

INTERACTION OF GYKI 52466, A SELECTIVE NON-COMPETITIVE ANTAGONIST OF AMPA/KAINATE RECEPTORS, WITH CONVENTIONAL ANTIEPILEPTIC DRUGS IN AMYGDALA-KINDLED SEIZURES IN RATS

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GYKI 52466 [1,4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine], a non-competitive AMPA/kainate receptor antagonist, administered *ip* at the dose of 5 mg/kg, exerted a significant anticonvulsant effect, as it decreased seizure and afterdischarge durations, being ineffective at 2 mg/kg. Subsequently, GYKI 52466 (2 mg/kg) was combined with antiepileptic drugs at doses ineffective in fully kindled rats. Co-administration of GYKI 52466 with clonazepam (0.003 mg/kg *ip*) resulted in a significant reduction of seizure severity (by 20%), seizure duration (by 31%) and afterdischarge duration (by 24%). Co-injection of GYKI 52466 with valproate (75 mg/kg *ip*) also resulted in the respective 8%, 16%, and 17% reductions of the three studied seizure parameters. No protection was observed when GYKI 52466 was co-administered with carbamazepine (20 mg/kg *ip*), phenobarbital (20 mg/kg *ip*), or diphenylhydantoin (40 mg/kg *ip*). Combinations of GYKI 52466 with antiepileptic drugs did not cause any significant motor (rotarod test) or long-term memory deficits (passive avoidance task). Only GYKI 52466 administered alone at 5 mg/kg, caused a significant impairment of retention in amygdala-kindled rats. The interaction at a pharmacokinetic level, at least in case of the combination of GYKI 52466 with valproate, can be excluded because GYKI 52466 did not interfere with the free plasma level of valproate. These results give further support to the idea of a potential clinical benefits of the combined treatment of AMPA/kainate receptor antagonists with some antiepileptic drugs.

Keywords: antiepileptics, GYKI 52466, kindling, seizures

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