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Neurosciences Plenary Session
Saturday, September 16th, 14h00

PS141

Paclitaxel-induced neuropathic pain: Unravelling the underlying mechanisms at the central nervous system

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Aim: Here we studied the effects of the cytostatic paclitaxel on: (i) the development of nociceptive and aversive behaviors; (ii) noxious-evoked-activation of spinal dorsal horn neurons and (iii) on descending noradrenergic modulation, which is the main spinal nociceptive inhibitory system.

Introduction: Chemotherapeutic drugs are widely used for cancer treatment but they also cause numerous deleterious side effects. Chemotherapy-induced neuropathy (CIN) is one of the most common side effects. The mechanisms underlying CIN are starting to be uncovered namely the alterations induced by cytostatics at the peripheral nervous system but the effects of these drugs at the central nervous system are still poorly studied.

Methods: Male Wistar rats were injected with paclitaxel (Taxol, 2.0 mg/kg) or the vehicle solution dimethyl sulfoxide on four alternate days. Nociceptive and aversive behaviors were assessed by the von Frey and conditioned place aversion (CPA) tests, respectively. Noxious-evoked-activation of spinal dorsal neurons was achieved at one month after CIN by evaluating the expression of c-fos expression upon cold stimulation. To study the descending noradrenergic pain modulation we assessed the effects of the α2-adrenoceptor agonist clonidine at 1 and 10 µg administered intrathecally, on the von Frey test. We further assessed the expression of the α2-adrenoceptor and dopamine-ß-hydroxylase (DBH), a noradrenaline biosynthetic enzyme expressed in noradrenergic fibers, at the spinal dorsal horn.

Results: Paclitaxel induced mechanical allodynia and aversive behaviors. c-fos and DBH expression were increased in paclitaxel-treated animals while α2-adrenoceptor expression remained unaltered. Clonidine induced antinociception at both doses with more pronounced effects in paclitaxel-treated animals.

Conclusion: Paclitaxel-treated animals showed neuropathic like-behaviors and increased spinal neuronal activation. It remains to ascertain if DHB upregulation results in increased spinal noradrenaline levels, but the increase of α2-AR antinociceptive potency in paclitaxel-treated animals indicates the recruitment of descending inhibition probably as a buffer to increased spinal sensitization.


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Oncology & Molecular Biology Plenary Session
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PS203

Is there horizontal transfer of the oncogene BCR-ABL mediated by extracellular vesicles released by chronic myeloid leukemia cells?

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(A. Teixeira).

Aim: The aims are to verify if: (i) EVs released by CML cells carry BCR-ABL in their cargo and if that BCR-ABL is captured by recipient cells; (ii) EVs released by a CML drug resistant cell line, with mutant BCR-ABL, may transfer mutant BCR-ABL and a resistant phenotype to sensitive cells.

Introduction: BCR-ABL, the fusion gene originated by the t(9;22) translocation, is responsible for Chronic Myeloid Leukemia (CML). BCR-ABL codes for a constitutively active tyrosine kinase (TK), deregulating downstream pathways and promoting cell survival. Imatinib mesylate (Gleevec), a TK inhibitor, is the gold standard treatment for CML; nevertheless, resistance to this drug often occurs, mostly caused by additional point mutations on BCR-ABL and representing a major clinical drawback. It was recently suggested that drug resistance might be horizontally transferred by EVs, from resistant to sensitive cells.

Methods: A pair of drug-sensitive BCR-ABL+ cell line (KBM5), and its drug-resistant counterpart (KBM5-STI, harboring mutated BCR-ABL) were used in this study. EVs were isolated by ultracentrifugation and characterized by Dynamic Light Scattering, BCR-ABL mediated by extracellular vesicles

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