TOCILIZUMAB'S EFFECT ON EPILEPTOGENESIS AND PSYCHIATRIC COMORBIDITY IN WAG/RIJ RATS

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Recent evidence demonstrated that epilepsy is associated with inflammation and with elevated levels of cytokines (1). Accordingly, epileptic seizures can induce the production of cytokines, which in turn influence the pathogenesis and course of epilepsies (2). Effectively all of the pro-inflammatory cytokines are elevated in tissue or cerebral spinal fluid (CSF) from patients with chronic seizure disorders (3). Inflammation and cytokine release has been suspected also to participate in the process of epileptogenesis (4,5). IL-6 is a multifunctional cytokine that regulates inflammatory responses and other immune reactions. The increased expression of IL-6 both in brain and blood is closely associated with seizures and epilepsy; this increased level of IL-6 has neurotoxic and proconvulsive effects (6, 7,4). At present, little is known about the role of this cytokine in childhood absence epilepsy.

Tocilizumab is a humanized antihuman IL-6 receptor antibody that recognizes both the membrane-bound and the soluble form IL-6R and specifically blocks the proinflammatory effects of IL-6 (8). Based on this background, we investigated the possible effects of Tocilizumab (10 and 30mg/kg/day, os) on the development of absence seizures (electroencephalographic [EEG] recordings), depressive-like behavior (forced swimming test [FST]) and anxiety levels (elevated plus maze test [EPM]) in WAG/Rij rats (9). For the early chronic treatment, drug effects on the development of absence seizure were measured on EEG both 1 and 5 months after treatment withdrawal; furthermore, the acute effects of Tocilizumab on absence seizures in 6-month-old WAG/Rij rats were EEG measured. Tocilizumab, at both doses, significantly reduced the development of absence seizures in adult WAG/Rij rats at 6 months of age (1 month after treatment suspension) compared with untreated controls showing clear antiepileptogenic effects. This effect was not maintained when reassessed 4 months later (10 months of age). Decreased absence seizure development at 6 months of age was accompanied by reduced depressive-like behaviour in FST whereas no effects were observed on anxiety-related behaviour both at 6 and 10 months of age. These results suggest the possible role of IL-6 and consequent neuroinflammation in the epileptogenic process underlying the development of absence seizures in WAG/Rij rats.

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