In the CNS, endogenous cannabinoids are synthesized "on demand" as a protection against the consequences of a variety of stress factors, in response to sustained neuronal depolarization and elevated intracellular calcium levels. Both these events occur with seizure activity. We hypothesize that the endocannabinoid system is important for the protection against seizures. Two experiments were conducted to test this hypothesis.

1) Long-term effects of the cannabis antagonist rimonabant were investigated in healthy Wistar rats, which had no susceptibility to seizures. The drug, 30 mg/kg/day, was administered during 3 weeks. EEG was recorded continuously. In 3 out of 13 rats, spontaneous limbic convulsions were observed after 5-8 days, which were not related to the time of drug administration. We hypothesize that an accumulation of micro-injuries in the brain is responsible for these seizures.

2) Pre-selected Wistar rats that were prone to audiogenic seizures were subjected to chronic sound stimulation (25 stimuli at 2-3 days intervals). Audiogenic seizures were seen as short episodes of wild running behavior. After 25 repeated sound stimulations, rats were given rimonabant (30 mg/kg). Three hours after treatment again sound stimulation was given. Vehicle given to control rats (n=5) did not change the pattern of the response: the sound stimulus induced only running with a duration similar to that before treatment. In rats of the experimental group that displayed only a running response to repeated sound stimulation before treatment (n=5), the rimonabant led to the appearance of an additional post-running limbic clonus. In two rats that did show limbic component of audiogenic seizures, rimonabant induced a prolongation of selective the limbic seizures.

In conclusion: Elimination of the endogenous cannabinoid tone may increase seizure susceptibility and thus it is likely that the endocannabinoid system protects the CNS against seizures.