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Abstract

Repositioning of Dantrolene as a Multitarget Agent for Neurodegenerative Diseases †

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Dantrolene is an orphan drug representing the sole therapeutic treatment for malignant hyperthermia, a life-threatening pathology affecting 0.2 in every 10,000 people in the EU. Its biological feature consists of the inhibition of ryanodine receptors, which are responsible for calcium recruitment in striatal muscles and brain. Several literature reports described the neuroprotection exerted by dantrolene in different animal models of AD and, recently, in contrasting neurotoxicity induced by MDMA. Indeed, few of these works investigated its effects at a molecular level, namely on putative targets involved in neuroprotection, and often with contrasting results. Here, we present, for the first time, a comprehensive hypothesis involving, in addition to the well-known calcium antagonism, inhibition of monoamine oxidase B (MAO B) and acetylcholinesterase (AChE) and activation of the carrier of L-acylcarnitine (CACT) as concomitant biological activities responsible for neuroprotection. Dantrolene acts in vitro as a reversible, competitive inhibitor of human MAO B (K_i = 1.0 μM), a reversible, noncompetitive inhibitor of human AChE (K_i = 6.3 μM), and an activator of CACT (EC_{50} = 28 μM). The potential of repurposing of dantrolene, and the design of dantrolene analogues, possibly endowed with the same activity profile and better pharmacokinetic properties, will be discussed and challenged.

Keywords: dantrolene; neurodegenerative diseases; multitarget agents; MAO inhibitors; AChE inhibitors; carnitine translocation