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Editorial Open Access

Insulin as Therapeutic Agent against Alzheimer's Disease

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Alzheimer's Disease (AD) is the most common form of dementia in the elderly and it is clinically characterized by gradual worsening of the symptoms. Patients affected by AD have, at the initial stage of the pathology, mild memory loss, difficulty performing routine tasks, trouble communicating and understanding written material. At the final stage of the disease they lose the ability to feed themselves, speak, recognize people and a constant care is typically necessary.

At microscopic level AD is characterized by neuronal cell loss and increasing deposition of Neurofibrillary Tangles (NTF) inside the cells and formation of amyloid plaques in the spaces among neurons and in the walls of blood vessels [1].

NTF are insoluble twisted fibers consisting primarily of the Tau protein, which, in physiological conditions, forms the microtubules. In Alzheimer's disease, however, Tau is chemically changed and the microtubule structures collapse.

Amyloid plaques are mainly composed by the amyloid beta peptide (A-beta), a 39-to-43 peptide originating from the sequential enzymatic cleavage of the larger trans-membrane protein called Amyloid Precursor Protein (APP). Accumulation of A-beta is hypothesized to trigger the pathogenic cascade leading to AD [2] and in the last decade, many observations confirm that small A-beta oligomers, (also called A-beta-Derived Diffusible Ligands (ADDLs)) instead of large fibril aggregates, are the most dangerous and toxic species in the AD onset [3,4]. Their accumulation and binding in the proximity of synapses causes oxidative stress, loss of spines and receptors critical for neuron plasticity and memory [5].

On the basis of the large number of observations, since the first years of the XXI century it has been suggested a close tie between AD and disorder in insulin signaling, in particular the insulin resistance associated to diabetes type 2 [6-10] so that AD is recognized as a neuroendocrine disorder and it has been defined as a type of "diabetes type 3" or "brain diabetes" [11,12].

It has been reported [13] that insulin can protect cultured rat neurons against A-beta induced toxicity. Experimental data [14] have demonstrated that A-beta competes for binding of insulin to its receptor. This results in a decrease in the autophosphorylation of the insulin receptor. Other studies indicate that insulin, interacting with A-beta, inhibits its fibrillar growth, as shown in a cell-free assay and in the cell surface of human brain pericytes, reducing the A-beta toxic effect [15]. Recently, it has been proposed that physiological insulin and pathological ADDLs are capable to regulate their mutual binding site abundance, creating a competitive balance between synapse survival and degeneration. The decline of the insulin signaling in the brain with the age displaces this delicate equilibrium in favor of the ADDLs [5]; thus, the use of new drugs recovering this balance could be a promising therapeutic strategy.

On these starting points, what is, at molecular level, the effect of insulin against A-beta toxicity? Some evidences indicate that insulin can recover the cell viability by inhibition of intrinsic apoptotic program, involving caspase 9 and 3 activation [10]. Moreover, insulin prevents mitochondrial dysfunction by inhibition of the Reactive Oxygen Species (ROS) formation and activation of specific cell signaling. Insulin activates the serine-threonine kinase Akt, a protein involved in survival pathway, suggesting that insulin signaling provides a physiological defense mechanism to contrast the death program triggered by A-beta oligomers [16,17].

Akt phosphorylation needs activation or inhibition of several proteins involved in the apoptotic signaling cascade such as the Bcl-2 protein family. Furthermore, insulin promotes its survival program by shuttling of Akt in different sub-cellular compartments [18]. Translocation of Akt from the cytoplasm to the nucleus, induces negative regulation of gene expressions via Foxo3a, a pro-apoptotic transcription factor. Akt translocation from the cytoplasm to the mitochondrion mediates, instead, the protection of this organelle through phosphorylation of Bad and probably HK-II, two proteins involved in cell death. Thus, the same molecule, depending on its phosphorylated or unphosphorylated state, can be present in different cellular compartments such as nucleus, cytoplasm and mitochondrion and this localization is essential to determine whether the cell will live or die. Therefore, a precise balance between signals promoting survival and apoptosis is important for determining cell fate [18]. Because insulin signaling in the brain is known to decline with age the result of this balance represents a risk factor for AD well suited for therapeutic intervention with the same insulin.

In the last few years many attempts have been done to slow or stop the AD progression with the aid of insulin but the usual method used to treat diabetes could be very dangerous for AD patients and for this reason alternative routes of administration have been explored.

The intranasal administration of insulin, already tested for diabetes treatment, to AD patients has improved delayed memory. Changes in memory and function were associated with changes in the A-beta 42 level and in the Tau protein–to-A-beta 42 ratio in cerebrospinal fluid [19]. Unfortunately, together with positive effects this method presents contraindications such as irritation and damage of the nasal mucosa [20] and, surely more important, increase of the systolic, diastolic and mean arterial blood pressures [21].

The improvement of delivery systems capable to overcome the blood brain barrier and deliver the insulin straight in the brain could be a promising route to avoid unpleasant side effects.

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