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*MEETING ABSTRACT*

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## The G protein-biased kappa opioid receptor agonist 6′-GNTI blocks hippocampal paroxysmal discharges without inducing aversion

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**Background:** Neuropsychiatric disorders are one of the main challenges of medicine with epilepsies representing some of the most frequent. Temporal lobe epilepsy (TLE) is the most common type of epilepsies and is often accompanied by marked neuronal degeneration. It was shown that the deletion of prodynorphin in mice and low expression in humans is associated with increased epilepsy vulnerability. Dynorphin targets opioid receptors and in particular the κ opioid receptor. Kappa receptors are located in strategically ideal places to control hippocampal excitability also in chronic TLE. The aim of this study was to investigate the potential of κ receptor agonists as anti-epileptic drugs (AEDs) in a mouse model of drug-resistant TLE.

**Methods:** Fifteen C57BL/6N male mice were injected unilaterally with kainic acid (KA; 1 nmol in 50 nl saline; $n = 10$) into the dorsal hippocampus. Four-channel EEG traces were recorded from ipsi- and contralateral hippocampi and motorcortices applying depth- and surface electrodes from freely moving mice, respectively. The κ receptor-specific agonist U-50488H, saline or one the new AEDs oxcarbazepine, lamotrigine and levetiracetam were applied i.p., while the biased κ receptor partial agonist 6′-GNTI was delivered i.c.v. through a guide canula. Number and duration of EEG seizures were automatically evaluated for the 60 min preceding and following the injections. Another group of animals (20 male mice C57BL/6N) was tested in the conditioned place avoidance (CPA) paradigm for U-50488H and 6′-GNTI.

**Results:** Spike trains and hippocampal paroxysmal discharges (HPDs) in the ipsilateral hippocampus were observed starting from day 5 after KA injection. Application of either U-50488H or 6′-GNTI decreases both spike trains and HPDs caused by KA in a dose-dependent manner. The AEDs lamotrigine and oxcarbazepine only reduced spike trains. As expected, the CPA experiments revealed that the animals conditioned to U-50488H developed avoidance for the compartment paired with this drug. On the other hand the biased κ receptor agonist 6′-GNTI did not produce any avoidance.

**Discussion:** Our data demonstrate the anticonvulsant action of κ receptor agonists in the chronic phase of epilepsy, comparable to the effect of 2.5 mg/kg diazepam. Furthermore, we demonstrate that the biased κ receptor partial agonist 6′-GNTI does not induce place avoidance in the CPA paradigm. The absence of κ receptor-induced dysphoria is probably due to the fact that 6′-GNTI does not recruit the β-arrestin pathway.

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