Neuropathic pain is defined as a chronic pain condition that occurs or persists after a primary lesion or dysfunction of the peripheral or central nervous system. Traumatic injury of peripheral nerves also increases the excitability of nociceptors in and around nerve trunks and involves components released from nerve terminals (neurogenic inflammation) and immunological and vascular components from cells resident within or recruited into the affected area. Action potentials generated in nociceptors and injured nerve fibers release excitatory neurotransmitters at their synaptic terminals such as L-glutamate and substance P and trigger cellular events in the central nervous system that extend over different time frames. Short-term alterations of neuronal excitability, reflected for example in rapid changes of neuronal discharge activity, are sensitive to conventional analgesics, and do not commonly involve alterations in activity-dependent gene expression. Novel compounds and new regimens for drug treatment to influence activity-dependent long-term changes in pain transducing and suppressive systems (pain matrix) are emerging.