In addition to the humoral pathway, neural reflexes are also involved in the transmission of inflammatory signals. The vagus nerve contains various cytokine receptors, which can rapidly transmit systemic inflammatory information to the brainstem (such as the nucleus solitarius), thereby affecting the hypothalamus and limbic system. These pathways together enable peripheral inflammatory mediators to affect central regulation, laying the foundation for hypothalamic inflammation associated with metabolic syndrome (Bourhy et al., 2022).

4.2 Inflammatory response of the hypothalamus

After peripheral inflammatory signals are transmitted to the hypothalamus, they will trigger a series of reactions and interfere with the regulation of energy balance. Metabolically sensitive regions such as the bow-shaped nucleus (ARC) are particularly sensitive to inflammatory stimuli due to direct exposure to circulating cytokines and fatty acids (Lee et al., 2020). After activating inflammatory pathways such as TLR4, NF-κB, and JNK, the expressions of pro-inflammatory factors such as IL-1β, IL-6, and TNF-α in the hypothalamus increase.

These inflammatory factors weaken insulin and leptin signaling by inducing inhibitory molecules such as SOCS3 and PTP1B, reduce the ability of neurons to perceive the body's energy state, and affect appetite regulation, energy expenditure and glucose metabolism (Lee, 2025). Long-term inflammatory stimulation can also lead to neuronal dysfunction, synaptic structural changes, and even a reduction in metabolism-related neurons, exacerbating insulin resistance and energy metabolism imbalance, and perpetuating metabolic abnormalities (Lee et al., 2020).

4.3 The role of glial cells

Microglia and astrocytes play a key role in the occurrence and maintenance of hypothalamic inflammation. Microglia are resident immune cells in the central nervous system. They are activated when encountering metabolic stress or peripheral inflammatory signals, transforming into a pro-inflammatory state and releasing factors such as IL-1β and TNF-α. This is an early event of diet-induced obesity and plays an important role in the early stage of inflammation (Lee, 2025).

Activated microglia produce inflammatory factors, recruit peripheral immune cells and amplify the inflammatory response (Figure 1) (Lee et al., 2020). Astrocytes undergo reactive changes in an inflammatory environment, releasing pro-inflammatory mediators. Abnormal function of astrocytes weakens support for neurons and impairs the hypothalamus' ability to regulate energy balance (Lee, 2025).

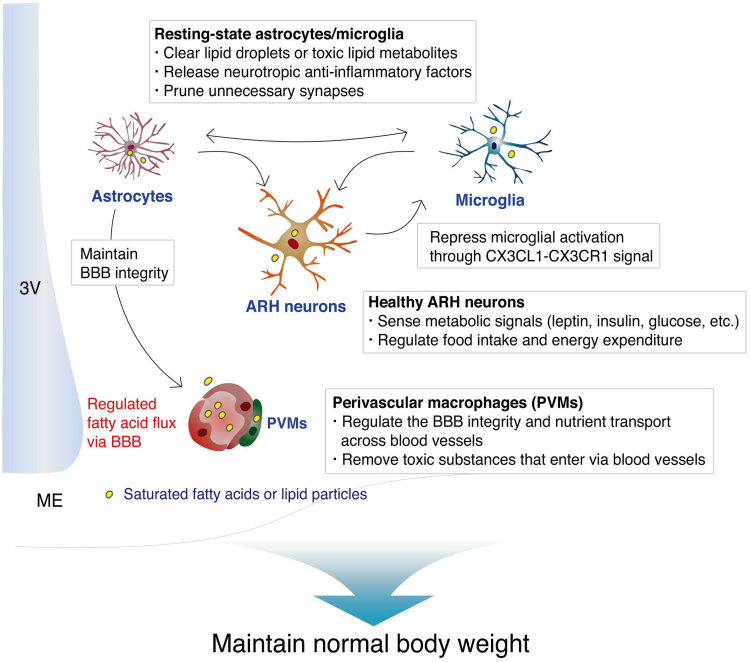

Figure 1 Homeostatic interactions between neurons and glia (microglia, astrocytes, and perivascular macrophages) in the hypothalamic ARH (Adopted from Lee et al., 2020)

Image caption: 3V, third ventricle; ME, median eminence (Adopted from Lee et al., 2020)