The typical signs of an infection—fever, listlessness, lack of appetite—are orchestrated by the brain in response to inflammatory cytokines, which are the immune system’s signaling molecules. Cytokines are generated at the site of infection, then circulate in the blood and communicate with neurons in the brain to engage the hypothalamic-pituitary-adrenal (HPA) axis, an integral part of the brain’s stress response machinery. But cytokines are big molecules, and how their reach extends beyond the almost impenetrable blood-brain barrier has been the topic of much dispute.

Earlier research by Sawchenko and others suggested a vascular route whereby cytokines interact with vessel walls to generate secondary messengers, which then engage the relevant circuitry in the brain. Tightly packed endothelial cells, which line narrow capillaries throughout the brain, are perfectly positioned to record circulating immune signals, but they require a very strong signal to become activated. Perivascular macrophages, on the other hand—specialized white blood cells that digest cellular debris and pathogens and are lined up along the blood-brain barrier—are more sensitive but lack direct access to the bloodstream.

To determine the role of these two cell types, Sawchenko’s group recently injected liposomes containing clodronate, a drug that can cause cell death, into the lateral cerebral ventricle of rodents. The liposomes were taken up by the macrophages, which were killed off. Without perivascular macrophages, the animals were unable to respond to blood-borne interleukin-1, which is a cytokine, and initiate the brain’s so-called acute phase responses, which help the body tackle the challenge at hand but also cause the feeling of “being sick.” To their surprise, however, Sawchenko’s team found that the same cells suppressed the pro-inflammatory activities of endothelial cells, which are only stirred to action when they encounter lipopolysaccharide, a key component of the cell walls of certain bacteria.

The identification of a potent anti-inflammatory mechanism in the brain may pave the way for new therapies for chronic neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson’s, Alzheimer’s and prion diseases, in which central inflammatory mechanisms play an important role.

For more information, please visit salk.edu/faculty/sawchenko.html