Lovastatin improves impaired synaptic plasticity and phasic alertness in patients with neurofibromatosis type 1.

Neurofibromatosis type 1 (NF1) is one of the most common genetic disorders causing learning disabilities by mutations in the neurofibromin gene, an important inhibitor of the RAS pathway. In a mouse model of NF1, a loss of function mutation of the neurofibromin gene resulted in increased gamma aminobutyric acid (GABA)-mediated inhibition which led to decreased synaptic plasticity and deficits in attentional performance. Most importantly, these deficits were normalized by lovastatin. This placebo-controlled, double blind, randomized study aimed to investigate synaptic plasticity and cognition in humans with NF1 and tried to answer the question whether potential deficits may be rescued by lovastatin. In NF1 patients (n = 11; 19-44 years) and healthy controls (HC; n = 11; 19-31 years) paired pulse transcranial magnetic stimulation (TMS) was used to study intracortical inhibition (paired pulse) and synaptic plasticity (paired associative stimulation). On behavioural level the Test of Attentional Performance (TAP) was used. To study the effect of 200 mg lovastatin for 4 days on all these parameters, a placebo-controlled, double blind, randomized trial was performed. In patients with NF1, lovastatin revealed significant
decrease of intracortical inhibition, significant increase of synaptic plasticity as well as significant increase of phasic alertness. Compared to HC, patients with NF1 exposed increased intracortical inhibition, impaired synaptic plasticity and deficits in phasic alertness. This study demonstrates, for the first time, a link between a pathological RAS pathway activity, intracortical inhibition and impaired synaptic plasticity and its rescue by lovastatin in humans. Our findings revealed mechanisms of attention disorders in humans with NF1 and support the idea of a potential clinical benefit of lovastatin as a therapeutic option.

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