ST-2 Deficiency Enhances Microglial Activation and Impairs Neurotrophic Expression in Hypothalamic Gliosis Induced by Short-Term High-Fat Diet

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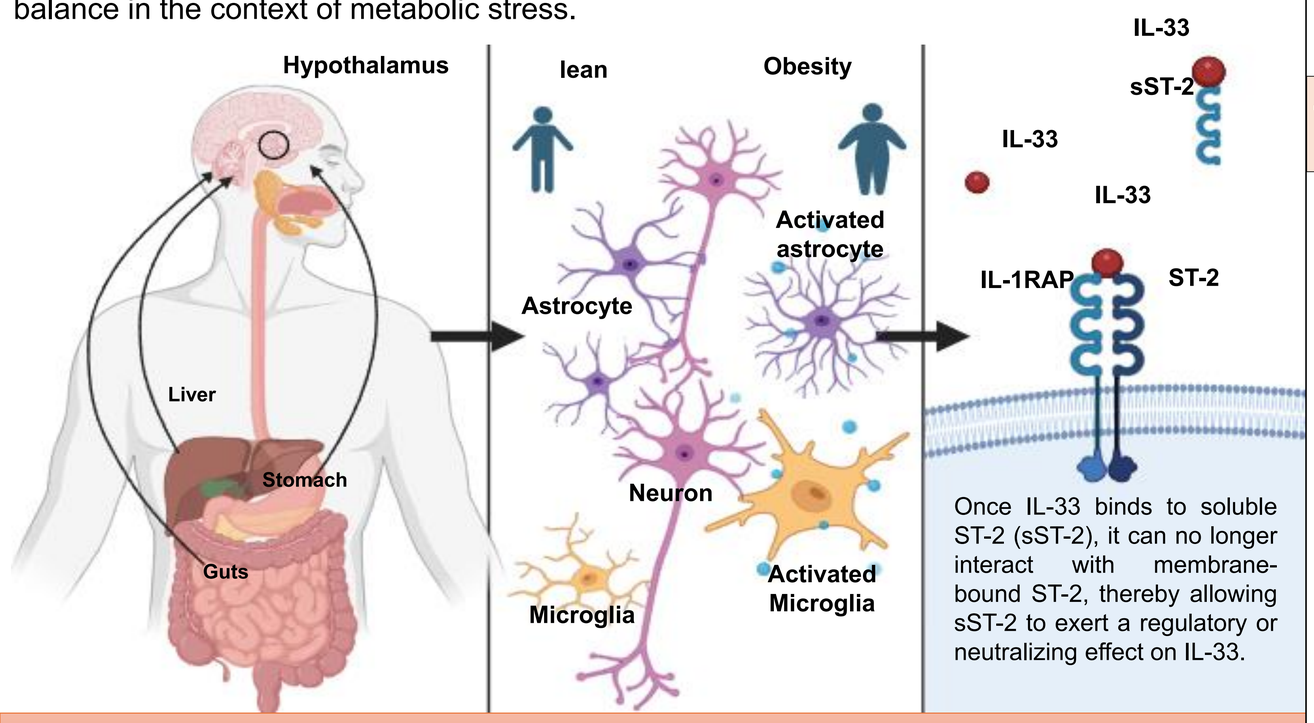
Background

The hypothalamus plays a central role in maintaining energy homeostasis, a function supported by the activity of glial cells, including astrocytes and microglia. Obesity is known to disrupt this homeostatic regulation, with the arcuate nucleus (ARC) being particularly susceptible to early inflammatory changes. Interleukin-33 (IL-33) functions as an alarmin released upon cellular stress or damage, while its receptor, Suppression of Tumorigenicity 2 (ST-2), mediates a range of immune responses. The IL-33/ST2 signaling axis has been implicated in the regulation of inflammation and glial activity. To investigate the role of this pathway in obesity-induced hypothalamic inflammation, we employed ST-2 knockout (ST-2^{KO}) mice under high-fat diet conditions, aiming to elucidate how the absence of ST-2 modulates glial responses and energy balance in the context of metabolic stress.



Once IL-33 binds to soluble ST-2 (sST-2), it can no longer interact with membrane-bound ST-2, thereby allowing sST-2 to exert a regulatory or neutralizing effect on IL-33.

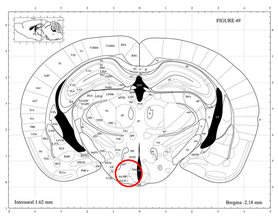
Experimental design

C57BL/6
C57BL/6 ST-2^{KO}

Male mice

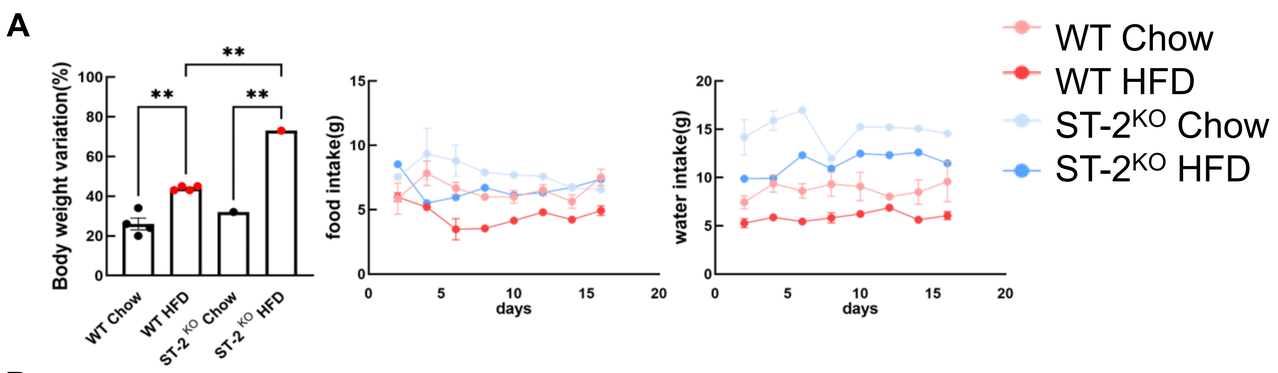
(1)Chow
(2)HFD

4-week-old genotyping — 2W — Arcuate nucleus (ARC) Hypothalamus — QPCR, IF, Plasma isolation

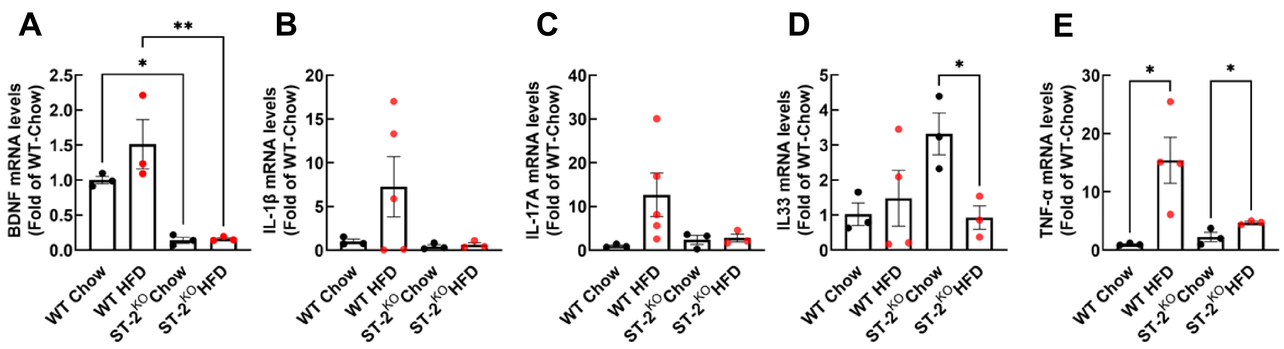


Results

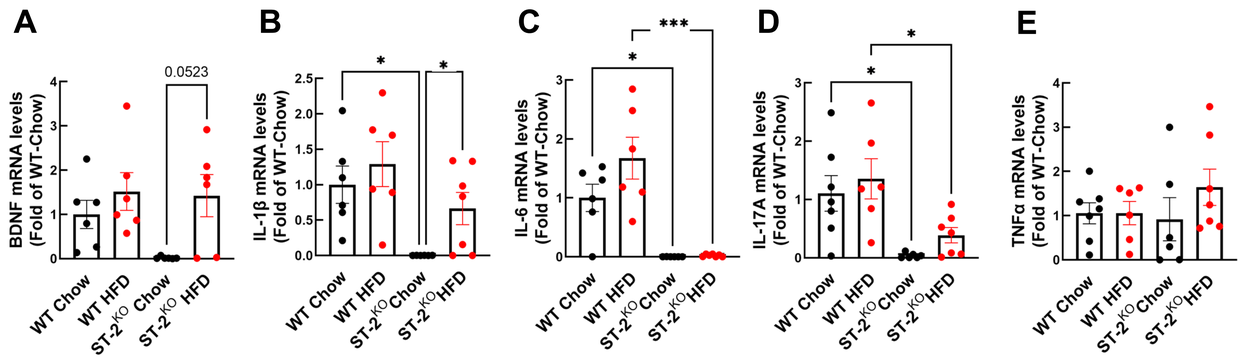
1. Short-term high-fat diet causes weight gain and reduces plasma IL-17A levels in ST-2^{KO} male mice



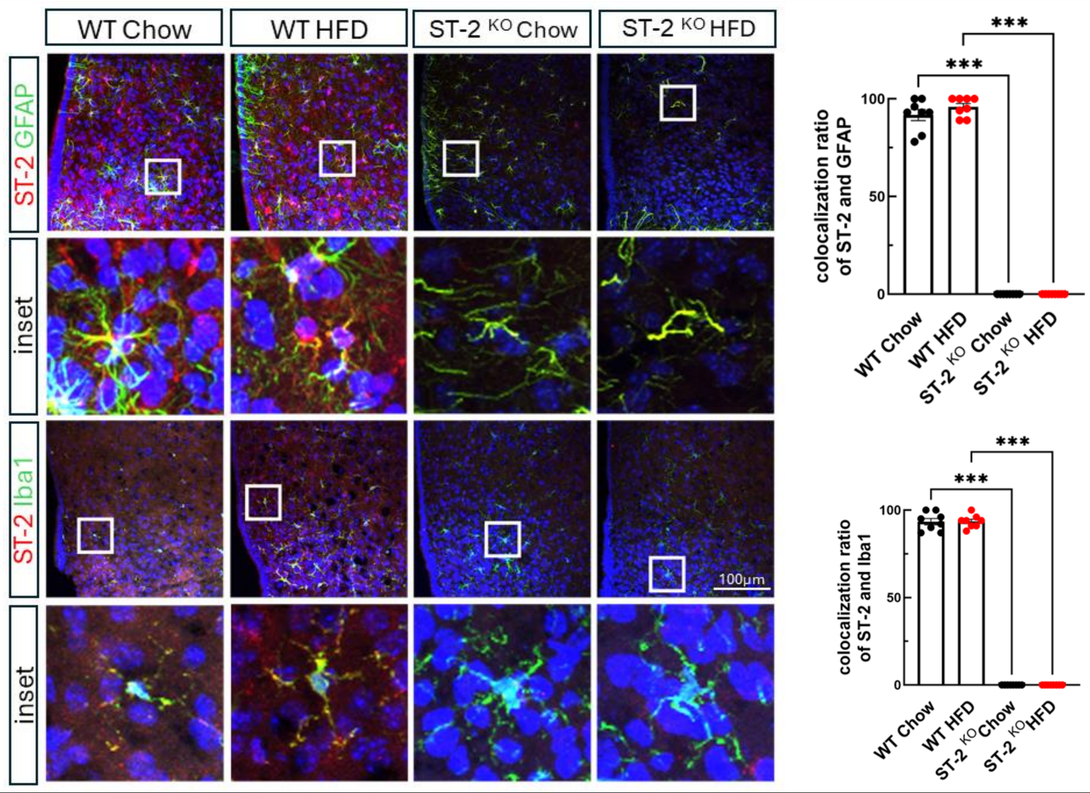
2. ST-2^{KO} downregulates the expression of brain-derived neurotrophic factor (BDNF) in the hypothalamus of male mice



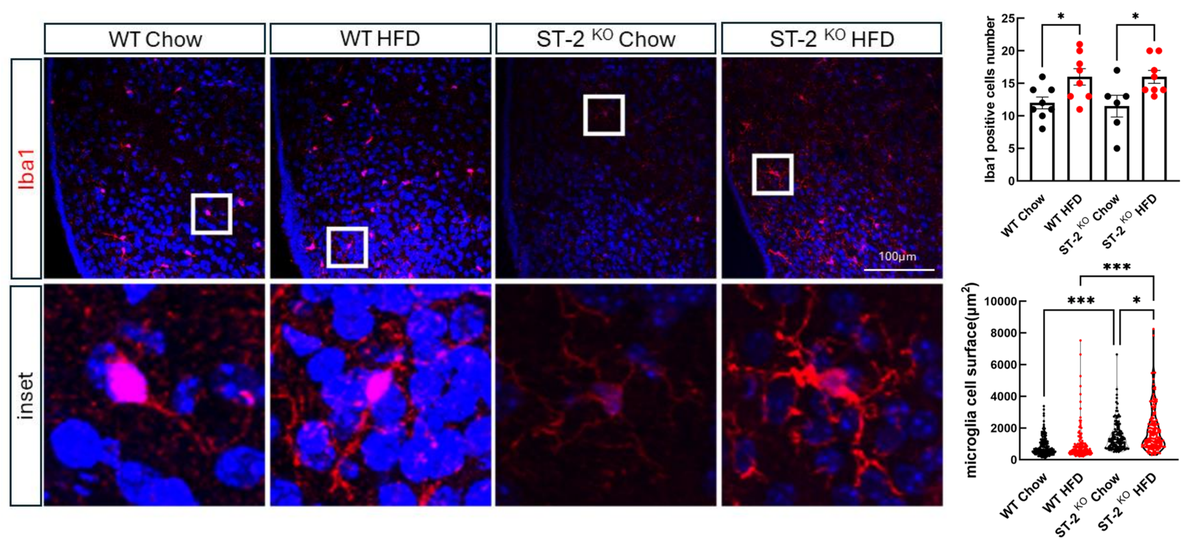
3. ST-2^{KO} caused declined expression of BDNF, IL-1β, IL-6, and IL-17A gene expression in the corpus callosum



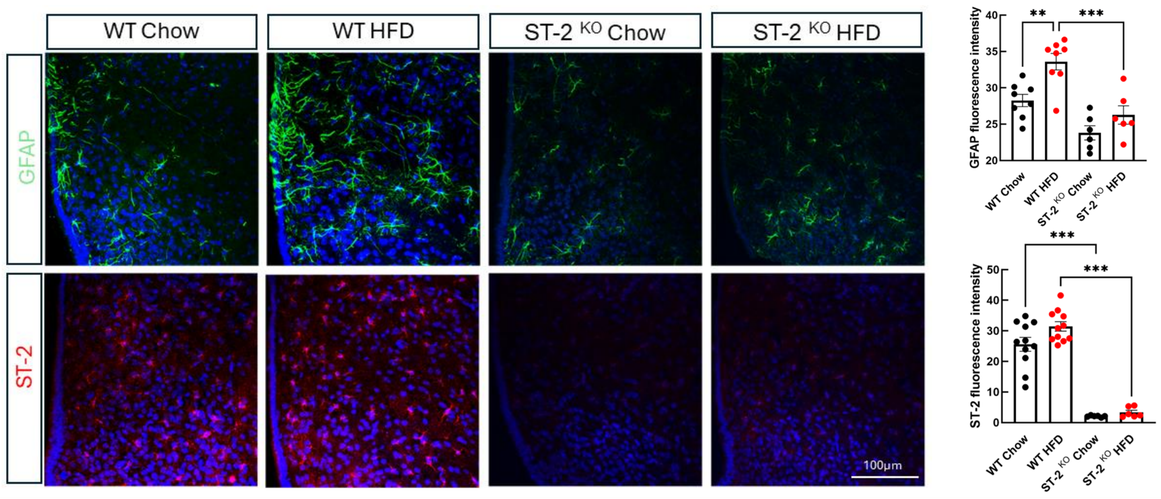
4. ST-2 is highly colocalized with GFAP^{+} astrocytes and Iba1^{+} microglia in the ARC



5. ST-2^{KO} aggravates high-fat-diet–induced increases in Iba1^{+} microglial density and cell surface in the ARC



6. ST-2^{KO} reduces high-fat diet-induced activation of hypothalamic ARC astrocytes



Conclusions

The results showed that ST-2^{KO} mice exhibited a significant increase in body weight following short-term HFD feeding, despite no notable changes in food intake. ST-2^{KO} mice showed greater weight gain and reduced hypothalamic BDNF mRNA expression compared to WT mice. In particular, the process length of GFAP-positive astrocytes was significantly reduced in ST-2^{KO} mice, suggesting that ST-2 deficiency may suppress astrocyte activation. In contrast, microglial surface area was significantly increased in ST-2^{KO} mice compared to the WT group, indicating that ST-2^{KO} promotes microglial activation. These findings suggest ST-2 deficiency enhances microglial activation and impairs neurotrophic signaling, contributing to increased weight gain in response to HFD.

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