Dose-dependence of the inhibition of LTP by NMDAR antagonists. (A) Application of conditioning high frequency stimulation (HFS, arrow) triggered robust LTP (132.2 ± 3.4%, n = 10, P < 0.05 compared to pre-HFS baseline, paired t test) in animals that received an intracerebroventricular injection of vehicle (asterisk, 5 μL). NVP-AAM077 (250 pmol or 1 nmol) (B), ifenprodil (6 nmol) (C), or UBP141 (12.5 nmol or 25 nmol) (D) inhibited LTP induction (108.0 ± 4.6%, 97.3 ± 3.3%, 102.1 ± 7.1%, 105.6 ± 3.9% and 106.1 ± 3.9% pre-HFS mean baseline EPSP amplitude ± SEM, respectively at 3 h post-HFS, n = 4–5 per group; P < 0.05 compared with vehicle-injected controls; one-way ANOVA followed by post hoc Tukey’s test). Values are the mean percentage of pre-HFS baseline EPSP amplitude (± SEM). Insets show representative EPSP traces at the times indicated. Calibration bars: vertical, 2 mV; horizontal, 10 ms.
Fig. S2. Dose-dependence of the effects of memantine on the inhibition of LTP by Aβ1–42. Systemic (i.p.) injection of memantine (5 mg/kg, n = 3; 10 mg/kg, n = 5, and 20 mg/kg, n = 3) only partly prevented the Aβ1–42-mediated inhibition of LTP (Aβ1–42 alone, n = 5). LTP values are expressed as the mean % control magnitude of LTP (±SEM).
Fig. S3. TNFα-dependence of Aβ1–42-mediated inhibition of LTP (A) i.c.v. injection of soluble Aβ1–42 (250 pmol, asterisk) inhibited LTP induced by high frequency stimulation (HFS, arrow) (n = 5; P < 0.05 compared with vehicle, n = 8). (B) Coinjection of the TNFα antibody infliximab, at a dose (25 µg, i.c.v., asterisk) that did not affect LTP on its own (n = 4), prevented the inhibition of LTP by Aβ1–42 (n = 5; P < 0.05). (C) Similarly coinjection of a TNFα binding peptide antagonist, at a dose (2 nmol, i.c.v., asterisk) that did not affect LTP on its own (n = 5), prevented the inhibition of LTP by Aβ1–42 (n = 5; P < 0.05). (D) Moreover systemic pretreatment (~2.5 h) with the TNFα production inhibitor thalidomide, using a dose (45 mg/kg i.p.) that did not affect LTP on its own (n = 6), also prevented the inhibition of LTP by Aβ1–42 (n = 4; P < 0.05). Values are the mean percentage of pre-HFS baseline EPSP amplitude (±SEM). Calibration bars for EPSP traces: vertical, 2 mV; horizontal, 10 ms.
Fig. S4. TNFα-mediated inhibition of LTP. Intracerebroventricular injection of TNFα (asterisk, 1.5 pmol) inhibited high frequency stimulation (arrow) -induced LTP (n = 5; P < 0.05 compared with vehicle, n = 8; P > 0.05 compared with baseline. Values are the mean percentage of pre-HFS baseline EPSP amplitude (±SEM). Calibration bars for EPSP traces: vertical, 2 mV; horizontal, 10 ms.