Identification and treatment of early cognitive deficits during ageing to prevent dementia

Individuals do not all show a reduction in mnemonic capacity with advancing age, but the ones who do, show it very early and, in general, the symptoms of mental decline are associated with the accumulation, in neurons, of alpha-synuclein and beta amyloid protein aggregates that can form fibrils - or filaments - potentially toxic to cells. In a young cell these aggregates, considered cellular waste, are enclosed within a vesicle (autophagosome) that carries them into lysosome, an organelle that breaks them down and recycles their constituents. With ageing, the aggregates increase and the lysosome's degradative capacity is reduced.

One of the lines of research in our laboratory deals with identifying the early mechanisms that precede the development of dementia in animal models. To identify middle-aged subjects with vulnerable memory, we set up and used a memory test in which we were able to manipulate the amount of information to remember (the number of objects), in order to make the task more difficult. This allowed us to separate subjects of the same age able to remember up to 6 different objects from those who are able to remember a maximum of 2 objects. In middle-aged subjects that fail the six different objects recognition task, the neuronal lysosomes are enlarged and engulfed with alpha-synuclein and beta amyloid aggregates in the hippocampus, a particular region of the brain that is crucial for memory.

The ultimate goal of our studies is to identify new therapies with symptomatic efficacy on cognitive symptoms and for this reason we have been working for some time on the use of dopaminergic drugs; at the same time we try to find molecules able to slow down the progression from mild cognitive symptoms to dementia.

In a recent study, we have shown that Spermidine, a polyamine naturally present in many foods, stimulates autophagy, and thus improves the degradative capacities of the cells. The study showed that one month treatment with Spermidine stimulates the expression of the transcription factor EB (TFEB), which controls the expression of genes responsible for autophagyllysosomal degradation and therefore promotes the cell cleaning from alpha-synuclein and beta amyloid aggregates. Once cleared the cell from these aggregates, we also observed that the synaptic communication, through the AMPA receptor, is restored and it allows the memory to function even under conditions of high information load in subjects with the deficit. In fact, in subjects with deficit in memory capacity we saw that the engulfment of lysosomes is associated with a defect in activating those communication processes between neurons that are necessary in young subjects to create new memories and that are transmitted by synapses through the glutamate receptor AMPA. Instead, these processes are preserved in young subjects, or in those aged but with intact memory. We will continue to study the effects of Spermidine in neurodegenerative diseases, alone and in combination with other treatments, and we will try to verify whether an enrichment of the diet may be sufficient to prevent the onset of dementia.

In the same project line we are studying how sex differences can affect not only the course of cognitive symptoms, but also the efficacy of pharmacological and behavioral treatments. Among the behavioral ones we are working on the efficacy of exercising and of neuronal stimulation; preliminary data in our laboratory suggest that both mechanisms are regulated by the sex of the subject.


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