Placebo-induced central μ-opioid receptor activation modulates plasma IL-18 concentration in pain states in humans

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Despite having powerful physical and emotional effects, neurobiological mechanisms underlying placebo analgesia are poorly understood. While existing evidence identifies opioid activating, analgesic effects, emerging evidence suggests placebo modulates central immune activity, effectively reducing concentration of specific "pro-inflammatory" cytokines. IL-18 is an IL-1 family cytokine with nociceptive properties that is secreted by microglia in response to various activating stimuli. In recent human PET studies, we identified proportional relationships between plasma IL-1 family cytokine concentrations, brain regional μ-opioid receptor (μ-OR) availability, and activation of this neuro-receptor following experimental pain and emotional challenges. While evidence suggests similar neuro-immune interactions underlie the impact of placebo on physical and emotional states, these mechanisms remain unclear. Understanding the impact of placebo on neuro-immune interactions involving μ-OR's and IL-18 will help unlock the healing potential of the mind-brain axis, reducing risk for depression, pain states, and ultimately, prescription drug abuse.

Methods: Using ^{11}C-carfentanil (^{11}C-CFN) PET and a repeated measures model in SPM12 (Wellcome Trust, UK), we investigated the impact of placebo on plasma IL-18 and its relation to central opioid neurotransmitter responses to standardized, sustained, muscular pain challenges in healthy humans. Within the PET scanner gantry, subjects experienced both a control condition (IM masseteric injection of normal saline) and a pain challenge (IM masseteric injection of hypertonic saline) each for 45 minutes. The PET scan was repeated, on alternating days, with and without pre-treatment with placebo (IV normal saline) under conditions of analgesic expectation. The individual pain experience was quantified using the McGill Pain Questionnaire (MPQ) and sensitivity to the experimental pain challenge was quantified using an objective measure of pain sensitivity as previously described. Plasma IL-18 was quantified using standard ELISA techniques from whole blood samples obtained following each experimental challenge (e.g. saline control, hypertonic saline) with and without placebo pre-treatment.

Results: Placebo pre-treatment reduced plasma IL-18 (mean reduction 97 ng/dl, 46%; $W_{74} = -3.5$, $p < 0.001$) prior to the pain challenge. Repeated measures testing on a voxel by voxel basis confirmed the placebo induced reduction in IL-18 was proportional to endorphin release (observed as a reduction in μ-OR BP_{ND}) within the right thalamus ($T_{1,74} = 3.2$; $p_{uncorr} < 0.002$) and the right nucleus accumbens ($T_{1,74} = 3.5$; $p_{uncorr} < 0.001$).

Placebo reduced the extent of pain experienced during the pain challenge ($W_{37} = 5.1$, $p < 0.001$) and significantly reduced pain sensitivity ($W_{74} = -2.1$, $p = 0.03$). The extent that subjects believed placebo reduced their pain (subjective measure) correlated with extent that placebo reduced pain sensitivity (objective measure) (rho = -0.69, $p < 0.001$). The extent that subjects desired placebo to have an analgesic effect correlated with placebo's reduction of MPQ Affective (rho = -0.34, $p = 0.04$), but not Sensory ($p > 0.05$) pain.

Over the entire experimental paradigm, changes to IL-18 were proportional to placebo-induced reduction in both MPQ pain scores (Affective Pain: rho = -0.43, $p = 0.008$; Sensory Pain: rho = -0.33, $p < 0.05$) and Pain Sensitivity (rho = -0.33, $p < 0.05$). Overall changes to IL-18 were proportional to impact of placebo on pain induced μ-OR activation (measured as an overall reduction in μ-OR BP_{ND}) within the left nucleus accumbens ($T_{1,148} = 3.3$; $p_{uncorr} < 0.001$), left anterior cingulate cortex ($T_{1,148} = 3.1$; $p_{uncorr} < 0.005$), left amygdala ($T_{1,148} = 3.3$; $p_{uncorr} < 0.001$), left entorhinal cortex ($T_{1,148} = 3.8$; $p_{uncorr} < 0.001$), right posterior insula ($T_{1,148} = 3.0$; $p_{uncorr} < 0.005$), and the right thalamus ($Z_{1,65} = 4.2$; $p_{uncorr} < 0.001$).

Discussion: These findings are consistent with a modulating effect of placebo on a potent nociceptive cytokine in humans and significant linear relationships to a neurotransmitter system critical to regulation of pain, stress, and mood states and one where dysregulation has been identified in opioid dependence. Identifying these

intricate neuro-immune interactions paves the way for future clinical translational studies aimed at reducing risk of prescription drug abuse by developing personalized approaches to delivering alternate treatments in negative affective states (depression, pain states), critical risk factors in prescription drug abuse.

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