mTOR inhibition modulates lipopolysaccharide inflammatory response in a genetic animal model of absence epilepsy

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The mammalian target of rapamycin (mTOR) signaling pathway has been recently indicated as a suitable drug target for the prevention of epileptogenesis[1] in view of its activation during the epileptogenic phase of several animal epilepsy models and the ability of its specific inhibitor, rapamycin (RAP), to prevent the development of spontaneous seizures (both convulsive and non-convulsive)[2;3]; however, the exact mechanism underlying this antiepileptogenic effect still remains unclear. The mTOR pathway is known for its involvement in the control of the immune system (as well as other important physiological functions)[4;5]. Since neuroinflammation is now recognized as a major contributor to epileptogenesis and associated changes in neuronal excitability[6;1], we wished to examine whether the beneficial neuroprotective effects of mTOR modulation could involve a suppression of the neuroinflammatory process in epileptic brain. We therefore examined the effects of rapamycin, an mTOR inhibitor, on the production of pro-inflammatory cytokines in a genetic (WAG/Rij) rat model of absence epilepsy. We have previously shown that rapamycin inhibits the aggravation of absence seizures produced by intracerebral administration of the bacterial endotoxin lipopolysaccharide (LPS) in WAG/Rij rats[2]. We now provide evidence that this effect is correlated with the ability of rapamycin to dampen and delay the increase in neuroinflammatory cytokines (IL-1β and TNF-α) produced by LPS, most likely through inhibition of the activation of nuclear factor-κB (NF-κB), a transcription factor known to be involved in the regulation of neuroinflammatory processes. Our results suggest that such a mechanism could contribute to the antiseizure and antiepileptogenic effects of rapamycin in this absence epilepsy model and further highlight the potential therapeutic usefulness of mTOR inhibition in the management of human epilepsy disorders.