PHYTOESTROGEN GENISTEIN REDUCES NOCICEPTIVE HYPERSENSITIVITY IN THE MOUSE CHRONIC CONSTRICTION INJURY MODEL

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There is great interest in soy isoflavones as a potential alternative to the synthetic selective estrogen receptor modulators for therapeutic use not restricted to hormonal ailments only, but also in inflammatory and painful diseases. In present work we investigated the effect on neuropathic pain of genistein (4',5-7 trihydroxyisoflavone), a nutraceutical present in soybeans. It is a phytoestrogen with a wide variety of pharmacological effects, including tyrosin kinase inhibition, as well as antioxidant activity. This compound shares structural features with the potent 17β-estradiol. These features confer ability to bind estrogen receptors; in fact, genistein binds both ERα and ERβ, with higher affinity for ERβ, expressed in neuronal and immune cells. Painful neuropathy was induced in C57BL/6J male mice by sciatic nerve chronic constriction injury (CCI). Responses to nociceptive stimuli were measured before, 3, 7 and 14 days after the surgical procedure, 24 h after the last administration. Heat hypersensitivity was assayed using Plantar test, mechanical allodynia by Dynamic Plantar Aesthesiomether. Hyperalgesia and allodynia were already maximal 3 day after CCI and remained unchanged for 14 days. Genistein (1, 3 and 7.5 mg/kg, s.c.), administered to neuropathic mice, once a day, for eleven days, starting from 3rd day after injury, significantly attenuated (1 mg/Kg) or reversed (3 and 7.5 mg/Kg) nociceptive hypersensitivity. Both the cytokine network and the NO/NOS system are well known involved in the neuropathic pain development and maintenance. To characterize the mechanisms involved in pain relief induced by genistein, the contents of inducibile and neuronal NOS in sciatic nerve, L4-L6 dorsal root ganglia, ipsilateral to surgery, L4-L6 dorsal spinal cord, finally, ipsi- and contra-lateral thalamus, were measured through Western blot analysis. The biochemical evaluations were performed on nervous tissues from mice receiving 3 mg/kg genistein, able to reverse nociceptive symptoms. Genistein decreased the overproduction of two NOS isoforms, at level of both peripheral and central nervous system, suggesting that its efficacy on neuropathic pain could be associated to this effect. We also evaluated if the effects of genistein could be attributed to the modulation of the release of IL-1β and IL-6, two major pro-infiammatory cytokines. Preliminary results obtained by real time RT-PCR seem to show a modulating effect of genistein on the cytokine expression at CNS level. Actually, we are studying also the antioxidant activity and the agonist properties to estrogen receptors, as mechanisms involved in genistein efficacy against neuropathic pain.