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-adrenoreceptor agonist clonidine at 1 and 10 μg administered intrathecally, on the von Frey test. We further assessed the expression of the α2-adrenoreceptor and dopamine-β-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-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 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.

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 significantly differences concerning LVEF and cardiac output (CO) could be detected between model and control rats (LVEF: 60.0 ± 4.5 vs. 63.7 ± 4.1%, p = 0.25 and CO: 90917 ± 14015 vs. 85208 ± 17511 μl/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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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 biotherapeutical 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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