

THE NITRIC OXIDE-RELEASING DERIVATIVE OF FLURBIPROFEN HCT1026 DECREASES VULNERABILITY OF NIGROSTRIATAL DOPAMINERGIC NEURONS TO MPTP VIA A SWITCH OF GLIA PROINFLAMMATORY PHENOTYPE: IMPLICATIONS FOR TREATMENT OF PARKINSON'S DISEASE

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Evidence from both experimental and post-mortem studies suggest a role of neuroinflammation in the pathogenesis of Parkinson's disease (PD) (1). Consistently, steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) exert neuroprotective effects in animal models of PD, via cyclooxygenase (COX)-dependent and COX-independent mechanism(s) (2,3). In keeping with these findings, epidemiologic studies have reported the ability of some NSAIDs to decrease the incidence of PD by 40%. Nonetheless, NSAIDs longterm therapies are limited by their significant gastrointestinal, renal and cardiovascular side-effects. HCT1026 [2-fluoro- α -methyl(1,1'-biphenyl)-4-acetic acid-4-(nitrooxy)]butyl ester], belongs to a novel class of anti-inflammatory agents obtained by derivatization of conventional NSAIDs with a nitric oxide (NO)-releasing moiety which strongly reduce their untoward side effects without altering the anti-inflammatory effectiveness. In view of the pivotal role of NO in inflammation coupled to recent evidences indicating significant neuroprotective effects of HCT1026 prompted us to investigate the oral activity of HCT1026 and of its parent molecule, flurbiprofen, (30 mg/kg/day administered in rodent chow) in mice exposed to increasing doses (5-30 mg/kg/day) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administered i.p. for 5 consecutive days. Mice were sacrificed 7 days after MPTP discontinuation, the brain isolated, the striatum and ventral midbrain quickly dissected for molecular and neurochemical determinations. Part of the animals were anesthetized and perfused, the brains processed for histopathological and immunohistochemical determinations. We herein report that grafting a NO moiety into the NSAID structure significantly potentiates the neuroprotective action of flurbiprofen, as revealed by the greater counteraction of MPTP-induced decreases in striatal synaptosomal [³H]dopamine uptake, tyrosine hydroxylase (TH) and dopamine transporter (DAT) expression in striatum, and the significant rescue of nigral TH- and DAPI-stained cell bodies. *In vivo*, *ex vivo* and *in vitro* experiments demonstrated inhibition of inducible nitric oxide (iNOS)/NO-mediated toxicity as one key mechanism responsible for decreased vulnerability of HCT1026 fed mice. This superior efficacy coupled to its safer profile indicates HCT1026 as a novel promising approach towards the development of effective pharmacological strategies against PD. 1. Morale MC et al. FASEB J. 2004 Jan;18(1):164-6. 2. Marchetti B, Abbraccio MP Trends Pharmacol Sci. 2005 Oct; 26(10):517-25; 3. Marchetti et al. Brain Res Reviews 2005 48/2: 302-321. 4. Marchetti B, Kettenmann H, Streit WJ (Eds) 2005 Brain Res Rev. 48/2: 129-408.