IGF-I-like effects of beta Amyloid monomers

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Amyloid beta protein (Aβ) is believed to play a major role in the development of Alzheimer's disease (AD) pathology. The attitude of Aβ to undergo conformational changes and subsequent aggregation has always been a limit in finding out the activities of the peptide. Over the years, by distinct approaches, the role of oligomeric forms has been clarified, and it is now accepted that soluble aggregates of Aß are the neurotoxic species in AD. However, increasing data suggest an emerging view of the Aß peptide as part of normal neuronal metabolism. Aß is secreted from healthy neurons in response to neuronal activity, and in turn it can down-regulate excitatory synaptic transmission (Kamenetz at al., 2003). More important, production of Aß seems to be related to the improvement in the neurological status of patients who undergo invasive intracranial monitoring after acute brain injury (Brody et al, 2008). Despite of data pointing to the role of Aβ under phisiological condition, the way by which the peptide exerts its activity is unclear.

We have found a protective activity of monomeric human $Aß_{1-42}$ in cultured cortical neurons, which was abrogated by inhibitors of insulin/insulin-like growth factor (IGF) receptor signaling (Giuffrida et al., 2009). Interestingly, a dysregulation of the insulin/IGF-1 signaling is thought to sustain a crucial role in the pathogenesis of late-onset AD (LiL. et al., 2007). We have elucidated the underlying mechanisms of the newly observed insulin/IGF-1-like activity of $Aß_{1-42}$. We have searched for a direct peptide-receptor interaction by using 3T3-like mouse fibroblasts with a disrupted IGF-IR gene and transfected with either human IGF-IR (R^+ cells) or type-A IR (IR-A) cDNA (Pandini et al., 2002). Data showed that $Aß_{1-42}$ was able to potentiate the ability of IGF-I to promote autophosphorylation of the receptor-kinase domain on immunoadsorbed IGF-IRs derived from R^+ cells. A slight enhancement of IGF-IR phosphorylation was also observed in the absence of IGF-1, while no effect was observed on immunoadsorbed IR-A, both in the absence and presence of insulin. IGF-1 is known to stimulate glucose uptake by mechanisms similar to those used by insulin, including membrane translocation of glucose transporters (GLUTs). We investigated the ability of $Aß_{1-42}$ to promote glucose uptake both in primary cortical neurons and in L6 rat skeletal muscle cells. A significant increase of the fluorescent non-hydrolyzable glucose analogue, 6-(N-(7-nitrobenzen-2-oxa-1,3-diazol-4-yl)amino)-6-deoxyglucose (6-NBDG), was observed in glucose starved neurons exposed for 30 min to either monomeric $Aß_{1-42}$ (100 nM) or recombinant rat IGF-1 at concentrations (5 ng/ml) that selectively activate IGF-IR. 6-NBDG up-take was assessed by confocal microscopy and flow-cytometry. Consistent with its ability to engage IGF-IRs, monomeric $Aß_{1-42}$ (100 nM) increased the population of 6-$NBDG^+$ neurons following starvation, and its action was inhibited by the IGF-IR inhibitor, PPP (500 nM). Our data demonstrate that monomeric $Aß_{1-42}$ acts as a mixed agonist/positive allosteric modulator of IGF-IR and could be therefore critical for maintaining neuronal glucose homeostasis. Accordingly, KCl-stimulated glucose uptake (40 mM for 15 min) in cultured neurons was blunted after blocking endogenous Aß production with the γ-secretase inhibitor IX (100 nM), and re-established by exogenous $Aß_{1-42}$ monomers or in the presence of cerebrospinal fluid Aß.

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