At the same time, the secretion of adipokines has changed. Pro-inflammatory factors such as leptin and chemokines have increased, while anti-inflammatory factors such as adiponectin have decreased, putting adipose tissue in a pro-inflammatory state. This imbalance can maintain local inflammation and also affect vascular endothelial function through the blood, promoting atherosclerosis. Moreover, the long-term activation of inflammatory pathways such as NF-κB and JNK in adipose tissue will inhibit insulin signaling and glucose uptake, forming a vicious cycle of inflammation and metabolic disorders and accelerating the occurrence of metabolic syndrome (Reddy et al., 2019; Saito et al., 2021).

3.2 Intestinal-related factors

The intestine is an important peripheral source of systemic inflammation caused by MetS. Under normal circumstances, the barrier formed by intestinal wall cells and tight junctions can prevent intestinal microbiota products from entering the bloodstream. However, poor diet, intestinal flora disorder, etc. can damage the barrier function, resulting in increased intestinal permeability (i.e., "leaky gut") (Ghosh et al., 2020; Di Vincenzo et al., 2023). At this time, bacterial components (such as lipopolysaccharide LPS) are prone to enter the bloodstream and cause endotoxemia. LPS binds to receptors such as TLR4 to release pro-inflammatory factors, amplifying systemic inflammation (Tilg et al., 2019; Mohammad and Thiemermann, 2021; Nozu and Okumura, 2022).

Damage to the intestinal barrier can also affect other organs. Inflammatory signals induced by LPS can activate inflammation in adipose tissue, liver and other areas, exacerbating insulin resistance (Nozu and Okumura, 2022). The gut microbiota participates in this process by regulating barrier integrity, and its imbalance will further aggravate inflammation (Tilg et al., 2019; Di Vincenzo et al., 2023), thus the gut-liver-fat axis is the key to connecting environmental factors, immune activation and systemic inflammation (Ghosh et al., 2020; Mohammad and Thiemermann, 2021).

3.3 Liver and skeletal muscle

The liver and skeletal muscle are key organs for energy metabolism and are highly sensitive to chronic inflammation and excessive lipids. In MetS, the excess free fatty acids released by inflammatory adipose tissue deposit in these two organs, causing fatty toxicity and activating inflammatory pathways (Meex et al., 2019; Da Silva Rosa et al., 2020). The liver will show an increase in pro-inflammatory factors and activation of kupffer cells. These inflammations will inhibit insulin signaling, increase hepatic glucose production, and aggravate systemic insulin resistance (Ghosh et al., 2020; Nozu and Okumura, 2022).

Skeletal muscle inflammation can lead to immune cell infiltration, continuous activation of signaling pathways such as PKC, JNK, and NF-κB, and pro-inflammatory factors (such as TNF-α and IL-1β) can interfere with insulin receptor signaling and reduce glucose uptake capacity (Meex et al., 2019; Da Silva Rosa et al., 2020). Furthermore, the interaction among the liver, skeletal muscle and adipose tissue enables the transmission of inflammatory signals between tissues, demonstrating the systemic nature of MetS inflammation-peripheral organs are both the source of inflammation and the target of inflammatory action (Ghosh et al., 2020; Nozu and Okumura, 2022).

4 The Triggering Process of Central Inflammation

4.1 Pathways for inflammatory signals to enter the brain

The brain protects the central nervous system with the blood-brain barrier (BBB), which is a structure that selectively blocks substances and cells from entering the brain tissue. However, under systemic inflammation or metabolic stress, the blood-brain barrier will be damaged and its permeability will increase, making it easier for cytokines and immune cells in the blood to enter the brain tissue, especially the hypothalamus. A high-fat diet or metabolic damage can also reduce the expression of tight junction proteins (such as claudin-5), promoting microglial proliferation and white blood cell infiltration.

Some brain regions, such as the periventricular organs (CVOs), become key channels for peripheral inflammatory signals to enter the brain due to the lack of a complete blood-brain barrier, such as the median bulge and the posterior brain region. These regions can sense peripheral metabolic and immune status and transmit information to the central regulatory network (Bourhy et al., 2022).