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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 α 2-adrenoreceptor agonist clonidine at 1 and 10 μ g administered intrathecally, on the von Frey test. We further assessed the expression of the α 2-adrenoreceptor and dopamine- β -hydroxylase (DBH), a nor-adrenaline 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 α 2-adrenoreceptor 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 nor-adrenaline levels, but the increase of α 2-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
Saturday, September 16th, 14h00

PS203

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

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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 arises, 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, Nanoparticle Tracking Analysis, Transmission Electron Microscopy and Western Blot. The resazurin assay was used to assess drug response of drug resistant cells, drug sensitive cells and of drug sensitive cells following co-culture with EVs released by drug resistant cells. BCR-ABL levels were analysed by Western Blot.

Results: A dose-response curve to imatinib was performed in both cell lines, to confirm their different responses to the drug. Regarding EVs characterization, they had between 10 and 1000 nm and presented several markers of EVs with no evidence of cellular contaminants. Interestingly, BCR-ABL protein was detected in the EVs.^{1–9}

Conclusion: These results suggest that there is selective packaging of BCR-ABL into EVs, promoting oncogenic protein shedding. Ongoing work will clarify if the EVs released by the resistant cells have mutant BCR-ABL and if they confer drug resistance to recipient sensitive cells.



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Physiology & Immunology Plenary Session
Saturday, September 16th, 14h00

PS030

Assessment of left ventricular systolic and diastolic function in diabetic rat model using Electrocardiography-gated 18F-FDG PET imaging



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Aim: In this study, we explore the potential of ECG-gated 18F-FDG PET to assess LV systolic and diastolic function in a well-established rat model of type 2 diabetes.

Introduction: Left ventricular (LV) diastolic dysfunction, defined as a disruption of the normal filling pattern of the ventricle but normal systolic function, is one of the early signs of cardiac involvement in diabetic patients.

Methods: List-mode gated 18F-FDG PET imaging was performed on a rat model of type 2 diabetes (ZDF fa/fa) ($n=6$) and ZL control rats ($n=6$) at age of 13 weeks 15–30 min after tracer-administration (37 MBq) via tail vein under hyperinsulinemic-euglycemic clamp using a dedicated small animal PET system (Siemens Inveon) with ECG signal recording for 20 min. List-mode data were sorted and reconstructed into tomographic images of 16 frames per cardiac cycle. PET images were resized to match human-scale pixels. Left ventricular functional parameters were calculated using standard clinical software program (Heart Function View).

Results: Hyperinsulinemic-euglycemic clamp and post mortem tissue analysis demonstrated the development of diabetes in the ZDF rats and of significant myocardial hypertrophy in ZDF rats at age of 13 weeks (994 ± 78 mg vs. 871 ± 44 mg in ZDF rats vs. ZL controls, $p < 0.01$, respectively). The PET images analysis showed a mild but significant decrease of LV PFR in the ZDF rats (10.4 ± 0.5 vs. 11.8 ± 0.4 EDV/s in ZDF rats vs. ZL controls, $p < 0.001$, respectively), whereas no significant differences concerning LVEF and cardiac output (CO) could be detected between model and control rats (LVEF: 60.0 ± 4.5 vs. $63.7 \pm 4.1\%$, $p = 0.25$ and CO: 90917 ± 14015 vs. 85208 ± 17511 μ l/min, $p = 0.90$, respectively).

Conclusion: In a rat model of type 2 diabetes, we demonstrated the ability of ECG-gated-18F-FDG PET together with a clinical ventricular edge detection software to assess reliable LV systolic and diastolic parameters and to detect the presence of a diastolic dysfunction in the diabetic rats.

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Public Health & Medical Informatics Plenary Session
Saturday, September 16th, 14h00

PS045

Prevalence of dietary supplements and over-the-counter drug use in patients with arterial hypertension



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Aim: Analysis of frequency of use of DS/OTC among patients with arterial hypertension as well as factors determining its use and patients' knowledge about possible interactions with conventional medication.

Introduction: Dietary supplements (DS) and over-the-counter drugs (OTC) are frequently advertised as a natural treatment of many disorders. DS/OTC can interfere with biotherapeutic action of prescribed medication and this is of particular concern in patients with cardiovascular disease, many of whom are on long term treatment.

Methods: The study was conducted in the Outpatient Hypertensive Clinic in the Tertiary Cardiac Center. Self-prepared questionnaire was administered among 151 hypertensive patients (58% females, age range 18–80 years). Regular DS/OTC use was defined as taking them at least 3 times per week.

Results: In the examined population regular use of DS/OTC was declared by 67% subjects. The most commonly, regularly used substances were minerals and microelements (60.4%), vitamins (48.5%), analgesics (18.8%), drugs increasing the immunity (18.8%), relieving the gastrointestinal symptoms (18.8%) and omega acids (18.8%). There were no differences in the frequency of DS/OTC use in relation to number of antihypertensive drugs, educational level, age and income. Women are more frequent regular users of DS/OTC than men ($n = 65$ vs. $n = 36$, $p = 0.03$). Only 38% of responders always consulted the use of DS/OTC with a doctor. The majority of responders (52%) is not aware of possible influence of DS/OTC on antihypertensive medication or blood pressure control. Cost of DS/OTC in 23% of responders is equal or higher than cost of prescribed drugs.

Conclusion: Two thirds of hypertensive patients are regularly using DS/OTC. Half of them are not aware of possible interactions with antihypertensive therapy and influence of blood pressure control. The perception that nonprescription therapies are unnecessary to report during medication history taking should be changed. DS/OTC are the important position in the responders budget.

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