CHEMOTHERAPY-INDUCED NEUROPATHIC PAIN: P2X7 RECEPTOR AND RECRUITMENT OF PANNEXIN1

1)Venturini A. 2)Marcoli M. 3)Di cesare mannelli L. 4)Cervetto C. 5)Tenci B. 6)Micheli L. 7)Maura G. 8)Ghelardini C.

University of Genova, Department of Pharmacy

Development of neuropathic syndrome limits anticancer therapy with oxaliplatin. Increasing evidence indicates that complex mechanisms and maladaptive plasticity of the central nervous system, including central sensitization, are involved in the pathophysiology of chemotherapy-induced neuropathies. The insufficient information on the pathophysiology and molecular basis of the chemotherapy-induced peripheral neuropathy is an important limit to the development of new effective treatments.

In a rat model of oxaliplatin-induced neuropathy, we found that activation of presynaptic P2X7 receptors for ATP evoked an increased glutamate release from cerebrocortical nerve terminals. The release was abolished by the P2X7 antagonists Brilliant-Blue-G and A-438079, and reduced by carbenoxolone and the Pannexin1 selective inhibitors erioglaucine and 10Panx, suggesting the recruitment of the accessory protein Pannexin1. Aimed to evaluate the significance of P2X7-Pannexin1 system activation in pain induced by oxaliplatin, pharmacological modulators were intrathecally infused in oxaliplatin-treated animals. Brilliant-Blue-G, erioglaucine and 10Panx reverted oxaliplatin-induced pain. Finally, the influence of the P2X7-Pannexin1 system blockade on oxaliplatin anticancer activity was evaluated on the human colon cancer cell line HT-29. Prevention of HT-29. Prevention of HT-29 apoptosis and mortality was dependent on concentration of P2X7R antagonists. On the contrary, the inhibition of Pannexin1 did not alter oxaliplatin lethality in tumor cells.

In summary, glutamate release dependent on P2X7 receptor is increased in cerebrocortical nerve terminals from oxaliplatin-treated rats; the increase is mediated by functional recruitment of the accessory protein Pannexin1; P2X7 antagonists and Pannexin1 inhibitors revert oxaliplatin-induced neuropathic pain; Pannexin1 inhibitors did not alter the oxaliplatin-induced mortality of cancer cells HT-29. In conclusion, our results highlight the relevance of P2X7-Panx1 complex in the maladaptative response of central nervous system to oxaliplatin neurotoxicity. P2X7 receptor-Pannexin1 participates in alteration of neuronal functions leading to central sensitization and pain chronicization. The selective inhibition of Pannexin1 channel is suggested as new pharmacological target for oxaliplatin-induced neuropathic pain relief.

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