Taking pain out of NGF: a new therapeutic approach for Alzheimer's Disease

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The clinical application of human Nerve Growth Factor (NGF) to prevent or slow human neurodegenerative diseases, and in particular Alzheimer's disease, has a strong scientific rationale, based on the actions of NGF on basal forebrain cholinergic neurons, but also on results linking alterations in the NGF/proNGF signaling to the activation of aberrant APP processing. However, NGF delivery to the brain in a safe and long-term manner, limiting the adverse effects of NGF in activating nociceptive responses, has represented a significant challenge. One severe limitation has been the pain inducing activity of NGF, linked to its physiological actions on the sensitization of nociceptors. We developed a recombinant form of human NGF (hNGFP61S/R100E, painless NGF), inspired by a mutation in the NGFB gene found in patients suffering from a form of congenital insensitivity to pain (Hereditary Sensory Autonomic neuropathy Type V (HSAN V)). Painless NGF has identical neurotrophic properties to human NGF, is traceable against endogenous NGF and has a greatly reduced ability to activate nociception. We recently demonstrated that the non-invasive intranasal delivery of painless NGF in anti-NGF AD11 and in APPxPS1 mice leads to an effective rescue of memory impairments and AD-like neurodegeneration in these mice (Capsoni et al., PloS One 2012). We now show that painless NGF, intranasally delivered to the 5XFAD mouse model of Alzheimer's disease, induces a complete rescue of spatial memory deficit and a decrease in the plaque load. The mechanisms underlying these therepautic effects are linked to a clear rescue of synaptic dysfunctions, measured electrophysiologically in the entorhinal cortex, as well a to a reduction of microglia phagocytic activity and of pathological APP processing. Moreover, we demonstrate that both acute and chronic intranasal administration of painless NGF does not trigger pain in 5XFAD mice, measured at the behavioural level.
In conclusion, this findings confirm that painless NGF is a viable, potentially disease modifying, therapeutic option to increase NGF activity in the brain in a safe and non invasive way, increasing its pharmacological therapeutic window and provide further proof that the neuroprotective activity of NGF goes well beyond the expected neurotrophic activity on cholinergic neurons.