Growing evidence indicates a role for inflammatory signaling in modifying neuronal excitability and promoting acquired epilepsies. Here we identify that signaling through an innate immune receptor toll-like receptor 4 (TLR4), in neurons, augments calcium permeable AMPA currents in the hippocampal dentate gyrus after brain injury. Blocking TLR4 signaling in vivo, early after brain injury, reduced dentate network excitability and epileptogenesis. TLR4 antagonism suppressed cellular inflammatory responses after injury without impacting controls. However, blocking TLR4 signaling augmented both network excitability and seizure susceptibility in uninjured controls. TLR4 antagonists failed to reduce post-injury seizure susceptibility when treatment was delayed was less efficacious when AMPA currents were transiently enhanced during TLR4 antagonist treatment. These data identify a novel immune receptor regulation of post-traumatic neuronal excitability which is independent of glia, demonstrate causal association between TLR4-dependent early increase in dentate excitability and epileptogenesis, and identify a promising mechanistic target to prevent posttraumatic epilepsy.