Transient receptor potential vanilloid type 1 (TRPV1) and neuropeptides in the dorsal root ganglia and spinal cord in a rat model of Bortezomib-induced neuropathy

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Bortezomib (BTZ) is an effective antineoplastic drug that acts by inhibiting the ubiquitin-proteasome cellular pathways. In clinical practice, its chronic administration triggers a significant neurotoxicity, which has been associated with impairment of Aβ, Aδ, and C type primary afferent fibers, though the mechanism underlying its harmful effects remains still to be fully clarified. In order to mimic the clinical use of the drug, we have recently designed an experimental model based on the use of 0,20 mg/kg drug concentration for 8 weeks followed by a follow-up period of 4 weeks. We have previously shown that, in these conditions, a hallmark of neurotoxicity is represented by a small fiber neuropathy, whereas dorsal root ganglia (DRG) neurons did not show any morphological alterations. In order to provide data regarding the mechanism underlying BTZ harmful effects, here we characterize the spinal primary sensory neurons on the basis of their expression of the transient receptor potential vanilloid type-1 (TRPV1) and sensory neuropeptides calcitonin gene-related peptide (CGRP) and substance P (SP). In fact, TRPV1 is expressed by sensory neurons where it functions as a molecular integrator for nociception. Its activation causes depolarisation leading to burning pain and release of CGRP and SP which, in turn, activate their effector cell receptors and enhance the sensitization of nociceptors. With this aim, lumbar DRG and spinal cord of BTZ-treated model rats were processed for avidine-biotin-peroxidase complex (ABC) or fluorescence immunohistochemistry. In the DRG, the immunolabelling for TRPV1 revealed a subpopulation of predominantly small- to medium-sized neurons which appeared more extensive in BTZ-treated rats. Centrally, TRPV1-LI labelled fiber tracts and terminal-like elements distributed in laminae I and II of the dorsal horn where they appeared widely codistributed with both CGRP-LI and SP-LI. With the exception of a slightly more intense TRPV1 staining in lamina I of the dorsal horn of BTZ-treated vs control rats, no clear-cut differences in the distribution and amount of immunoreactivity for the three markers could be observed.