ADAM10 nella Malattia di Huntington: studio molecolare e funzionale della sinapsi. ADAM10 in Huntington’s disease: molecular and functional study of the synapse

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ADAM10 nella Malattia di Huntington: studio molecolare e funzionale della sinapsi. ADAM10 in Huntington's disease: molecular and functional study of the synapse

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Research Abstract
Huntington’s disease (HD) is a genetic disease caused by the expansion of a polyglutamine tract in huntingtin protein (htt) (HDCRG, 1993). different pathogenetic mechanisms have been proposed to explain the neurodegeneration in HD. To date the dysfunction of excitatory synaptic

circuits are one of the most validated mechanisms of pathology and significant are the efforts to identify drugs that normalize the activity (Zuccato, 2010). Some compounds that have proven effective in murine models, have not led to significant benefits in patient causing side effects. The search for new drugs that counter the dysfunction of glutamatergic synapses remains, therefore, an important aspect of HD research.

This project aims to study the metalloproteinase ADAM10 in HD. Recently associated with the activity of the glutamatergic synapses, ADAM10 is a new HTT activities target in Huntington brain. Our studies have, in fact, demonstrated that htt healthy controls the ADAM10 activity both during development of the brain that in the adult brain (Lo Sardo and Zuccato, 2012).

ADAM10 has proteolytic activity on a wide range of synaptic proteins. And 'it implicated in the development of the central nervous system and in maintaining the structure and function of synapses (Yang, 2006). Alterations in the activity of ADAM10 are therefore dangerous for the brain. Dysfunction of the enzyme are described in Alzheimer's Disease (Postina, 2004) and the overexpression of ADAM10 in mouse brain causes problems with memory and learning (Schmitt, 2006).

Our preliminary studies have revealed that:

the. levels of the active mature form of ADAM10 increase in brain tissue samples of three different murine models and MH in the patient's post-mortem tissue.

ii. administration of GI254023X, an inhibitor of ADAM10, significantly recovers main morphological defects observed in zebrafish embryos that express the human mutant htt.

On the basis of these data suggest that the increased levels of the active form of ADAM10 in the brain Huntington is the start of a series of events that determine the proteolytic cleavage of the synaptic enzyme substrates and, finally, dysfunction of the structure and of 'activities of glutamatergic synapses, contributing to the disease.

The first objective of the project will extend and validate the preliminary data by analyzing the levels of the active form of ADAM10 in brain samples of mouse models of HD during the progression of the disease and in the post-mortem patient. We will analyze also the proteolytic cleavage of synaptic targets the enzyme and attempt to determine if a failure ADAM10 is an early event. Finally, we will study, using functional proteomics approaches, the mechanism by which the mutant htt results in increased levels of the active form of ADAM10 in Huntington brain.

The second objective will be to normalize the levels of ADAM10 active in the brains of mice MH line transgenic R6 / 2 (Mangiarini, 1996) to determine if this intervention can improve the activity of synaptic circuits in addition to neuropathological and behavioral phenotype. We will use a strategy based on the peripheral administration of a Tat peptide that reaches the brain, and that it interferes with the mechanism that controls the transport of ADAM10 to the post-synaptic membrane and its activation. ADAM10 binds a protein called cargo SAP97 (Associated synaptic 97) that carries the enzyme to the post-synaptic compartment where it is converted into its active form (Marcello, 2007). Somministreremo to mice R6 / 2 the Tat-Pro peptide ADAM10709-729 that, by blocking the formation of the complex ADAM10 / SAP97, reduces the transport of ADAM10 to the post-synapses and hence its conversion to mature form (Marcello, 2007; Epis,

2010). ADAM10 and its substrates are critical for the development of synapses and neuronal survival. We are therefore aware that its excessive inhibition may be harmful to the brain (Saftig and Reiss, 2011; Epis, 2010). We will identify the peptide doses that normalize the levels of mature ADAM10 in mouse brain Huntington, making sure not to bring the levels of ADAM10 under physiological threshold. Using differential proteomic approaches will study whether the treatment allows the recovery of the synaptic proteome alterations observed in Huntington's mice. We will evaluate, in addition, the functional activity of the synapse through the analysis of the frequency of excitatory and inhibitory synaptic potentials that are altered in the R6 / 2 model. Finally, we take neuropathological and behavioral analysis.

Positive results will allow to propose ADAM10 as a new target for developing drugs that normalize the activity of synaptic circuits in HD.

Further information available at:

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