BEHAVIOURAL AND NEUROPATHOLOGICAL EFFECTS OF INTRANASAL INSULIN TREATMENT IN A TRIPLE-TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE (3×TG-AD)

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive cognitive impairment and by the appearance of non-cognitive or behavioural symptoms. Currently there is no cure for AD and, to this regard, it's growing the interest in the identification of novel therapeutic targets for the development of new promising drugs. Recently, it was observed that insulin is able to play a neuroprotective and a neurotrophic action within the central nervous system (CNS) (Craft and Watson, 2004; Hoyer, 2004; Stockhorst et al, 2004).

In particular, recent evidence have shown that CNS insulin is widely involved in cognition, especially in memory and learning processes, suggesting a strict relation between AD and diabetes (Ott et al, 1996; Arvanitakis et al, 2004; Banks et al, 2012). In fact, type 2 diabetes mellitus (T2DM) patients present several alterations of insulin signaling that lead to cognitive and no cognitive symptoms, such as those manifested by AD patients. To this regard, diabetes mellitus (DM) is fully recognized as an additional risk factor of AD (Janson et al, 2004; Craft and Watson, 2004).

Although it's not yet entirely clear what is the neuropathological link between AD and DM, in support of this hypothesis it was demonstrated that AD patients show a central insulin-resistance condition (Steen et al, 2005; De La Monte, 2008), characterized by a reduced brain insulin receptor (IR) sensitivity, hyperphosphorylation of IR and insulin receptor substrate-1 and 2 (IRS-1/2), as well as decreased expression of insulin and insulin-like growth factor (IGF) receptor (Bedse et al, 2015).

On the other hand, it cannot be excluded that these alterations may be involved in the neuropathology of AD by one of the following mechanisms: increased expression of the amyloid precursor protein (APP), excessive formation and accumulation of the amyloid-β peptide (Aβ), impaired Aβ clearance and increased phosphorylation of tau protein (Steen et al, 2005; Zhao et al, 2009).

Based on these assumptions, the aim of the present study was to analyse the behavioural and neuropathological effects induced by insulin treatment in triple-transgenic mouse model of AD (3×Tg-AD). 3×Tg-AD model faithfully reproduces the cognitive impairment and the neuropathological alterations observed in human patients. In particular, 3×Tg-AD mice develop age-dependent Aβ and tau accumulation (Oddo et al, 2003) associated with cognitive decline and a depressive-like phenotype (Romano et al, 2014).

In this study, 4- and 10-month-old 3×Tg-AD mice and non-transgenic control mice (Non-Tg) were treated intranasally every other day for 2 months with human insulin (Humulin R U-100) or with vehicle (saline). The effects of the treatment were evaluated on mice at 6 or 12 months of age, that represents respectively the early- and the late-stage of AD-like pathology.

To evaluate the effects of the treatment on the cognitive domain, all mice were tested by the morris water maze test and the novel object recognition test. Instead to evaluate the effects of insulin on the emotionality domain, in particular to the depressive-like phenotype, mice were tested by the forced swimming test and the tail suspension test.

The expression levels of the main neuropathological hallmarks of AD (APP, Aβ and tau) were evaluated in frontal cortex and hippocampus of treated mice by western blotting and immunohistochemical experiments.

Overall, our results highlighted that the intranasally insulin treatment is able to modulate the behavioural phenotype of 3×Tg-AD mice in both the cognitive and the emotional domain. In particular, insulin administration seems to improve the short-term memory as well as the depressive-like phenotype in both 6- and 12-month-old 3×Tg-AD mice.

Moreover, these results are accompanied by a reduction of Aβ oligomers and hyperphosphorylated tau levels mainly in frontal cortex and hippocampus of 12-month-old 3×Tg-AD mice.

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