High-fat diet (HFD) consumption is known to be associated with ovulatory disorder among women in reproductive age. Previous studies in animal models suggest that HFD-induced microglia activation contributes to hypothalamic inflammation. This causes the dysfunction of hypothalamic-pituitary-ovarian (HPO) axis, leading to subfertility. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of lipid-soluble antidiabetic drugs that target primarily the early proximal tubules in kidney. Recent evidence revealed additional expression site of SGLT2 in the central nervous system (CNS), indicating a promising role of SGLT2 inhibitors in the CNS. In type 2 diabetes (T2D) patients and rodent models, SGLT2 inhibitors exerted the neuroprotective properties through antioxidative stress, alleviation of cerebral atherosclerosis, and the suppression of microglia-induced neuroinflammation. Furthermore, clinical observations in patients with polycystic ovary syndrome (PCOS) demonstrated that SGLT-2 inhibitors ameliorated the patient anthropometric parameters, body composition, and insulin resistance. Therefore, it is of importance to explore the central mechanism of SGLT-2 inhibitors in the recovery of reproductive function in patients with PCOS and obesity. Here, we review the hypothalamic inflammatory mechanisms of high-fat diet-induced microglial activation, with a focus on the clinical utility and possible mechanism of SGLT2 inhibitors in promoting reproductive fitness. Abstract figure legend Abstract figure legend: Summary of HFD feeding-induced anovulation and SGLT2 inhibitors ameliorate this dysfunction. This diagram illustrates that hypothalamic inflammation caused by HFD impairs GnRH surge release and ovulatory dysfunction, a progression mediated by proinflammatory factors secreted by activated microglia. In addition, the improvement of ovulatory dysfunction by SGLT2 inhibitors may be mediated by repair of GnRH surge release and neuroprotective properties. The pathways for how SGLT2 inhibitors have neuroprotective properties is that A. Inhibition of microglial activation results in decreasing proinflammatory factors release and neuroinflammation; B. Alleviation of cerebral atherosclerosis; C. Reduction of oxidative stress in neuron; D. Inhibition of ROS-dependent neuronal apoptosis [1)].

1)
Chen X, Huang L, Cui L, Xiao Z, Xiong X, Chen C. SGLT2 inhibitor ameliorates high-fat diet induced hypothalamic-pituitary-ovarian axis disorders. J Physiol. 2022 Sep 1. doi: 10.1113/JP283259. Epub ahead of print. PMID: 36048516.