Rats, mice and dementia: a classical neurochemical approach

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Alzheimer's disease is characterized by several neurochemical defects among which two occur during the mild to moderate phase, that is beta amyloid (BA) deposition and cholinergic neuronal loss. Within this general context the present work examines the interplay between BA and cholinergic transmission using a classical neurochemical approach based on in vivo transdialysis techniques and on in vitro isolated synaptosome preparations.
Within this conceptual framework, BA needs to be framed in a more complex context compared to the past, considering not only its accumulation and neurotoxicity, but also the possibility that the peptide exerts various biological effects within the time course of the disease. Accordingly, it is relevant to study the amyloid-cholinergic relationship, in order to understand whether the mutual interactions between these two main players in AD pathogenesis may open new perspectives in drug treatment or at least explain the limitations of the current interventions and the failure so far recorded of the amyloid targeted therapies.
Within this context, by using a classical neurochemical approach, i.e. by administering the peptide by reverse dialysis and then examining the brain dialysate for neurotransmitter content or by using isolated synaptosmes, we explored the mutual interaction of nicotinic stimulation and beta amyloid in the modulation of neurotransmitter release from synaptic terminals, an event that may occur before neurodegeneration. The results of our studies (summarized in references 1-3) reveal that beta-amyloid may reduce the synaptic release of several neurotransmitters, including glutamate, aspartate, GABA, glycine and dopamine, when the release is elicited through cholinergic stimulation but not following depolarization. The effect of beta-amyloid has been observed both in vitro and in vivo in at least three different brain areas (nucleus accumbens, striatum, hippocampus) and also when working with gliosomes. The data suggest that the peptide may exert some general effects even if not all the brain areas have been evaluated. These actions, diverging from neurotoxicity exerted by high beta-amyloid concentrations, may cause dysfunctions in the neurotransmitter activity, in turn leading, at least from a theoretical point of view, to early neuropsychiatric disturbances in the disease. These observations underscore the inherent difficulty of targeting beta-amyloid in a context in which the peptide exerts several actions beyond neurotoxicity and drive the attention to the importance of further exploring the putative physiological role of beta amyloid.

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