ROLE OF PROKINETICIN SYSTEM IN A MURINE MODEL OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY.

1)Moschetti G.. 2)Amodeo G.. 3)Lattanzi R.. 4)Sacerdote P..

Università degli Studi di Milano

Chemotherapy Induced Peripheral Neuropathy (CIPN) is one of the most frequent and disabling forms of neuropathic pain and it represents a dose-limiting side effect of several antineoplastic agents. Up to now there are no valid treatments to cure it; its main consequence is dose reduction or treatment cessation which can increase cancer-related mortality; therefore new therapeutic approaches are needed. CIPN is known to be a multifactorial pathology due to mitochondrial toxicity, oxidative stress, ion channels and interactions between immune and nervous cells. In this complex network cytokines and chemokines have an important role. Among chemokines, Prokineticins (PKs) have a fundamental role in the development and maintenance of other types of painful neuropathies. For these reasons the aim of this study was to elucidate the role of the Prokineticin in different cells involved in CIPN. Prokineticins could represent a starter in the process which leads to CIPN pathogenesis and maintenance and their block, through the use of an antagonist (PC1), may represent a new opportunity to handle this type of pain. CIPN was induced in C57BL6J male mice by the administration of Bortezomib (BTZ; 0,4mg/kg, intraperitoneally injected, i.p., 3 times a week for four consecutive weeks) and Vincristine (VCR; 0,1mg/kg, i.p. injected once a day for 14 consecutive days). Development of painful neuropathy was evaluated over time by measuring the presence of allodynia (Von Frey and Acetone test) and hyperalgesia (Plantar test).When allodynia and hyperalgesia appeared during chemotherapy treatment, we started the administration of PC1 (150µg/Kg, subcutaneously injected twice a day), that was daily administered until the end of BTZ and VCR treatment. Temporal and anatomical expression of Prokineticin 2 (PK2), PK receptors (PKR1 and PKR2), pro/anti inflammatory cytokines and CD68, marker of activated macrophages, in the main sites involved in pain transmission (spinal cord, dorsal root ganglia and sciatic nerve) were evaluated as mRNA (RealTime-PCR) and protein (ELISA assay). Besides to evaluate tissue damage we analysed ATF3 levels in the same nervous tissues. Seven days after the first BTZ administration and four days after the first VCR administration mechanical and thermal allodynia as well as hyperalgesia were developed. The antagonist administration was able to ameliorate hypersensitivity. The effect was present after just one administration and remained constant for all the duration of chemotherapy treatment. Prokineticin system was overexpressed in dorsal root ganglia and sciatic nerve by the pathology and PC1 treatment was able to induce a rebalance of PK2 and its receptors. No differences due to the pathology were seen at spinal cord level. Also cytokines and CD68 expression levels were altered in neuropathic mice DRG and were restablished by PC1 administration. Furthermore ATF3, typical marker of tissue damage and cell stress, resulted upregulated both in DRG and sciatic nerves and PC1 was able to modulate also this parameter. These results show that PK system may be involved in CIPN development and maintenance and suggest that PK antagonism could be a new pharmacological strategy to contrast CIPN.