PPAR-alpha agonists as novel antiepileptic drugs: preclinical findings and preliminary clinical results

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Nicotinic acetylcholine receptors (nAChRs) are involved in seizure mechanisms. Hence, nocturnal frontal lobe epilepsy (NFLE) was the first idiopathic epilepsy linked with specific mutations in α4 or β2 nAChR subunit genes. These mutations confer gain of function to nAChRs by increasing sensitivity toward acetylcholine. Consistently, nicotine elicits seizures through β2 subunit containing nAChRs (β2*nAChRs) and mimics the excessive nAChR activation observed in animal models of the disease.These effects might be based on the extensive expression of β2*nAChRs in thalamo-cortical, hippocampal and frontal regions, which are considered amongst the structures most prone to initiate and maintain epileptic activity. Thus, negative regulation of β2*nAChRs might represent a potential therapeutic approach in NFLE.

We previously discovered that nicotine-induced electrophysiological and behavioral effects are suppressed by ligands to the peroxisome-proliferator-activated receptor-α (PPARα). PPARα are nuclear receptors, are expressed by neurons in many brain regions, and are activated by endogenous ligands, such as fatty acids and eicosanoid derivatives, and by synthetic ligands such as hypolipidemic fibrates. Thus, in light of the potential therapeutic efficacy of PPARα agonists in nAChR-mediated epilepsies, we investigated whether treatments with PPARα ligands (WY14643 and fenofibrate) reduce the severity of nicotine-induced seizures in experimental animals and are effective in pharmacoresistant NFLE patients.

Preclinical studies. We utilized behavioural and electroencephalographic (EEG) experiments in C57BL/J6 mice and in vitro patch clamp recordings from mice and rats. WY14643 (WY) was acutely administered at the dose of 80 mg/kg i.p. Fenofibrate, clinically available for lipid disorder metabolism, was chronically administered with food (0.2% w/w). The fenofibrate containing diet was administered for 14 days. Control mice were fed with an identical and equicalorical diet, without fenofibrate. In each animal, EEG electrodes were implanted 7 days before the beginning of the treatments.

Convulsive dose of nicotine (10 mg/kg s.c.) evoked seizures and bursts of spike-waves discharges in all treated mice. Mice acutely pre-treated with the PPARα agonist WY were significantly protected against nicotine-induced seizures when compared with controls. The protective effect of WY was reverted by the PPARα antagonist MK886 (MK, 3 mg/kg). Fenofibrate-treated mice were also significantly protected against nicotine-induced seizures when compared with controls. Following drug washout for 14 days the convulsive effects of nicotine were restored.

We performed patch clamp recordings of spontaneous inhibitory postsynaptic currents (sIPSCs) from frontal cortex layer II/III pyramidal neurons and we found that both acute and chronic treatment with PPARα agonists abolished nicotine-induced sIPSC increases.

Cinical study. 600 mg/die fenofibrate was administered as add-on therapy to 8 refractory NFLE patients. Preliminary data indicate that all patients who completed the initial 6-month trial reported significant subjective and objective (polysomnographic EEG recordings) improvement and requested to carry on with the treatment.

Our study shows that acute or chronic PPARα agonists, including the clinically available fenofibrate, reduce nicotine-induced behavioral and EEG seizure expression in animals and improves NFLE symptoms. These effects are mediated by the regulation of β2*nAChRs induced by PPARα via phosphorylation of the β2 subunit.

The present data confirm the relationship between nAChRs and epileptogenesis and give support to the role played by nuclear receptors PPARα in the modulation of nAChR function in the CNS. These effects can be therapeutically exploited for idiopathic or genetically determined forms of epilepsy where nAChRs play a major role.

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