

Proceeding Paper

Quercetin Suppresses mRNA Expression of Fto and the TNF- α /NF- κ B/NLRP3 Inflammasome Pathway in Hypothalamus of Diet-Induced Obese Rats [†]

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Abstract

Background: The NLRP3 inflammasome is a key driver of obesity-associated chronic low-grade inflammation, contributing to hypothalamic neuroinflammation and disruption of energy homeostasis. Quercetin, a bioactive flavonoid, has been proposed as a modulator of inflammatory and metabolic pathways, including the fat mass and obesity-associated gene (FTO). **Objective:** This study evaluated the effects of quercetin on hypothalamic mRNA expression of Fto and components of the TNF- α /NF- κ B/NLRP3 pathway. **Methodology:** In a high-fat diet (HFD)-induced obesity model, male Wistar rats ($n = 18$) were divided into three groups: standard diet (SD), HFD, and HFD + Q (supplemented with quercetin 50 mg/kg/day for 12 weeks). Gene expression was analyzed by quantitative PCR using the $2^{-\Delta\Delta C_t}$ method. **Results:** HFD significantly increased the expression of Fto and pro-inflammatory genes, including Tnf, Nlrp3, Casp1, Il1b, and Il18. Quercetin supplementation attenuated this upregulation, restoring expression levels toward baseline. **Conclusions:** These findings indicate that quercetin reduces hypothalamic neuroinflammation and modulates Fto expression, likely through inhibition of NF- κ B signaling and suppression of NLRP3 inflammasome activation. Quercetin may represent a potential molecular modulator of obesity-associated neuroinflammatory processes.

Keywords: neuroinflammation; FTO; NLRP3 inflammasome; quercetin; hypothalamus; high-fat diet; obesity; Wistar rats; NF- κ B signaling



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1. Introduction

The NLRP3 inflammasome plays a critical role in obesity-associated chronic low-grade inflammation, contributing to systemic inflammation and hypothalamic neuroinflammation [1,2]. Activation of this pathway disrupts energy homeostasis and impairs central regulation of appetite.

Quercetin, a bioactive flavonoid abundant in fruits and vegetables, possesses potent anti-inflammatory and antioxidant properties. It has been shown to modulate inflamma-

tory signaling pathways, including TNF- α /NF- κ B signaling and NLRP3 inflammasome activation, as well as metabolic regulators such as the fat mass and obesity-associated gene (FTO), whose rodent ortholog is *Fto* [3,4].

FTO is a key metabolic regulator associated with obesity and body mass index. It is highly expressed in the hypothalamus, where it influences appetite and satiety, and emerging evidence suggests a role in inflammatory signaling [5,6]. Dysregulation of FTO expression has been associated with metabolic disorders and inflammation-related pathologies [7].

Previous studies in animal models have shown that quercetin attenuates hypothalamic inflammation induced by high-fat or high-fructose diets, primarily through suppression of NF- κ B signaling and NLRP3 activation [3,4]. We hypothesized that quercetin inhibits *Fto* overexpression and inhibits activation of the TNF- α /NF- κ B/NLRP3 inflammasome pathway in the hypothalamus of high-fat diet-fed Wistar rats.

The aim of this study was to evaluate hypothalamic mRNA expression of *Fto* and key components of the TNF- α /NF- κ B/NLRP3 inflammasome pathway using quantitative real-time PCR (qPCR).

2. Materials and Methods

After a two-week acclimation period, male Wistar rats (initial body weight: 200 ± 20 g) were randomly assigned to three groups ($n = 6$ per group): (a) standard diet (SD), (b) high-fat diet (HFD), and (c) high-fat diet plus quercetin (HFD + Q). Quercetin ($\geq 95\%$ purity by HPLC; Sigma-Aldrich, Q4951, St. Louis, MO, USA) was administered intragastrically at a dose of 50 mg/kg/day for 12 weeks.

At the end of the experimental period, rats were euthanized, and hypothalamic tissue was rapidly dissected and stored at -80°C until further analysis. Total RNA was extracted using the TRIzol reagent method according to the manufacturer's instructions, followed by purification with isopropanol and 75% ethanol. RNA concentration and purity were assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

First-strand cDNA was synthesized from 100 ng of total RNA using random primers. Quantitative PCR was performed to evaluate the mRNA expression of *Fto*, *Tnf*, *Tnfrsf1a*, *Tradd*, *Ripk1*, *Map3k7*, *Ikbkb*, *Ikbkg*, *Nek7*, *Nfkb1a*, *Nlrp3*, *Pycard*, *Casp1*, *Il1b*, *Il18* and *Gsdmd*. β -Actin was used as the housekeeping gene for normalization. Relative expression was calculated using the $2^{-\Delta\Delta C_t}$ method.

Statistical analysis was performed using GraphPad Prism (version 10.1.2). Data are presented as mean $\pm$ standard deviation (SD). Differences between groups were analyzed using one-way ANOVA followed by Tukey's post hoc test. A p -value < 0.05 was considered statistically significant.

3. Results and Discussion

The high-fat diet (HFD) group exhibited significant upregulation of *Fto* and multiple pro-inflammatory genes associated with the TNF- α /NF- κ B/NLRP3 inflammasome pathway compared to the standard diet (SD) group ($p < 0.005$) (Figure 1).

In contrast, quercetin supplementation (HFD + Q group) significantly downregulated *Fto* and key pro-inflammatory genes including *Tnf*, *Tnfrsf1a*, *Tradd*, *Ripk1*, *Map3k7*, *Ikbkb*, *Ikbkg*, *Nek7*, *Nfkb1a*, *Nlrp3*, *Pycard*, *Casp1*, *Il1b*, and *Il18* relative to the HFD group ($p < 0.0001$) (Figure 1).

These findings indicate that high-fat-diet-induced obesity promotes coordinated upregulation of *Fto* and inflammasome-related genes in the hypothalamus, supporting a mechanistic

link between metabolic regulation and neuroinflammatory signaling, closely linking obesity-associated diseases, including neurodegenerative diseases, with systemic inflammation.

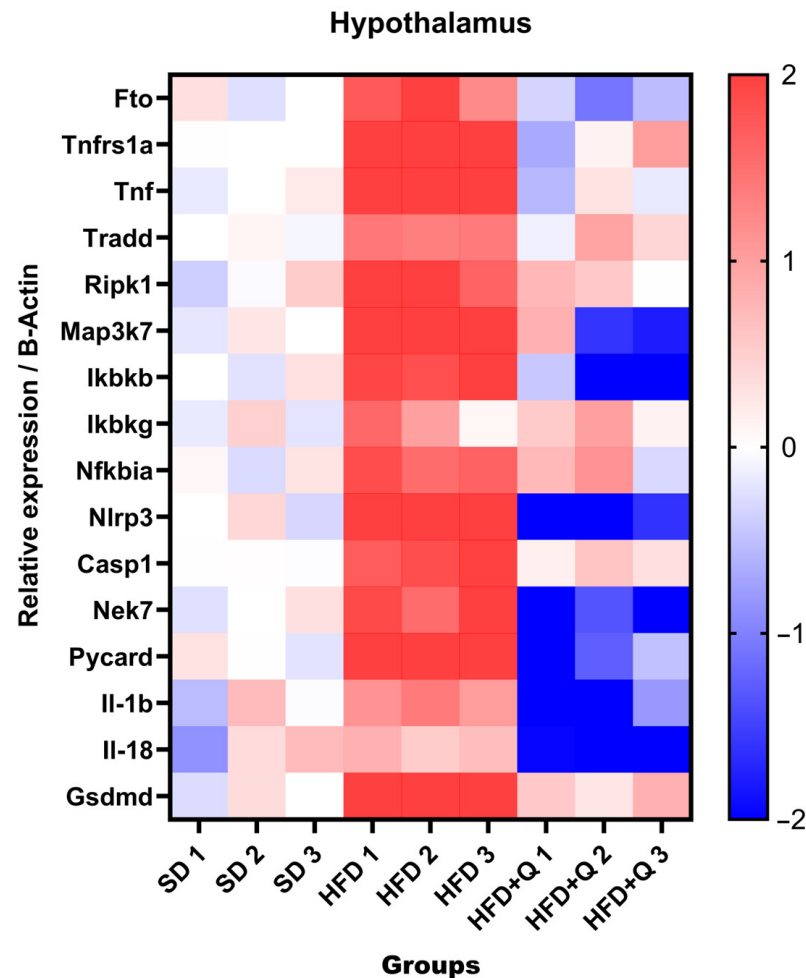


Figure 1. Heatmap showing the relative mRNA expression of Fto and TNF- α /NF- κ B/NLRP3 inflammasome pathway-related genes in the hypothalamus. The color scale represents relative gene expression (red = upregulation, blue = downregulation and white = without change in expression). Columns correspond to individual animals from three experimental groups: standard diet (SD 1–3), high-fat diet (HFD 1–3), and high-fat diet supplemented with quercetin (HFD + Q 1–3). Rows display the genes analyzed: Fto, Tnfrsf1a, Tnf, Tradd, Ripk1, Map3k7, Ikbkb, Ikbkg, Nfkbia, Nlrp3, Casp1, Nek7, Pycard, Il1b, Il18, and Gsdmd. The heatmap clearly illustrates a marked upregulation of most genes in the HFD group compared to the SD group, while quercetin supplementation (HFD + Q) significantly attenuates this overexpression, particularly in Fto, Nlrp3, Casp1, Il1b, and Il18.

Our results demonstrate that chronic high-fat diet consumption induces overexpression of Fto and activates the TNF- α /NF- κ B/NLRP3 inflammasome pathway in the rat hypothalamus, consistent with the role of neuroinflammation in obesity pathogenesis. Fto upregulation in the hypothalamus is consistent with previous studies [8].

Quercetin supplementation effectively reversed these changes by significantly reducing the mRNA levels of Fto and key inflammasome components. These findings support the hypothesis that quercetin possesses anti-inflammatory and anti-obesity properties at the hypothalamic level, potentially through inhibition of NF- κ B signaling and NLRP3 activation (Figure 2).

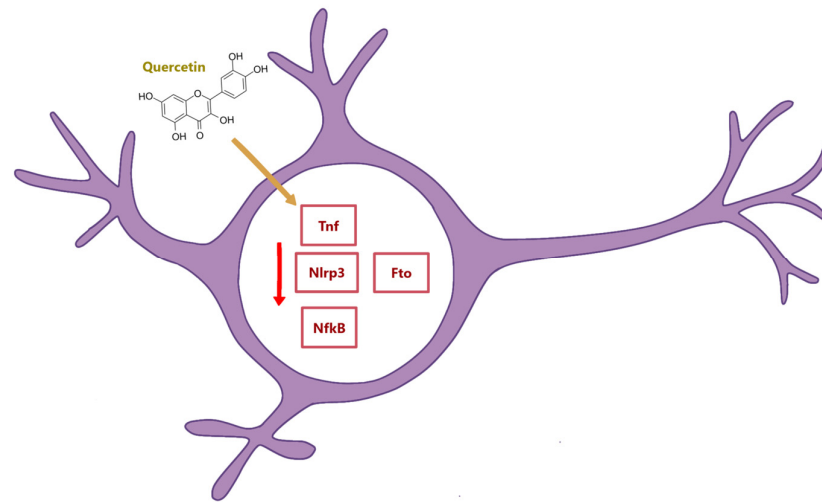


Figure 2. Schematic representation of the inhibitory effect of quercetin on the TNF- α /NF- κ B/NLRP3 inflammasome pathway and Fto expression in hypothalamic neurons of high-fat-diet-fed rats.

4. Conclusions

Quercetin downregulates mRNA expression of Fto and critical components of the TNF- α /NF- κ B/NLRP3 inflammasome pathway in the hypothalamus of high-fat-diet-fed Wistar rats. These results highlight quercetin as a promising natural therapeutic candidate for targeting obesity-associated neuroinflammation and metabolic dysfunction.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Fto	Fat mass and obesity-associated gene (rat)
FTO	Fat mass and obesity-associated gene (human ortholog of Fto)
NLRP3	NOD-like receptor protein 3
SD	Standard diet
HFD	High-fat diet
HFD + Q	High-fat diet plus quercetin

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