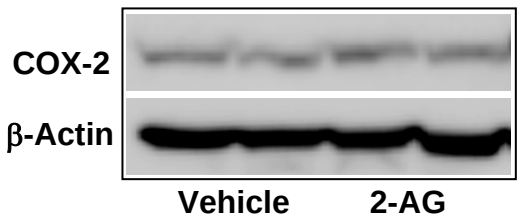
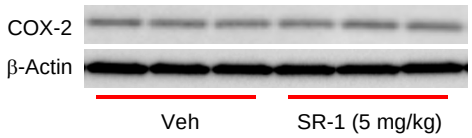
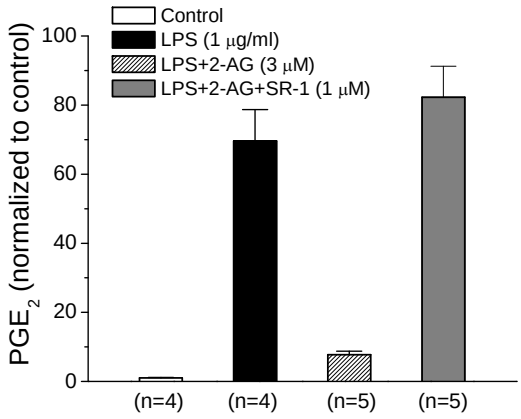


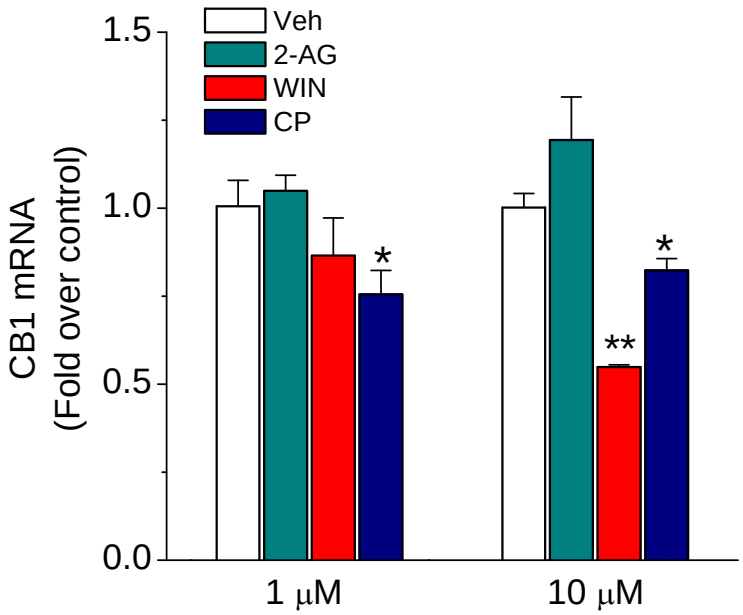
Supplemental figure 1. 2-AG does not significantly induce a change in COX-2 expression in the hippocampus. Immunoblot analysis of COX-2 expression in hippocampal tissue from mice injected with 2-AG (3 mg/kg, i.p.).



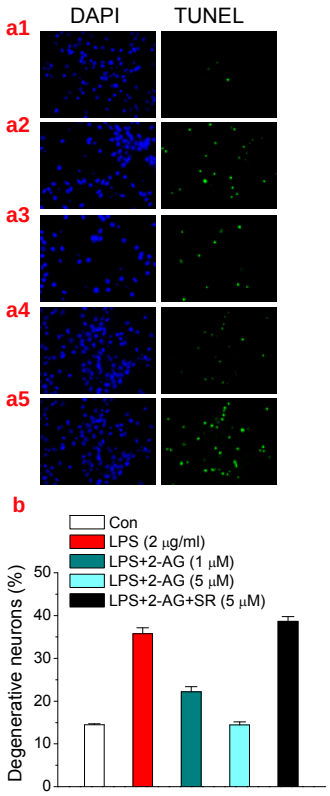
Supplemental figure 2. SR141716 (SR-1) does not significantly induce a change in COX-2 expression in the hippocampus. Immunoblot analysis of COX-2 expression in hippocampal tissue from mice injected with SR-1 (5 mg/kg, i.p.).



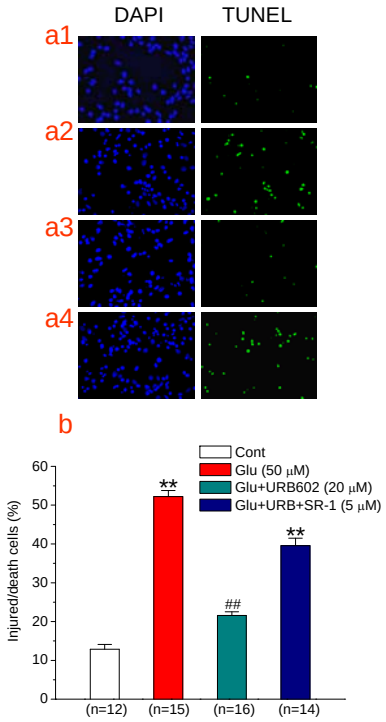
Supplemental figure 3. 2-AG decreases LPS-induced increase in production of PGE2, and the reduction is prevented in the presence of SR-1. PGE2 was detected in mixed culture of hippocampal neurons and astroglial cells using PGE2 EIA kit according to manufacture's instructions (Caymanchem, MI).



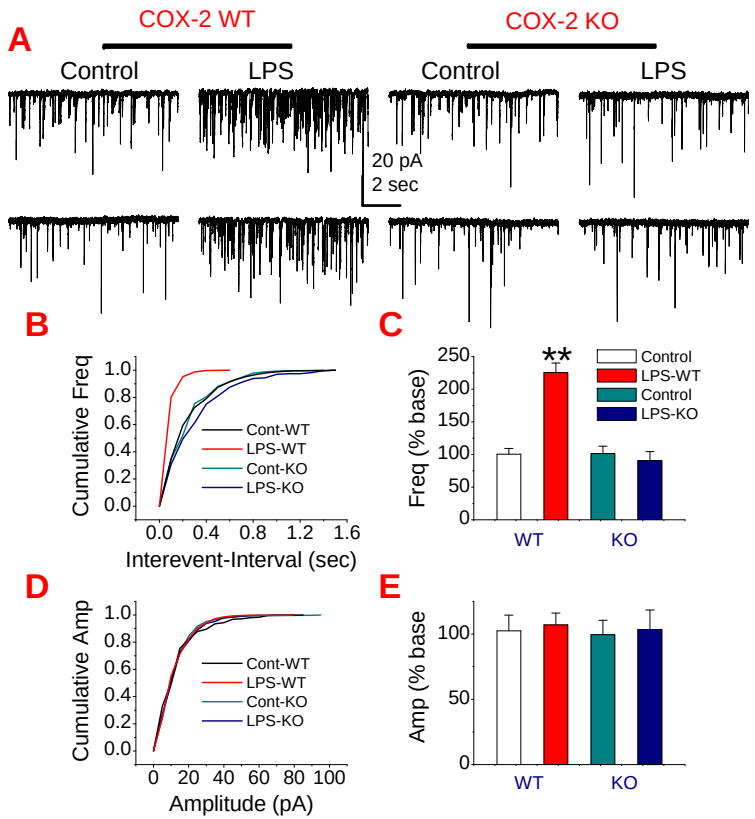
Supplemental figure 4. Real-time PCR analysis of CB1 expression in mixed culture of hippocampal neurons and astroglial cells (n=3). The culture was treated with 2-AG, WIN 55,212-2 or CP55,940, and mRNA of the CB1 was assayed 6 hr after treatments. Results are from three independent cultures with duplicated wells. *P<0.05, **P<0.01 compared with vehicle controls.



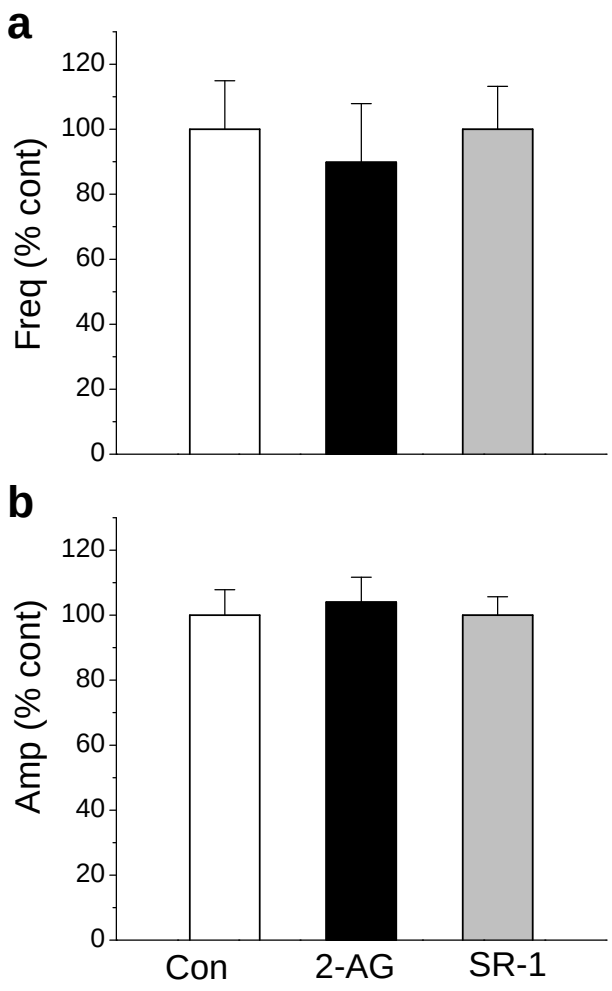
Supplemental figure 5. 2-AG protects hippocampal neurons from the LPS insult. (a1-5). TUNEL images of hippocampal neurons in control (a1), LPS (2 μg/ml, a2), LPS+2-AG (1 μM, a3), LPS+2-AG (5 μM, a4), and LPS+2-AG (5 μM) + SR-1 (5 μM, a5) for 24 hrs. (b). Percentages of injured neurons under different treatments. **P<0.01 compared with vehicle controls; ##<P<0.01 compared with LPS (N=10 to 12).



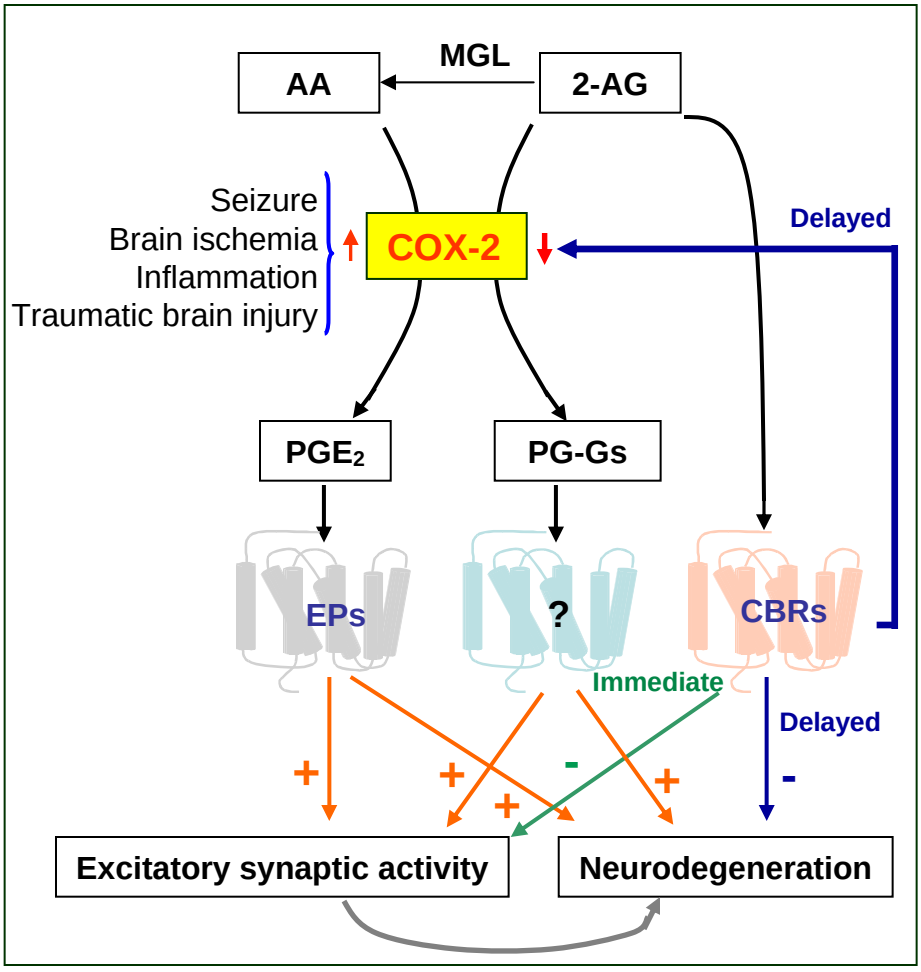
Supplemental figure 6. Endogenous 2-AG protects hippocampal neurons from excitotoxicity. (a1-4). TUNEL images of hippocampal neurons in vehicle control (a1), glutamate (Glu 50 μM, a2), Glu+URB602 (20 μM, a3), Glu+URB602+SR-1(5 μM, a4) for 24 hrs. (b). Percentages of injured neurons under different treatments. **P<0.01 compared with vehicle controls; ##<P<0.01 compared with Glu.



Supplemental figure 7. LPS fails to enhance mEPSCs in cultured hippocampal neurons from COX-2 null mice. Hippocampal neurons from COX-2 null and wild type mice were cultured as described in the manuscript. The culture was treated with LPS (1 μg/ml) for 24 hrs. While LPS elevates the frquency of mEPSCs in neurons from the COX-2 wild type aniamls, it fails to enhance the frequency of mEPSCs in neurons from COX-2 knockout mice.



Supplementary figure 8. 2-AG or SR-1 do not alter basal synaptic transmission in hippocampal neurons in culture. The culture was individually treated with 2-AG (1 μM), or SR-1 (1 μM) for 12 hrs. Miniature EPSCs were recorded in cultured hippocampal neurons as described in methods.



Supplemental figure 9. A hypothetic scheme illustrating the role of COX-2 oxidative metabolism of AA and 2-AG, and 2-AG suppression of COX-2 in synaptic signaling and neurodegeneration. Brain ischemia, neuroinflammation, epileptic activity and traumatic brain injury elevate COX-2 expression and activity, which oxygenates AA and 2-AG to PGE_2 and PG-Gs. PGE_2 activates EPs, PG-Gs bind to novel receptors, leading to an increase in excitatory glutamatergic synaptic transmission and neurodegeneration, while 2-AG activates CBRs, resulting in a decrease in synaptic activity and neuroprotection by limiting COX-2 overexpression. AA: arachidonic acid; 2-AG: 2-arachidonoylglycerol; MGL: monoacylglycerol lipase; PG-G: prostaglandin glyceryl esters; EPs: prostaglandin E_2 receptors; CBRs: cannabinoid receptors.