WHY SHOULD WE USE DIRTY MULTIMODAL DRUGS TO TREAT ALZHEIMER'S DISEASE

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Alzheimer's disorders (AD), is initiated by cascade of neurotoxic events, that includes oxidative stress, brain iron dysregulation, glutamate excitotoxicity, inflammatory process, neurotoxic processing of APP and misfolding of proteins Aβ peptide. Significant percentage of AD subjects also suffers from extrapyramidal symptoms (Lewy Body disease) and depression. These subjects are benefiting from drugs developed to act on a single molecular target. Such drugs have limited symptomatic activities and current pharmacological approaches are highly limited in their ability to modify the course of the disease, offering incomplete and transient benefit to patients. However, the new therapeutic strategies for neurodegenerative diseases, such as AD are those in which drug candidates are designed expressly to act on multiple neuronal and biochemical targets involved in the neurodegenerative process and neurotransmission. Monoamine oxidase (MAO) B activity, iron, and glutamate excitotoxicity increase in ageing brain and AD. They are thought to contribute to oxidative stress dependent neuronal death. The iron deposition in hippocampus, microglia, amyloid plaques, neurofibrillary tangles can induce oxidative stress via interaction with hydrogen peroxide produced by MAO-B and other oxidative processes to promote the Fenton chemistry and generate the neurotoxic reactive hydroxyl radical. Thus we have developed molecular entities that combine two or more of cholinesterase inhibition, brain selective MAO inhibition, iron chelation, inhibitors of glutamate release, anti apoptotic-neurorescue and neurorestorative activities. These drugs are also inhibitors of iron dependent prolyl-4-hydroxylase, which results in activation of hypoxia inducing factor (HIF) and increased release of neuroprotective and neurotrophic erythropoietin. Two of such compounds presently under development are ladostigil, a derivative of rasagiline (azilect) and M30. These drugs possess iron chelating-radical scavenging, brain selective MAO-A and B inhibitory activity, except that ladostigil is also a choline and butyrylcholinesterase inhibitor. Animal behavioral and neurophramacological studies have shown their anti Alzheimer, anti Parkinson and anti depressant activities. Both drugs also have neuroprotective and neurorestorative activities in neuronal cell cultures and in vivo. These properties indicate that ladostigil and M30 might serve as an ideal drug for treatment of AD, for which they are being developed.