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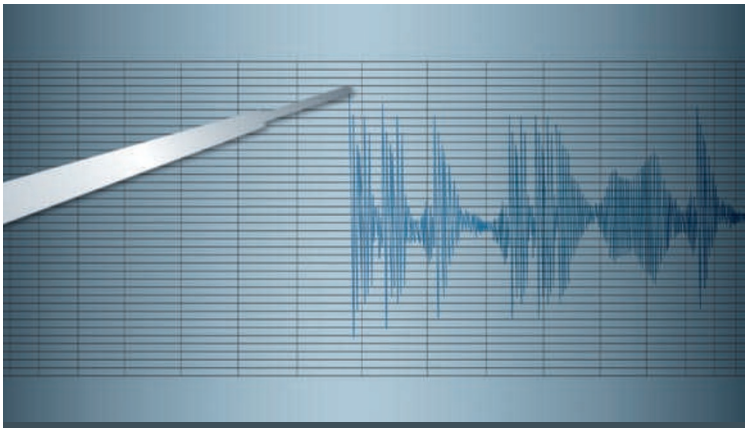

INNATE IMMUNITY

Toll tremors

Epilepsy is a chronic neurological disorder in which affected individuals suffer from recurring, unprovoked seizures. There is evidence to suggest that inflammatory processes can promote seizures, and damage to the brain following neurotrauma, stroke or infection is associated with a high risk of developing epilepsy. Now, a study in *Nature Medicine* has shown that the chromatin component high-mobility group box 1 (HMGB1), an endogenous Toll-like receptor 4 (TLR4) ligand, is released by stressed neurons and glial cells and has proconvulsant effects.

An emerging concept in immunology is that TLRs can be activated in sterile conditions in response to molecules released by damaged tissues. As epileptic seizures usually occur in the absence of infection, Maroso *et al.* hypothesized that damage-associated molecular patterns might be involved in triggering convulsions. Using mouse models of acute seizures, induced by activating glutamate receptors or inhibiting γ-aminobutyric acid (GABA) receptors in the brain, the authors observed increased and extranuclear expression of HMGB1 in astrocytes and microglial cells in the first few hours following seizure onset. In addition, although not detected in control hippocampi, TLR4 was expressed by hippocampal neurons and astrocytes after the onset of seizures, but not by the macrophage-related microglial cells. Importantly, similar patterns of HMGB1 and TLR4 expression were observed in the hippocampus of patients with temporal lobe epilepsy but not in control hippocampal tissue.

Next, to examine the functional relevance of increased levels of HMGB1 and TLR4 in epilepsy, the authors explored seizure development in mice treated with HMGB1. Strikingly, intrahippocampal injection of HMGB1 was found to increase the frequency and duration of experimentally induced seizures in a dose-dependent manner. To determine whether HMGB1 promoted seizures through TLR4 signalling, the authors induced experimental seizures in TLR4-deficient C3H/HeJ mice. Interestingly, C3H/HeJ mice were intrinsically less susceptible to experimental seizures, and intrahippocampal injection of HMGB1 could not induce seizures in these animals. Moreover, treating TLR4-sufficient mice with various TLR4 antagonists delayed the precipitation of seizures and decreased their frequency and duration. This was true both in acute seizure models and in chronic epileptic mice, which develop seizures that are resistant to anticonvulsant drugs.

This study has identified a new function for sterile TLR activation in the brain in promoting the development of seizures. Furthermore, these findings suggest that the pharmacological targeting of HMGB1 or TLR4 could prove to be an effective therapy for types of epilepsy that are currently untreatable.

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ORIGINAL RESEARCH PAPER Maroso, M. *et al.* Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. *Nature Med.* **16**, 413–419 (2010)