DIMETHYL FUMARATE REDUCES TACTILE ALLODYNIA IN A GENDER DEPENDENT MANNER IN TWO DIFFERENT MODELS OF PERIPHERAL NEUROPATHIC PAIN

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Neuropathic pain is a debilitating disease and its management is currently focused only on reducing symptoms, generally by suppressing neuronal activity. However, neuropathic pain has many features of a neuroimmune disorder, and modulating the immune response by targeting non-neuronal cells may offer new opportunities for a more successful management of pain. Recent studies showed that immune cells could be specifically involved in the gender differences occurring in chronic pain development. Dimethyl fumarate (DMF) is a fumaric acid ester that is effective in the treatment of relapsing/remitting multiple sclerosis. Its potential neuroprotective effect has been attributed to the activation of the antioxidative transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway. Beside this mechanism a possible effect mediated by the HCA2 receptor has been proposed. In this study, we have, firstly, assessed whether DMF acute administration affects thermal nociception by applying tail flick and hot plate tests. Then we have investigated the effect of DMF(administered in both acute and chronic regimen) on the tactile allodynia, in two different genders and two models of neuropathic pain: chronic constriction injury (CCI) and spared nerve injury (SNI). We also measured the DMF capability to modulate the ascending and descending pain circuitries by recording the pro-nociceptive ON cells in the periaqueductal grey area-rostral ventromedial medulla axis (PAG-RVM-axis) through single unit extracellular recording in vivo. The results showed that DMF single injection did not alter the normal thermal threshold in both male and female mice. Moreover, both male and female mice developed alteration of mechanical threshold after CCI or SNI induction. Single injection of DMF reduced the tactile allodynia, measured in the ispilateral paw, at peak mechano-allodynia day 7. The antiallodynic effect, that lasted at least 90 minutes, was greater in female as compared to male mice. In fact, while the effective dose of DMF was 150 mpk in male, half dose (75 mpk) already reduced tactile allodynia in female mice. However, in both male and female mice the lowest dose (30 mpk) was ineffective, whereas highest dose (300 mpk) lost its efficacy. Interestingly, the effectiveness of DMF single injection in reducing allodynia was much greater in CCI model as compared to SNI. Finally, our recordings, confirmed previous evidence of pro-nociceptive changes in spontaneous and mechanical -evoked activityof ON-cells, in SNI mice, 7 days after nerve injury. A single intra-PAG microinjection or repeated oral administrations of DMF (75 and 150 mg/Kg) restored in a dose dependent manner the RVM ON-cells SNI- induced hyperexcitability in female mice. These findings, highlighted the importance of different type of immune cells in the genesis of allodynia in male and female gender, and showed the anti-neuropathic profile of DMF in an animal models of mononeuropathies. DMF, beside the immunomodulatory effect for relapsing-remitting multiple sclerosis (MS), may represent a promising target for neuropathic pain therapy.