**Neuronal-derived exosomes: a promising tool to identify alterations of brain insulin signaling in Alzheimer disease and Down syndrome**

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**Background/objectives:** Altered brain insulin signaling with reduced downstream neuronal plasticity mechanisms parallel cognitive decline during ageing and Alzheimer disease (AD). Down Syndrome (DS) brain, early recapitulates many features of ageing and even AD suggesting that alterations of brain insulin signaling may contribute to the observed phenotype. Absence of biomarkers for altered brain insulin signaling limit studies in living subjects, although recent analyses proposed the use of neuronal-derived exosomes (NDE) as a reliable diagnostic tool. We, therefore, aimed to investigate whether alterations of brain insulin signaling can be identified through the evaluation of NDE cargo in DS population.

**Methods:** Levels of insulin receptor (IR), phospho-IRS1Ser636 (inhibited form), and biliverdin reductase-A (BVR-A, a regulator of IR/IRS1 axis) were evaluated in plasma-resident NDE collected from a cohort of young DS and matched Ctrl (n=10/group). To validate changes observed in NDE and to unravel whether alterations of b-IS could be associated with impaired synaptic processes, we evaluated levels of IR/pIRSSer636/BVR-A along with changes of syntaxin, PSD95 and atypical protein kinase Cζ (PKCζ) – that are well-established player in LTP maintenance – in post-mortem cortical samples from young DS and age-matched Ctrl (n=8/group).

**Results:** Reduced IR levels (~60%, p<0.05) without changes of pIRSSer636 and BVR-A in NDE from DS subjects, were found. Similarly, reduced IR levels (~50%, p<0.05) were observed in DS cortical samples confirming NDE-related observations. Moreover, reduced levels of synaptic proteins in DS brain [syntaxin (~50%, p<0.05); PSD95 (~40%, p<0.05); and PKCζ (~70%, p<0.01)], were observed. Spearman correlation analyses showed a significant association between (i) IR and either syntaxin (r=0.58, p<0.05) or PSD95 (r=0.62, p<0.05); and (ii) PKCζ and PSD95 (r=0.54, p<0.05), suggesting that reduced IR levels might be associated with an impaired synaptic plasticity early in DS.

**Conclusions:** Reduced IR levels in NDE highlight premature alterations of brain insulin signaling that could be targeted to slow cognitive decline in DS.