Genetic moderation of human sTNFR1 response to experimental pain: potential homeostatic mechanisms underlying endogenous analgesia.

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Over 100 million Americans suffer with chronic pain. Long-term pharmacological treatment of chronic pain increases risks of both prescription drug abuse and drug diversion. Novel, non-addictive approaches to treating pain states are critical in combatting the American prescription drug abuse epidemic. Etanercept is a structural variant of soluble tumor necrosis factor receptor 1 (sTNFR1). A non-addictive, anti-inflammatory medication, it acts as a decoy, binding TNF-α, a potent inflammatory protein, to maintain homeostatic balance in disease critical inflammatory pathways. Etanercept's analgesic effects suffer substantial inter-individual variance, complicating its clinical utility in pain states. Understanding variance factors associated with sTNFR1's involvement in pain states will facilitate repurposing of etanercept in a personalized manner. To enhance understanding of sTNFR1's role in pain states, we analyzed data from 34 healthy humans (12 males, 22 females) who completed 90 min PET scanning with [C^{11}]carfentanil, a μ-opioid receptor (MOR) specific radiotracer. Scans included a control condition (45 min) followed by standardized experimental pain (45 min) as described elsewhere. sTNFR1 was quantified via standard ELISA from venous blood obtained following control and pain conditions. We tested whether sex, age, and the A118G G-allele accounted for variance in sTNFR1 during the pain challenge. T-tests showed females (compared to males) had lower plasma sTNFR1 before (T_{35} = -4.1, $p < 0.001$) and after (T_{35} = -2.7, $p = 0.01$) pain, but no difference in pain-induced change ($p > 0.05$). Pearson correlation coefficients showed a non-significant relation between age and sTNFR1 ($p > 0.05$). Repeated measures ANOVAs showed the presence of the A118G G-allele had a significant effect on pain-induced change in plasma sTNFR1 (F_{32} = 9.1, $p = 0.005$) wherein a pain-related sTNFR1 increase was seen in subjects with the G-allele and a sTNFR1 reduction in those without the G-Allele (T_{32} = 2.9, $p = 0.007$). Pain-induced changes in sTNFR1 were inversely correlated with MPQ affective (but not sensory) pain scores ($r = -0.43$; $p = 0.01$). Voxel-by-voxel whole brain analysis in SPM5 showed proportional relations between plasma sTNFR1 and MOR activation bilaterally in the nucleus accumbens (R: Z_{25} = 6.1, $p < 0.001$; L: Z_{25} = 5.9, $p < 0.001$), left ventral pallidum (Z_{25} = 6.6, $p < 0.001$), and right amygdala (Z_{25} = 7.7, $p < 0.001$) regions during the pain challenge. Follow-up studies to assess etanercept's analgesic potential during an experimental sustained pain in subjects with the G-allele of the A118G MOR polymorphism are warranted.