

Figure S1. Loss of p75NTR leads to an increase in tPA mRNA levels and proteolytic activity in the CNS. (a) In situ zymographies on cerebella from wt ($n = 6$) and $p75^{NTR-/-}$ ($n = 5$) mice reveal enhanced proteolytic activity in $p75^{NTR-/-}$ cerebella compared to wt. Quantification is shown in panel b. (c) Quantitative real-time PCR analysis of mRNA isolated from primary CGNs from wt and $p75^{NTR-/-}$ animals revealed a fourfold increase in tPA levels in $p75^{NTR-/-}$ neurons.

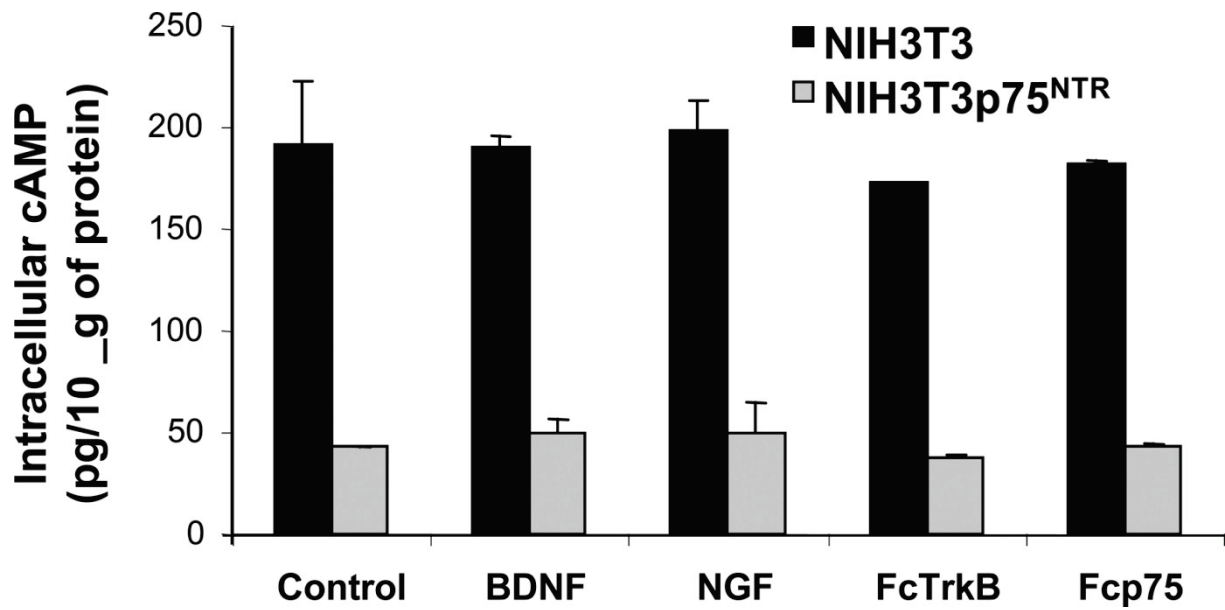


Figure S2. p75NTR decreases intracellular cAMP in a neurotrophin-independent manner. Expression of p75NTR is sufficient for the reduction of intracellular cAMP (control). Addition of neurotrophins, such BDNF or NGF or inhibition of neurotrophins in the cell culture medium either by Fc-TrkB or Fc-p75NTR does not affect the levels of intracellular cAMP in either NIH3T3 or NIH3T3p75NTR cells. Experiments were performed five times in duplicate.

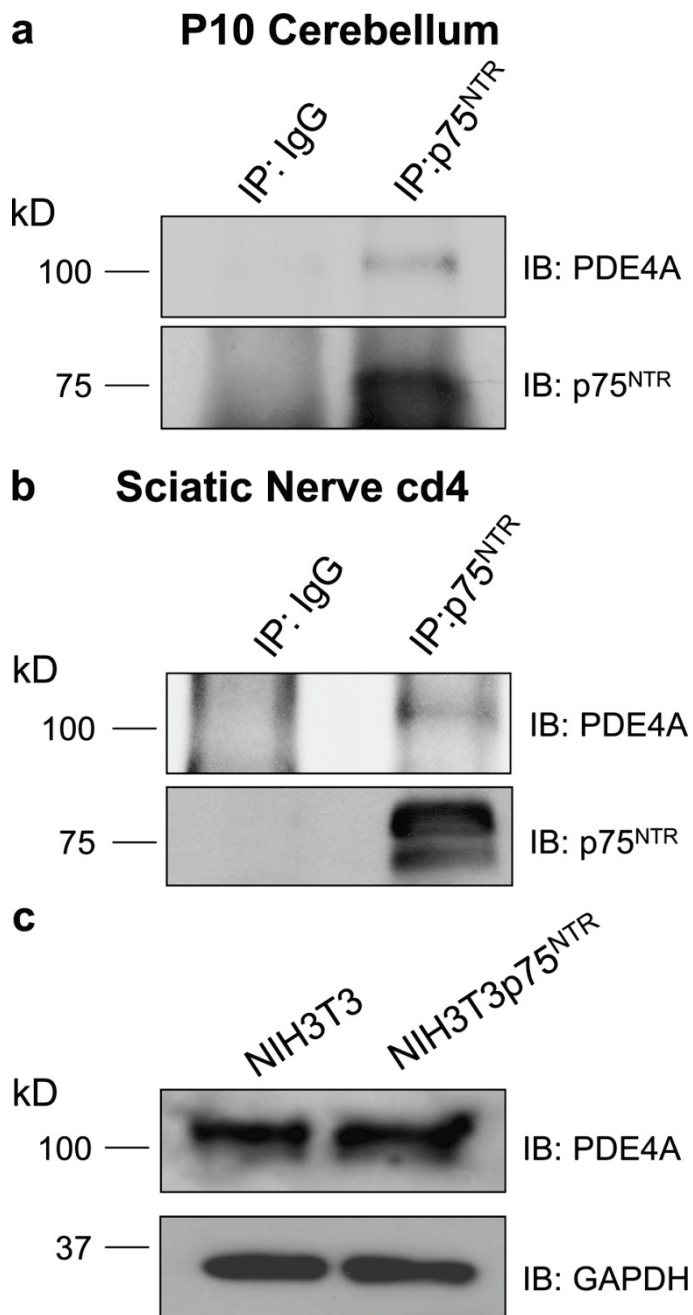


Figure S3. Endogenous co-IP between p75^{NTR} and PDE4A5 in freshly isolated CGNs and in injured sciatic nerve. Co-immunoprecipitation (IP) experiments from wt CGNs reveal that endogenous levels of PDE4A5 and p75^{NTR} are able to form a complex in wt CGNs (a). IP with rabbit IgG is used as negative control. Co-IP experiments from crushed wt sciatic nerves reveal that endogenous levels of PDE4A5 and p75^{NTR} are able to form a complex in the injured sciatic nerve as well (b). Western blot demonstrating similar levels of PDE4A5 expression in NIH3T3 and NIH3T3p75^{NTR} cells (c).

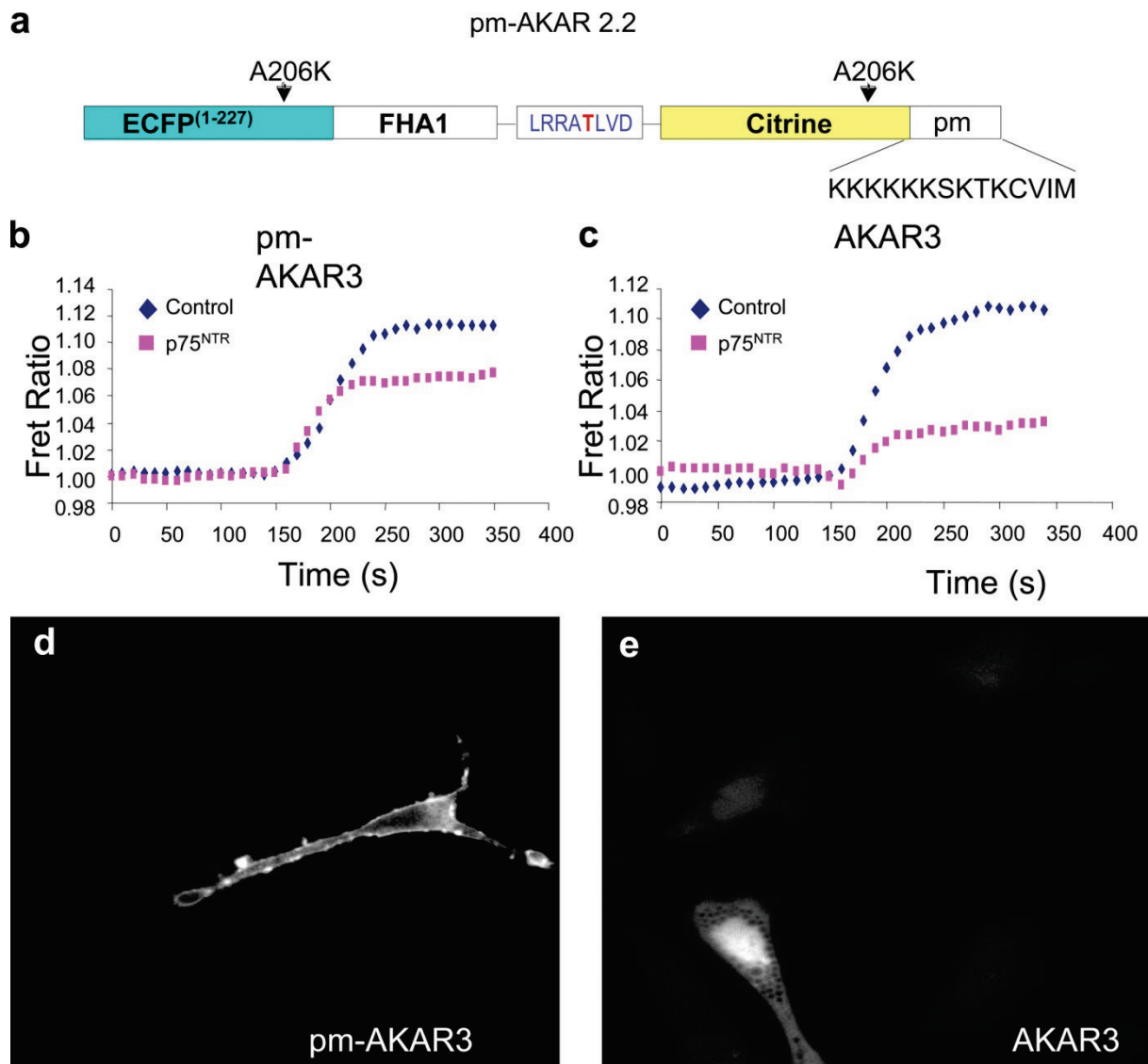


Figure S4. Analysis of p75NTR-mediated inhibition of cAMP using FRET-based PKA biosensors. (a) Generation of plasma membrane targeted PKA fluorescent indicator (pm-AKAR 2.2) domain structures of pm-AKAR2.2. The C-terminal sequence from K-Ras KKKKKKSKTKCVIM, containing a six lysine repeat and a CAAX box, was added to target the construct to the plasma membrane. ECFP, enhanced cyan fluorescent protein; FHA1, forkhead associated domain 1; LRRATLVD, PKA substrate sequence; Citrine, an improved version of yellow fluorescent protein; pm, plasma membrane targeting sequence. pm-AKAR2.2 is a novel membrane-targeted fluorescent reporter of PKA activity that could be a useful tool in studying spatial and temporal regulation of cAMP/PKA signaling in living cells. FRET emission ratio change of control NIH3T3 cells and NIH3T3 cells transiently transfected with p75NTR and co-transfected with the pm-AKAR3 (b) or AKAR3 (c) in response to forskolin, which activates adenylyl cyclase at the plasma membrane. Images show the localization for pm-AKAR3 (d) and AKAR3 (e). pm-AKAR3 localizes at the membrane (d). Experiments for b and c were performed three times in triplicate.

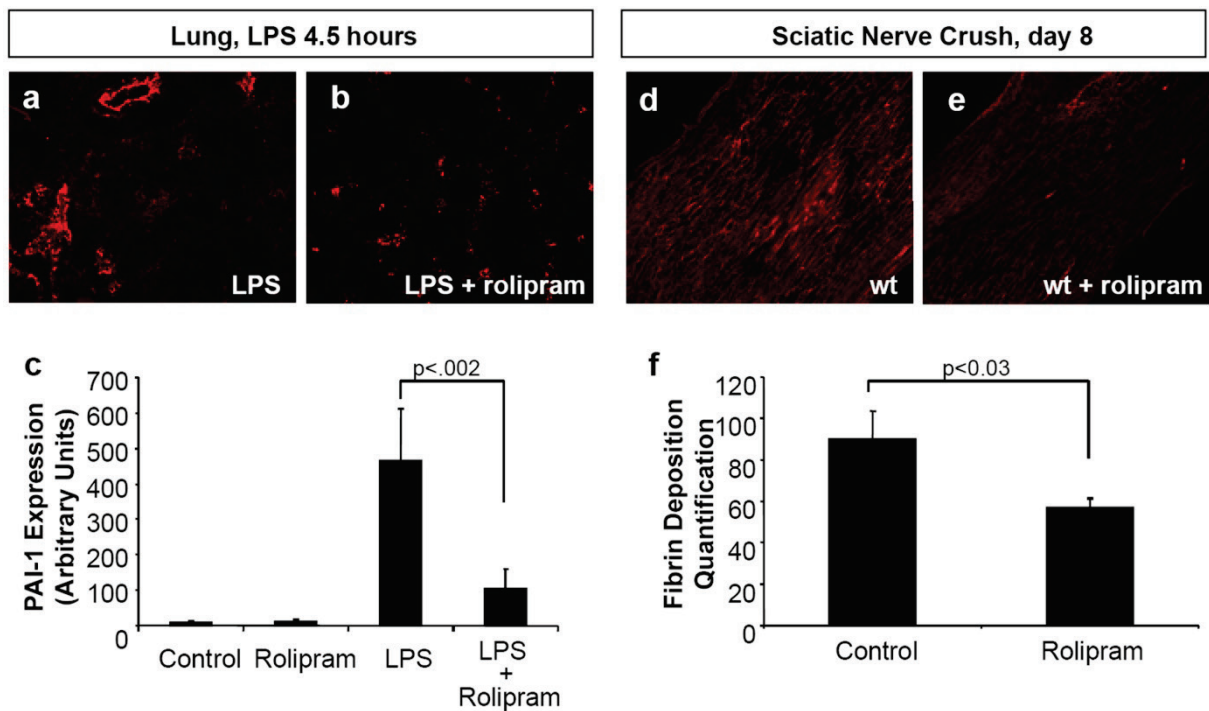


Figure S5. Rolipram decreases fibrin deposition both in LPS-induced lung fibrosis and sciatic nerve crush injuries. Fibrin deposition (red) is decreased in the lung in rolipram treated mice after induction of LPS-induced acute lung injury (b), when compared with mice treated with LPS alone (a). Quantification shows a 34% decrease in fibrin rolipram vs. control treated wt lungs after LPS-induced lung fibrosis (not depicted). Quantitative PCR of PAI-1 transcripts show a reduction of LPS-induced PAI-1 upregulation after rolipram treatment, but no effect of rolipram treatment alone (c). Rolipram treatment led to decreased levels of fibrin deposition in wt nerves 8 d after sciatic nerve crush injury (e), when compared with untreated wt nerves (d). Quantification revealed statistically significant reduction of fibrin deposition after rolipram treatment (f). Quantification of the lung samples is based on $n = 7$ LPS treated mice, $n = 4$ LPS+rolipram treated mice, $n = 5$ rolipram treated mice, and $n = 7$ control untreated mice. Quantification of the sciatic nerve samples is based on $n = 9$ wt and $n = 9$ wt+rolipram-treated mice.