACCTGTTGC	CTCACCGGGCTTAGATCG
Nr4a2	TATTCCAGGTTCCAGGCAAA	CCTCTGATGATCTCCATAGA
Snf1lk	GGTTATGGAGACAAAAGACATGC	CAAGTGCCCGTTGGAAGT
Trib1	GACCTGAAGCTTAGGAAATTCG	ATCTCAGGGCTCACATAGGC

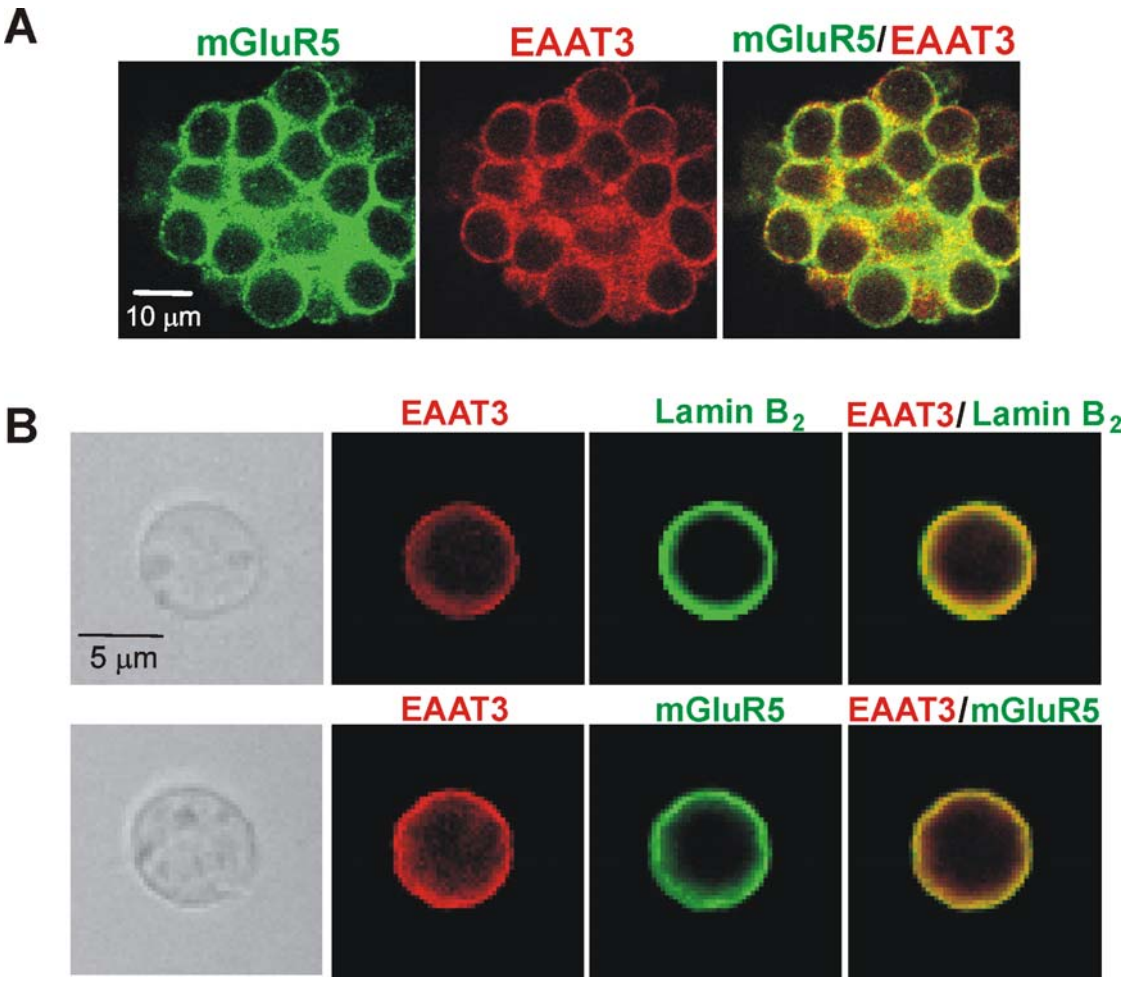
Gene-specific primers for quantitative RT-PCR were designed using Primer3 v.0.4.0 software (20) according to Applied Biosystems guidelines. The primers were designed such that they cross exon-exon junction or lie on two exons to ensure specificity for RNA. For intronless genes, no-RT controls were kept and difference of 7 C_T between +RT and –RT was considered to account for < 1% contribution by DNA to signal (Applied Biosystems).

Supplemental Figure S1



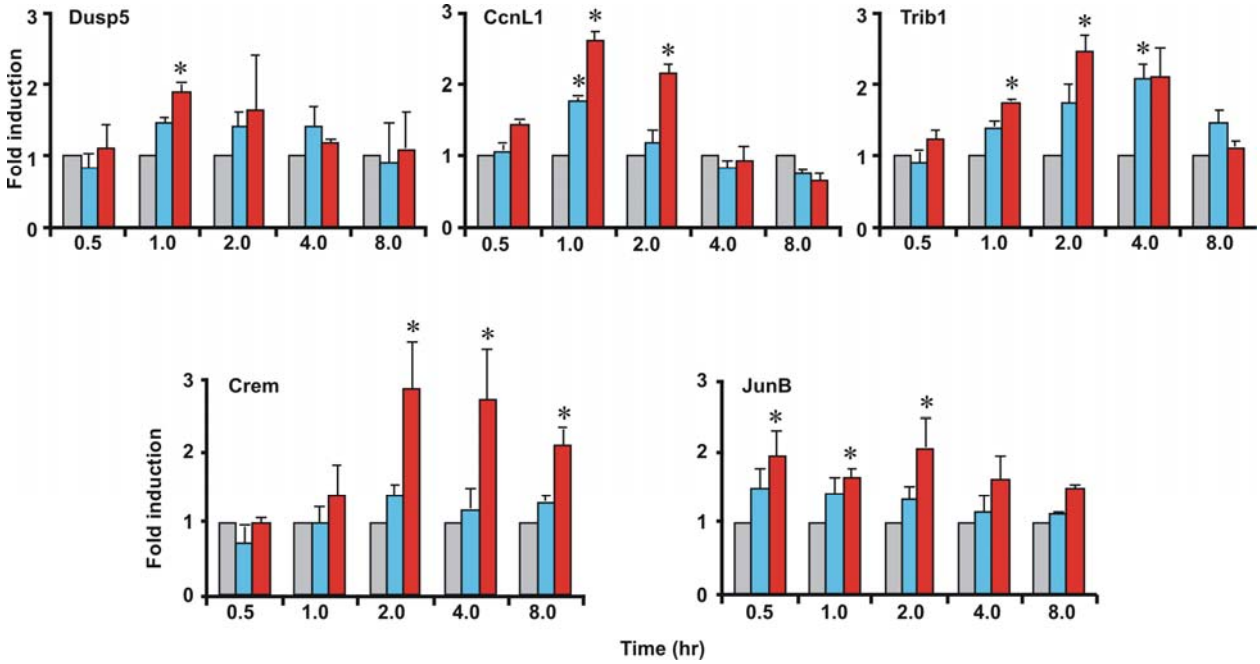
Supplemental Figure S1. Quis is transported in striatal neurons and nuclei. *A*, Demonstration of Quis uptake using anti-Quis antibody. *B*, Quis uptake using chloride free conditions (gluconate buffer) or in presence of EAAT3 inhibitor TBOA, or in sodium and chloride free ringer solution (NMDG). *C*, Quis dose-dependency in Ca^{2+} responses; only single transient peak (*blue*) observed at Quis doses < 250 nM whereas both transient and sustained peaks (*red*) are seen with higher Quis concentrations (>5 µM).

Supplemental Figure S2



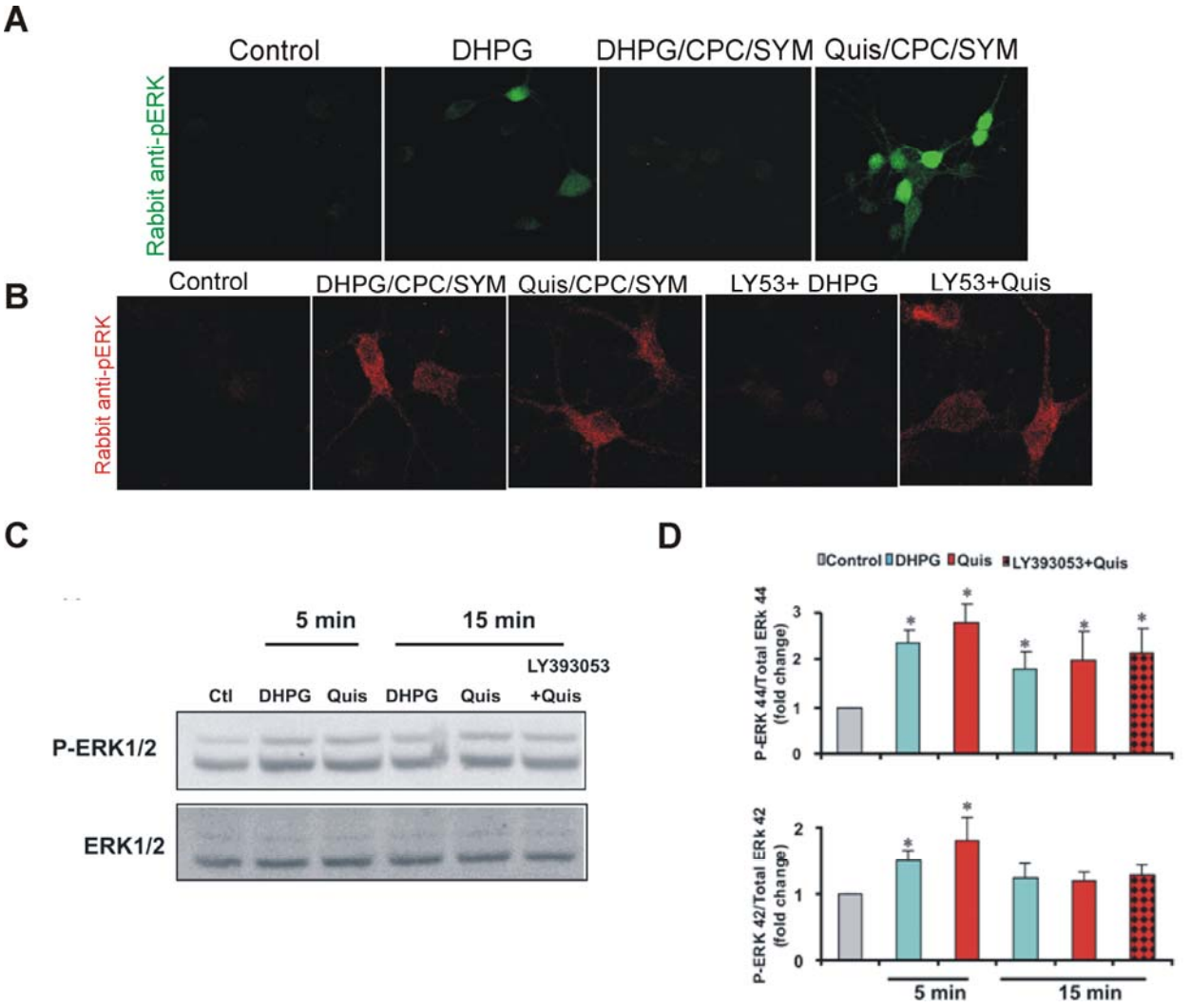
Supplemental Figure S2. EAAT3 (*red*) is expressed in mGluR5-positive striatal (*A*) and nuclei (*B*) where it co-localizes with mGluR5 (*green*) and Lamin B_2 (*green*).

Supplemental Figure S3



Supplemental Figure S3. Quantitative RT-PCR validates microarray data. Dissociated striatal neurons were treated with either Quis (*red*) or DHPG (*blue*) for indicated time points. Total RNA was isolated and subjected to quantitative RT-PCR using SYBR Green and gene-specific primers. Bars represent fold change (mean $\pm$ S.E.M.) compared to the control (*gray*) from three independent experiments; *, $p<0.05$ *versus* control.

Supplemental Figure S4



Supplemental Figure S4. DHPG and Quis treatment lead to ERK1/2 phosphorylation in dissociated striatal and hippocampal cultures. ***A,*** Striatal neurons were untreated (control, panel 1), treated with DHPG alone (panel 2) or pre-treated with 25 μM SYM2206 and 20 μM CPCCOEt and then treated with DHPG (panel 3) or Quis (panel 4) and stained for phospho ERK1/2 using rabbit anti-phospho ERK1/2 antibody. *B*, DIV 14 dissociated hippocampal neurons were pre-treated with SYM2206 and CPCCOEt and then treated with indicated drugs. Neurons were fixed and stained for phospho ERK1/2 using rabbit anti-phospho ERK1/2 antibody. ***C,*** Western blot analysis of hippocampal lysates treated with agonists for indicated times. ***D,*** Quantitation of blots from three separate experiments ± S.E.; *,$p<0.05$ versus control levels.