colonic tissues from obese mice was assessed by RT-PCR and ELISA. The alterations of intestinal barrier (epithelial tight junctions) and the activation of gut resident macrophages were assessed by confocal immunofluorescence. The role of NLRP3 in *in vitro* colonic tachykininergic contractile activity was evaluated. The effect of substance P (SP) on NLRP3 pathway was tested in macrophages. HFD mice displayed increased plasma LPS as well as colonic IL-1β levels and ASC and caspase-1 mRNA expression. HFD animals were characterized by a decreased claudin expression in epithelial cells along with an increased ASC immunopositivity in F4/80-positive macrophages in colonic wall. *In vivo* colonic transit were decreased while *in vitro* colonic tachykininergic contractions were increased in HFD mice. NLRP3 gene deletion in HFD mice was associated with lower increase in systemic and bowel inflammation. The NLRP3 gene deletion was associated with a recovery of colonic transit and a normalization of of tachykinergic neuromuscular contractions were normalized. In macrophage cell lines, SP induced IL-1β release. Such an effect was abrogated in the presence of caspase-1 inhibitor or NK_1 receptor antagonist and was not observed in $ASC^{-/-}$ cells. In the setting of obesity, the activation of NLRP3 inflammasome in tissue-resident macrophages contributes to enteric motor disorders. Thus, the NLRP3 inflammasome may represent a suitable molecular target for the development of novel pharmacological approaches for the treatment of digestive symptoms associated with obesity.

NERVE INVOLVEMENT OF THE E51G TRANTHYRETIN VARIANT

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The hereditary transthyretin amyloidosis (hATTR) is the most common hereditary systemic amyloidosis. hATTR is a multiorgan disease affecting the heart, the gastrointestinal tract, the kidneys, the eyes and the nervous system. hATTR generally presents with the typical length-dependent small fiber neuropathy, also named familiar amyloidotic polyneuropathy (FAP) type I. But, alterative presentations are common, including the FAP type 2 in which mixed axonal and demyelinating neuropathy is the typical of late onset cases with cardiac involvement. Cardiac involvement without neuropathy, also name familiar amyloidotic cardiomyopathy, is also well defined form of hATTR. Specific TTR gene mutations were associated with neurologic and cardiac presentations respectively. The underlying mechanisms of these genotype phenotype correlations are still poorly understood. To describe the nerve involvement of the rare, cardiac E51G (p.Glu71Gly) TTR variant in a Piedmontese family with heterozygous and homozygous carries. A clinical, neurophysiological, molecular and morphological study was carried out. Four siblings (1M and 3 F) were investigated. The age of onset ranged from 53 and 63 with median age of onset 58. Insidious lower limb polyneuropathy was the presentation in three subjects, while pure cardiac presentation was the onset of the fourth patient. Neurophysiological findings revealed mixed axonal and demyelinating polyneuropathy in two subjects. Sensitive skin innervation study and intraepidermal nerve fiber density identified a small fiber neuropathy in a third subject, while they were normal in the fourth sibling. Autonomic involvement was demonstrated in all patients with neuropathy. The TTR gene sequencing disclosed the p.Glu71Gly mutation coding the E51G variant. Two subjects were heterozygous for this mutation while two siblings were homozygous. Homozygous condition anticipated the onset but did not correlate with a more severe disease. This is the first report of nerve involvement of the E51G TTR variant, which was previously associated with pure cardiac phenotype. Our report extend the spectrum of multi-organ involvement of E51G variant, supports the hypothesis of nerve involvement also in cardiac TTR mutations and underlines the importance of searching for polyneuropathy in all amyloidogenic TTR variants, as disease modifying therapies are available only for hATTR with neuropathy.

ENDOCANNABINOID SYSTEM IN BORTEZOMIB NEUROTOXICITY

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Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common complication in the successful treatment of cancer. This side effect is dose-limiting and clinically reflects in an axonal peripheral neuropathy with sensory loss, combined often with neuropathic pain. These symptoms may be disabling, adversely affecting the quality of life of patients. Here we focussed on bortezomib (BTZ), a first-in-class proteasome inhibitor used for the treatment of multiple myeloma, which is associated with a relatively high incidence of CIPN. The pathogenesis of CIPN has not been completely understood, and there are no effective strategies or drugs to prevent or treat this side effect. Among possible pharmacological treatments of CIPN, modulation of the endocannabinoid system might be particularly promising. To investigate this hypothesis, we performed electrophysiological, behavioral and pathological analyses in a rat model of painful CIPN induced by BTZ-treatment. Animals were intravenously injected with BTZ 0.20 mg/kg, 3 times a week for 8 weeks. Moreover, localization of CB1R/CB2R-like immunoreactivity (LI) and protein quantification for CB1R/CB2R were performed in dorsal root ganglia (DRG) and in the spinal cord. In addition, cd68-LI macrophages in the peripheral nerve as well as resident Iba-1 positive cells, macrophages or microglia, were also evaluated in the DRG and spinal cord dorsal horn (DH), respectively. BTZ induced alterations in rat electrophysiological endpoints and behavioral studies of pain associated with a reduction in intraepidermal nerve fiber density if compared to control rats. Moreover, huge M1 proinflammatory infiltrating cells in caudal nerves and increased Iba-1 positive cells in DRG and microglia in the DH of rats after 8 weeks of treatment were also observed. In addition, BTZ induced an increase in the number of CB1R- and CB2R-LI DRG neurons, as well as an increase in CB1R and CB2R protein expression in DRG. The densitometric analysis on BTZ-treated DH showed an increase in CB1R-LI. In conclusion, the results suggest that the alteration of the endocannabinoid levels in peripheral and central nervous tissues appears involved in the development and progression of CIPN. Therefore, improved understanding of the pathophysiology of BTZ-induced neurotoxicity will inevitably assist in the development of effective pharmacological intervention on the cannabinoid system as potential therapy for CIPN.