Targeting metabolic disturbances of central cholinergic circuits to recover cognition in AD and T2D

The signalling pathway activated by NGF, a key neurotrophin for the metabolism of basal forebrain cholinergic neurons (BFCN), is one of the first homeostatic systems affected in prodromal Alzheimer’s Disease (AD). BFCN projections to cortical and hippocampal target circuits are key to LTP, learning and memory and higher cognition in the mammalian brain. In line with this, we recently demonstrated the molecular mechanisms underlying NGF control of Amyloid Precursor Protein (APP) phosphorylation at key C-terminal sites, shuttling APP to the Golgi system and leading to preferential anti-amylodogenic processing in physiological conditions (Triaca et al., 2016; Triaca et al., 2018).

Of note, BFCN demise and NGF signalling dysfunctions have been thought for decades to occur in AD late stages, as a mere consequence of amyloid-driven disruption of the retrograde axonal transport of neurotrophins to BFCN. Nowadays, a wealth of knowledge from neuroimaging studies in humans affected by Mild cognitive impairment (MCI) and AD is potentially opening a new scenario: neurotrophic pathways impairment in BFCN occurs, possibly because of their higher metabolic requirements, at the onset of AD and correlates better than amyloid load with cognitive decline. Central metabolic dysfunction is considered a well-established feature of AD, and brain glucose hypometabolism is associated with AD dementia (Whitmer et al. 2008; Craft 2009) even before early AD manifestation, and proposed as good predictor of MCI progression toward AD, although the underlying mechanisms are still under debate.

To investigate these mechanisms, we developed an in vitro model of insulin resistance in rat cholinergic neurons. In particular, employing hyperinsulinemic culture conditions, BFCNs were shown to develop insulin resistance that was revealed by reduced activation of both Insulin receptor (IR) and insulin substrate receptor 1 (IRS1). Further, insulin-resistant neurons expressed a higher level of serine phosphorylated IRS1, a well-known hallmark of insulin resistance, and showed reduced glucose transporter 2 (Glut2) translocation to plasma membrane resulting in lower glucose uptake. Also, neuronal activity was repressed as seen by a decrease in nuclear c-Fos expression. Significantly NGF was shown to improve insulin resistance by TrkA-driven tyrosine phosphorylation of IRS1 and its consequent activation, both in the in vitro model and 3xTg-AD mice. Indeed, nasal administration of NGF in 3xTg AD mice rescued insulin resistance in the medial septum in the pre-symptomatic phase several months before it is detectable in the neocortex and hippocampus (Sposato et al. 2018).

Further, the involvement of cholesterol derivatives is under scrutiny as key driver of neuronal insulin resistance in AD and T2D, focusing on the 27-hydroxycholesterol (27-OH), a peripherally generated cholesterol metabolite able to enter the brain modulating local cholesterol biosynthesis and detoxification. Increased 27-OH level in brain, blood and CSF is a characteristic AD trait and our preliminary data indicate a role for 27-OH in perturbing NGF and insulin signalling in BFCN in vitro and in vivo (Fico et al., 2019).

Taken together, these findings are of potential clinical relevance for both AD and Type 2 diabetes (T2D) cognitive deficits. Thus, neurotrophins and NGF have been long time ago suggested for neuroprotection in cholinergic diseases, although with poor clinical outcomes.

To overcome the well-known limitation of Blood-Brain Barrier transport to the brain of a macromolecules like NGF, brain targeting via the nasal route is currently under investigation. The use of small peptides like human NGF 1-14 (hNGF) to reach relevant brain target areas in animal models of age and/or diet- related neurodegeneration has recently been addressed in vitro in NGF responsive neurons (BFCN and DRG; Triaca et al., 2020). We investigated the NGF-like properties of the human NGF 1-14 sequence (hNGF-1-14), by resorting to primary dorsal root ganglia and cholinergic neurons. We found that hNGF-1-14 peptides retain biological activity of the whole NGF molecule fully sustaining survival and neurites elongation of primary dorsal root ganglia (DRG) neurons. Further, hNGF-1-14 peptides activate the early and late NGF-TrkA pathway.
signalling intermediates, resulting in CREB nuclear translocation, Immediate Early Gene c-Fos transcription, ChAT level increase and finally miniEPSP potentiation.

Thus, the findings here reported pinpoint the hNGF (1-14) peptide, and in particular its acetylated monomeric form, as novel promising therapeutic tools to achieve TrkA-specific efficient activation of the NGF pathway in NGF-target neurons in vitro. The feasibility and efficacy of nasal administration of the NGF mimetic hNGF in vivo will open the way to novel and non-invasive therapeutic approaches with the final goal to improve brain resilience to cognitive ageing and AD pathology.

References:


Keywords: NGF, BFCN, brain insulin resistance, oxysterols, Alzheimer’s Disease, T2D

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Grants: CNR partner, “Grandi Progetti La Sapienza” to Prof. A. Greco.