Might G-CSF-induced pain depend on increased production and release of PK2?

S. Squillace[1], V. Marconi[1], R. Lattanzi[1], D. Maftei[1], I. Fusco[1], L. Rossi[2], S. Tomao[2], G. Balboni[3], L.Negri[1]

[1] Department of Physiology and Pharmacology 'Vittorio Erspamer', Sapienza University of Rome, Italy; [2] Department of Experimental Medicine, Sapienza University of Rome, Italy; [3] Department of Life and Environmental Science, University of Cagliari, Cagliari, Italy.

Background: Granulocyte-colony stimulating factor (G-CSF) is a current therapy to increase neutrophil counts in peripheral blood of patients that underwent chemotherapy or radiotherapy for cancer treatment. The G-CSF therapy is well tolerated, but some side effects such as abdominal pain, bone pain and muscle-skeletal pain, limit its applicability.
It has been established that G-CSF is the major inducer of Prokineticin 2 (PK2) expression in bone marrow mononuclear cells (BMMC) and in circulating and tissue-infiltrating granulocytes [1,2]. PK2 belongs to a new family of chemokines, which activate two G-protein linked receptors, prokineticin receptor 1 and 2 (PKR1 and PKR2) expressed in peripheral nerves, in different regions of nervous system involved in the modulation of pain and in cells participating to immuno-inflammatory responses. We have already demonstrated that the up-regulation of PK2 in granulocytes infiltrating inflamed tissues is a major determinant in triggering and maintaining inflammatory pain [3].
Aim: The aim of our research was to verify whether G-CSF-induced pain was related to an increase of PK2 expression and its release and if G-CSF-induced pain could be reduced blocking the prokineticin receptors.
Methods and Results: In 8 female patients bearing breast cancer, mastectomized, subjected to intravenous chemotherapy according to the scheme FEC100 (5-Fluorouracil, Epirubicin, Cyclophosphamide), treated with G-CSF (Pegfilgrastim, 100 mg/Kg, s.c.), we measured PK2-mRNA levels in circulating granulocytes and PK2 serum levels. G-CSF treatment induced a significant increase in granulocyte PK2-mRNA levels (RT-PCR analysis) and a significant increase in PK2 protein levels in serum (ELISA assay, 1890 ± 212 pg/ml six days after G-CSF vs 756 ± 127 pg/ml after chemotherapy). Unfortunately, the low number of patients didn't allow us to obtain a significant temporal correlation between PK2 serum levels and painful state.
We evaluated G-CSF-induced pain behaviour in groups of mice pre-treated with saline or with the PKR1 preferring antagonist, PC1, and correlated the behavioural data with granulocytes mobilization and PK2 expression levels.
In mice, allodynia (Von Frey Filament) and hyperalgesia (Plantar Test) are induced by a single administration of G-CSF (10 μg, s.c.) within just 1h, peaked after 5h and recovered to baseline values 8/10 hours later. The treatment with PC1 (150 μg/kg, s.c) ten minutes before G-CSF, inhibited the development of allodynia and hyperalgesia for 2h. When PC1 was injected shortly before the peak (3h after G-CSF) abrogated tactile allodynia and thermal hyperalgesia for 3h and anticipated the recovery to baseline values.
Repeated administration of G-CSF (10 μg, s.c.) for 6 days did not affect the thermal baseline threshold but it induced a significant decrease of allodynic baseline threshold since day 3. Such a decrease correlated with the increase of PK2 serum levels. Chronic treatment with PC1 (150 μg/kg, s.c. twice a day, for 6 days) ameliorates systemic allodynia.
Real time PCR analysis revealed a significant increase in mRNA levels of PK2 in circulating leucocytes, bone marrow, sciatic nerve, dorsal root ganglia and spinal cord of mice treated with a single injection of G-CSF compared to controls.
The up-regulation of PK2 is much more evident after 6 days of G-CSF administration, particularly in DRG, which showed a 80-fold increase of PK2 mRNA levels compared to saline group. PC1 treatment had no effect on PK2 mRNA expression levels in all examined tissues.
Conclusions: Our data on mice correlate G-CSF-induced pain with the activation of the prokineticin system, and demonstrate that blocking PK-receptors might be a promising therapeutic strategy to control G-CSF-induced pain in cancer patients in substitution of the usual opioid therapy.

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