

NEUROCHEMICAL CHARACTERIZATION OF BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY: EXPRESSION OF TRPV1, CGRP AND SUBSTANCE P IN THE RAT DRG AND DORSAL HORN OF SPINAL CORD.

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Bortezomib (BTZ) is a potent, selective first-in-class ubiquitin-proteasome inhibitor that is mainly used for the treatment of relapsed, refractory multiple myeloma. A painful peripheral neuropathy (PN) is a significant side effect of BTZ-based chemotherapy and one of the major reasons for a dose reduction and discontinuation of therapy. Even if metabolic changes in the dorsal root ganglia (DRG), mitochondrial dysregulations as well as deficits of A β , A δ , and C primary afferent fibers contribute to the pathogenesis of the PN, the mechanisms underlying its harmful effects remain still to be fully clarified.

In order to examine possible neurochemical alterations involved in neuropathic pain development, we investigated the occurrence of the transient receptor potential vanilloid type-1 (TRPV1) receptor and of the sensory neuropeptides calcitonin gene-related peptide (CGRP) and substance P (SP) in the DRG sensory neurons and in the dorsal horn of spinal cord. In fact, TRPV1 receptor 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, enhance the sensitization of nociceptors. We used a well-established rat model of BTZ-induced PN whose hallmarks are allodynia, neurophysiological impairments, morphological alterations of myelinated and unmyelinated fibers of sciatic nerve and of DRG neurons and satellite cells. Rat L4-L5 DRG and spinal cord were processed for avidin-biotin-peroxidase complex or fluorescence immunohistochemistry.

We demonstrated that TRPV1, CGRP and SP were immunohistochemically detectable in the DRG and spinal cord in both control and BTZ-treated animals. In the DRG, the immunolabelling occurred mainly to the perikarya of sensory neurons. In the BTZ-treated rats, the proportion of DRG neurons expressing TRPV1 and CGRP was higher, though not significantly, than in control animals, whereas number of SP-immunoreactive neurons was similar to control values. Morphometric analysis of labelled neurons showed that they fell predominantly in the class of small- and medium-sized cells. In the dorsal horn, TRPV1-positive fibers and terminals occurred in the Lissauer's tract and lamina I while CGRP and SP also occurred in laminae III and V. A decrease of TRPV1- and CGRP-positive structures occurred in the Lissauer's tract and superficial layers of the dorsal horn of BTZ-treated compared to control animals.

These observations will be useful to deeply understand the pathophysiology of the BTZ-induced neuropathic pain and allow potential more targeted therapies.

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