Targeting pathologic amyloid without perturbing amyloid physiological activity.

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If I had to resume the struggle for the search of drugs to treat Alzheimer's disease (AD), justifying the lack of success, I would bring the examples of cancer research, and of… "The War of the Worlds" (Wells H.G., 1898) versus a Civil War. From a pharmacologist's point of view, the determinants of the success in the search of drugs able to contrast cancer are based on the increasing knowledge that cancer cells are "aliens" that can be characterized using specific genetic markers allowing individualization of the therapy. As in the War of the Worlds or in antibiotic therapy the hope is to find the Erlich's "magic bullet", killing the alien and not the host. In a civil war friends and enemies are indistinguishable, there is no a "magic bullet". Identification of the differences becomes more and more difficult. This is exactly the story of AD drug therapy and of beta amyloid (BA) targeting, an approach that has so far largely failed to reach a significant clinical outcome. Several thousands of patients have been treated with anti-BA drugs showing that plaques may be cleared, so far with no significant clinical advantage. Therefore, at late time points, even if drugs can remove BA from plaque deposits, this action will not affect the ongoing degenerative processes. When 10 years ago, in 2007, we started to explore the possible non-neurotoxic effects of BA on neurotransmission we soon realized that the peptide had important interactions with neurotransmitter release mechanisms in conditions not leading to neurotoxicity (1). In particular, when examining the interactions between cholinergic transmission and BA, we suggested a continuum in the action of BA that at low concentrations (picomolar-low nanomolar) may stimulate nicotinic cholinergic receptor while desensitizing them at increasing concentrations (high nanomolar-low micromolar). In addition high BA concentrations (not yet neurotoxic) reduced the synaptic release of several neurotransmitters, when the release was elicited through cholinergic stimulation but not following depolarization. The effects of BA were observed both in vitro and in vivo in various brain areas suggesting that the peptide may exert some general effects. We proposed that these actions may cause dysfunctions in the neurotransmitter activity, in turn leading or participating to early neuropsychiatric disturbances in the disease. This view is somewhat supported by emerging clinical data showing a relevant interaction between BA deposition rate and neuropsychiatric manifestations and the importance of the molecular species of amyloid deposition. Cumulatively these observations underscore the difficulty of targeting beta-amyloid in a context in which the peptide exerts several actions beyond neurotoxicity. Briefly: we still do not know enough of BA physiology to target it with drugs. Moreover, the great advance in cancer therapy has come from a thorough study of intracellular targets (think to the kinase inhibitors or to the monoclonal based immunotherapy), a field still to be fully explored at brain level in relation to pathology. The suggestion that lessons learned from oncology may be relevant for AD come also from the increasing number of molecular and epidemiological observations of complex, perhaps inverse relationships between cancer and AD (2). Within this context, it can still be thought that BA, after having better identified its cellular activities, will be confirmed as a target, but likely only for well characterized subgroups of patients.

References

1. Govoni S, et al., Dangerous liaisons between beta-amyloid and cholinergic neurotransmission. Curr Pharm Des. 2014;20:2525-38.

2. Frain L. et al., Association of cancer and Alzheimer's disease risk in a national cohort of veterans. Alzheimers Dement. 2017 Jul 12. pii: S1552-5260(17)30218-2.