Subject: Deciphering the physiology underlying the rapid clinical effects of perispinal etanercept in Alzheimer's disease.

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Excess tumor necrosis factor (TNF) plays a pivotal role in the pathogenesis of Alzheimer's disease(AD). Clinical improvement following perispinal administration of etanercept in patients with Alzheimer's disease and other forms of dementia and brain dysfunction is characteristically evident within minutes. The rapidity and constellation of the clinical effects across multiple domains (cognition, mood, memory, motor function, and attention) suggest they are mediated by non-synaptic signaling mechanisms previously unrecognized for etanercept. These mechanisms likely extend beyond the known roles of TNF as a gliotransmitter that modulates synaptic strength, synaptic scaling, and AMPA receptor trafficking. Preliminary basic science and clinical investigation suggests that perispinal administration of etanercept may lead to its rapid penetration into the cerebrospinal fluid (CSF) within the cerebral ventricles. Diffusion of large molecules into the periventricular brain parenchyma is known to occur, but this process may not be sufficient to explain the rapidity of the clinical effects. There exist populations of cells, including CSF-contacting neurons and modified ependymal cells called tanycytes, that have receptive surfaces in direct contact with the CSF. It is hypothesized that the rapid clinical effects of perispinal etanercept involve non-synaptic signal transduction across the ependymal barrier and into neuronal networks via these CSF-contacting cells. This hypothesis challenges the dogma that penetration of a therapeutic into the cerebral parenchyma through the endothelium of the cerebral vasculature (the so-called blood- brain barrier) is necessary to produce rapid clinical effects in AD. CSF-contacting cells may constitute a therapeutic target for a diverse group of brain, psychiatric and spinal disorders.