Pharmacological effect of a new idebenone formulation in a model of carrageenan-induced inflammatory pain

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Inflammatory pain represents an important unmet clinical need with important socioeconomic implications. In the last years, considerable evidence demonstrates the central role of reactive oxygen species and reactive nitrogen species (ROS and RNS) in inflammation and subsequent development of inflammatory pain. Indeed, their involvement in central sensitization has been reported during the development of thermal hyperalgesia associated with acute and chronic inflammation, in response to spinal activation of the NMDAR.

Idebenone, a synthetic analogue of coenzyme Q10 (CoQ10) named idebenone (2,3-dimethoxy-5-methyl-6-(10-idroxydecyl) -1,4-benzoquinone; IDE), is a drug active at the level of the central nervous system, showing a protective action in a wide range of neurological disorders including trauma, cerebral ischemia, and hypertension-induced vascular lesions. Different technological approaches have been explored to increase the solubility of idebenone, a highly lipophilic molecule, poorly water soluble and highly bound to plasma proteins; all these features will therefore affect the absorption and bioavailability. The aim of this study was to confirm the involvement of oxidative stress in the development and mainteinance of thermal hyperalgesia and to assess the antinociceptive effect of idebenpne vehicolated β-cyclodextrins (β-CD) in a model of carrageenan-induced inflammation.

All male rats used for these studies received a subplantar injection of carrageenan into the left hindpaw in the presence or absence of non-vehiculated IDE and β-CD-IDE complex. Hyperalgesic responses to heat were determined as described by the Hargreaves method and changes in paw volume was measured with a plethysmometer. Thermal hyperalgesia and paw edema were performed every hour up to 6 h postcarrageenan. After testing, all the animals were sacrificed and the lumbar spinal cord (from L4 to L6) was removed for MDA assay.

We could observe that not vehiculated idebenone poorly reduces the painful effects of carrageenan, limiting the protective effects of this compound. On the other side, the β-CD-IDE formulation is able to prevent the carrageenan induced hyperalgesia and edema in a dose-dependent manner while β-cyclodextrins alone do not exert any pharmacological effect. Furthermore, β-CD-IDE complex is able to reduce the formation of spinal MDA.

Our result demonstrate that inclusion of idebenone in β-CD improves the therapeutic efficacy of this drug and that, in this formulation, is able to reduce inflammation and the accumulation of free radicals formation, crucial mediators hyperalgesia.