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## In response to: Etanercept for sleep in patients with Alcohol use disorder – mechanisms need to be elucidated

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### Dear Editor

We thank Dr. Krishnadas for his interest in our manuscript “Tumor Necrosis Factor Antagonism Normalizes Rapid Eye Movement Sleep in Alcohol Dependence” and his questions about the mechanisms that transduce peripheral blockade of proinflammatory cytokine activity (e.g., administration of an antagonist of tumor necrosis factor) to alterations in brain function and behavior (e.g., sleep). Although it was beyond the scope of this experimental, clinical trial to evaluate the pathways that signal changes in peripheral proinflammatory cytokines to changes in sleep in alcohol dependence, the mechanisms that might contribute to these behavioral changes have been extensively reviewed (1,2). As previously reviewed, basic research has implicated four relevant pathways that are thought to communicate peripheral proinflammatory cytokine activity to the brain. These pathways include the following: 1) in a neural pathway, local levels of proinflammatory cytokines activate primary afferent nerves, such as the vagal nerves; 2) in a humoral pathway, macrophage-like cells residing in the circumventricular organs and the choroid plexus produce proinflammatory cytokines, and these cytokines can enter the brain by volume diffusion; 3) in a cytokine transporter pathway, saturable transport systems at the blood–brain barrier facilitate pro-inflammatory cytokines overflowing in the systemic circulation to gain access to the brain through active transport; and 4) activation of IL-1 receptors that are located on perivascular macrophages and endothelial cells of brain venules results in the local production of prostaglandin E<sub>2</sub>. Together, these immune to immune-to-brain communication pathways ultimately leads to the production of proinflammatory cytokines by microglial cells, which in turn is thought to induce changes in brain function and behavioral responses. We agree that clinical translational studies are needed to understand the relevant pathways by which antagonism of peripheral cytokine activity leads to changes in sleep and possibly other behaviors (e.g., depressive symptoms) in humans (3)

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