Perampanel effects in the WAG/Rij rat model of epileptogenesis, absence epilepsy and comorbid depressive-like behaviour

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Perampanel (PER), a selective non-competitive AMPA receptor antagonist(1), has demonstrated efficacy and tolerability for patients with partial seizures in three multinational phase III studies(2;3). PER is approved for adjunctive treatment of partial seizures with or without secondarily generalized seizures in patients with epilepsy. Furthermore, PER exhibited broad-spectrum efficacy in several animal models of seizures(1). PER efficacy on spontaneous seizures in animal models of chronic epilepsy has not yet been reported. Prevention of epileptogenesis is a priority research in the field of epilepsy. Most of the marketed antiepileptic drugs have been developed primarily in models of acute seizures (not of epileptogenesis) and do not have antiepileptogenic effects. A potentially promising therapeutic target to prevent epileptogenesis is the AMPA-type glutamate receptor. We have demonstrated that epilepsy in WAG/Rij rats results from an epileptogenic processes, and pharmacological intervention can prevent absence seizure development(4).
Here, we investigated for the first time, the effect of some treatment schedules (i.e. early chronic, sub-chronic and acute) with PER (1 and 3mg/Kg per o.s.) on the development of absence seizures and related psychiatric/neurologic comorbidity in WAG/Rij rats, a genetic model of absence epilepsy, epileptogenesis and mild-depression comorbidity following our previously validated protocol(5). 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 sub-chronic (7 days of treatment) and acute effects of PER on spike-wave discharges (SWDs) in 6-month-old WAG/Rij rats were EEG measured.
PER only at the dose of 3mg/kg significantly reduced the development of absence seizures in adult WAG/Rij rats both at 6 months of age (1 month after treatment suspension) and at 10 months of age (5 months after treatment suspension) compared with untreated controls showing clear antiepileptogenic effects. Sub-chronic and acute PER were completely ineffective against absence seizures since all measured SWDs parameters were not significantly different from control.
In the forced swimming test (FST), sub-chronic and acute PER treatment did not induce any significant change in immobility time (IT), however, decreased total distance moved and mean velocity were observed and accompanied by clear signs of drug-induced ataxia as also showed by motor deficit in the activity cage test. This effect disappeared in the chronic treatment at both 5 and 10 months of age. In the two anxiety models used, Elevated plus maze test (EPM) and Open-field test (OF), PER showed only minor effects because only acute treatment showed some anxiolytic properties improving all parameters in OF. In conclusion, our results suggest that PER might be a possible strategy for preventing epileptogenesis without affecting animal behaviour and comorbidity.

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