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Original Article

Long-term Effects of Gamma-aminobutyric Acid on Lipid Metabolism, Inflammatory Responses, and Insulin Sensitivity in 3T3-L1 Adipocytes

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Abstract

Interest in gamma-aminobutyric acid (GABA) as a metabolic modulator has increased, yet its direct role in adipocyte function remains unclear. This study assessed the prolonged effects of GABA on lipid metabolism, inflammatory responses, and insulin sensitivity in an in vitro adipocyte model. Adipocytes were treated with GABA for up to 21 days. GABA significantly reduced intracellular lipid accumulation at high concentrations, with approximately a 20% decrease observed at 1000 µM, without inducing cytotoxicity. During adipogenesis, interleukin 6 (IL-6) secretion increased in a time-dependent manner, whereas tumor necrosis factor alpha (TNF-α) levels remained unchanged. GABA markedly suppressed IL-6 secretion in fully mature adipocytes, demonstrating anti-inflammatory activity. Stage-specific analysis revealed that GABA treatment during the early differentiation phase (D0–D3) was sufficient to inhibit lipid accumulation and IL-6 release, with effects comparable to treatment throughout the entire adipogenesis period, highlighting the critical role of early differentiation in GABA-mediated inhibition. Mature adipocytes exhibited insulin resistance, as indicated by impaired insulin-stimulated glucose uptake. Long-term GABA treatment enhanced functional insulin responsiveness under insulin-stimulated conditions, while direct GABA exposure enhanced insulin-stimulated glucose uptake in mature adipocytes. Collectively, these findings suggest that GABA reduces intracellular lipid accumulation and inflammation and improves functional insulin responsiveness in this in vitro adipocyte model.

Keywords

GABA, pro-inflammatory cytokine, insulin resistance, 3T3-L1 adipocytes, obesity

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Introduction

Obesity has become a major public health concern due to its strong association with metabolic disorders, including impaired insulin signaling, Type 2 diabetes mellitus (T2DM), and cardiovascular pathology.[1] Age-related adipose tissue expansion alters body composition and promotes adipocyte dysfunction, a central driver of obesity-associated metabolic complications whose mechanisms are not fully elucidated.[2]

Chronic inflammation in adipose tissue is marked by enhanced production of pro-inflammatory cytokines, particularly interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α).[3,4] Cytokine-driven inflammation disrupts glucose uptake in insulin-responsive tissues[5,6] and promotes immune cell infiltration into adipose tissue, thereby sustaining chronic low-grade inflammation and worsening obesity-associated

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metabolic disturbances.[7,8] Therefore, inflammation and insulin resistance are considered to be strongly interconnected pathways that link adipocyte dysfunction to obesity, T2DM, and their associated health complications.

Increasing attention has been given to natural compounds and functional foods that may alleviate age-related disorders, including gamma-aminobutyric acid (GABA), a biologically active amino acid present in plant-based and fermented foods.[9] Beyond neural systems,[10] GABA has been implicated in physiological processes in peripheral tissues, including the pancreas and gastrointestinal tract.[11,12] Several studies have described associations between GABA and alterations in adipose tissue metabolism, including changes in lipid handling and increased lipolytic activity in adipocytes.[13,14] Moreover, GABA has been associated with reduced inflammatory cytokine levels and improved glucose tolerance in animal models[3,15] and type 2 diabetic patients.[16] However, the underlying cellular mechanisms remain to be further explored. Accordingly, the effects of GABA on inflammatory markers and insulin responsiveness were examined in cultured mature adipocytes during prolonged culture. In addition, because most studies treat adipocytes with test compounds throughout the entire maturation period, adipocytes in this study were exposed to GABA at different phases of adipogenesis to determine stage-specific sensitivity.

Materials and Methods

Chemicals

Reagents used in this study included GABA, 3-isobutyl-1-methylxanthine (IBMX), dexamethasone, Oil Red O, isopropanol, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), and insulin, all obtained from Sigma–Aldrich (St. Louis, MO, USA). Cell culture media and supplements, namely Dulbecco's modified Eagle's medium (DMEM), calf bovine serum (CBS), fetal bovine serum (FBS), trypsin–EDTA, and penicillin–streptomycin, were supplied by Gibco (Carlsbad, CA, USA). The fluorescent glucose probe 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino)-2-deoxyglucose (2-NBDG) was sourced from Invitrogen (Thermo Fisher Scientific, Waltham, MA, USA). Quantification of cytokines was performed using murine IL-6 and TNF-α ELISA kits (Cat. Nos. 900-T50 and 900-T54, respectively) from PeproTech (Thermo Fisher Scientific, Waltham, MA, USA).

In Vitro Culture and Adipogenic Differentiation of 3T3-L1 Cells

The murine 3T3-L1 preadipocyte cell line (RCB1124) was obtained from the RIKEN BioResource Research Center Cell Bank (BRC; Saitama, Japan). Preadipocytes were maintained in high-glucose DMEM supplemented with 10% CBS, 100 U/mL penicillin, and 100 μg/mL streptomycin, and cultured at 37 °C in a humidified atmosphere containing 5% CO_2. Adipogenic differentiation was induced by culturing cells in high-glucose DMEM containing 10% FBS, 1 μM dexamethasone, 0.5 mM IBMX, and 10 μg/mL insulin for 3 days. Thereafter, cells were maintained in high-glucose DMEM supplemented with 10% FBS and 10 μg/mL insulin until Day 21, with the culture medium renewed at 3-day intervals.

Cell Treatments

GABA (62.5–1000 μM) was freshly dissolved in sterile water, and sterile water was used as a vehicle control. For treatment, 3T3-L1 adipocytes were continuously exposed to GABA over a 21-day period spanning the differentiation phase, during which the culture medium was replenished at 3-day intervals.

Cell Viability Determination

Cell viability of 3T3-L1 cells was assessed using the MTT assay. Cells were plated in 96-well plates at a density of 5×10^3 cells per well and exposed to varying concentrations of GABA for 21 days. MTT solution (0.5 mg/mL) was subsequently added and incubated for the final 2 h. Formazan produced by metabolically active cells was solubilized in 200 μL DMSO, and absorbance was recorded at 595 nm using a microplate reader.

Measurement of Intracellular Lipid Accumulation

Lipid content was determined by Oil Red O staining after exposure to GABA at concentrations of 62.5, 125, 250, 500, and 1000 μM. Cells were sequentially washed with PBS, fixed with 10% formalin for 1 h, and equilibrated in 60% isopropanol before staining with Oil Red O (3.5 mg/mL) for 10 min. After solubilization of the intracellular lipid-associated dye with 100% isopropanol following PBS washes, absorbance was quantified at 510 nm using a microplate reader.

Determination of Pro-inflammatory Cytokines by ELISA

Cells were exposed to various concentrations of GABA (125–1000 μM), and the culture media were collected at the indicated time points depending on the experiment. Concentrations of the pro-inflammatory cytokines IL-6 and TNF-α in the culture medium were quantified using commercial ELISA kits, following the manufacturer's instructions.

Quantification of Glucose Uptake in Differentiated Adipocytes

3T3-L1 adipocytes were seeded in black, clear-bottom 96-well plates and treated with GABA at concentrations (125–1000 μM) for 21 days to evaluate the effects of long-term GABA exposure on glucose uptake. Following treatment, the culture medium was replaced with glucose-free DMEM containing 25 μM 2-NBDG (fluorescent glucose analog) in the presence and absence of 1 μg/mL insulin, and cells were incubated for 4 h without GABA. After washing with PBS, fluorescence intensity was measured at excitation/emission wavelengths of 485/535 nm using a microplate reader.

To evaluate the direct effect of GABA on glucose uptake, mature adipocytes cultured for 21 days without GABA were incubated in glucose-free DMEM containing 25 μM 2-NBDG together with GABA (125–1000 μM), in the presence or absence of 1 μg/mL insulin, for 4 h. Fluorescence intensity was subsequently determined using the same conditions described above.

Statistical Analysis

Data are reported as mean ± standard deviation (SD) from at least three independent experiments. Statistical analysis was performed using analysis of variance with Tukey post hoc test, and statistical significance was defined as $p \leq .05$.

Results

Effect of GABA on Lipid Accumulation and Viability of 3T3-L1 Adipocyte

3T3-L1 adipocytes were treated with GABA for 21 days. Oil Red O staining showed that GABA reduced intracellular lipid accumulation at high concentration, with approximately 20% decrease observed at 1000 μM (Figure 1C). No cytotoxicity was observed (Figure 1D), indicating that adipocytes tolerated long-term GABA exposure (21 days). These results suggest that high concentrations of GABA suppressed intracellular lipid accumulation in 3T3-L1 adipocytes without affecting cell viability.

Effects of GABA on Pro-inflammatory Cytokine Secretion in 3T3-L1 Adipocytes

Pro-inflammatory cytokine secretion (IL-6 and TNF-α) was quantified at 3-day intervals over the 21-day culture period (Figure 2A). TNF-α levels were not significantly different throughout the culture period (Figure 2B). In contrast, IL-6 secretion increased in a time-dependent manner and became significant at later stages of adipogenesis (after Day 9)

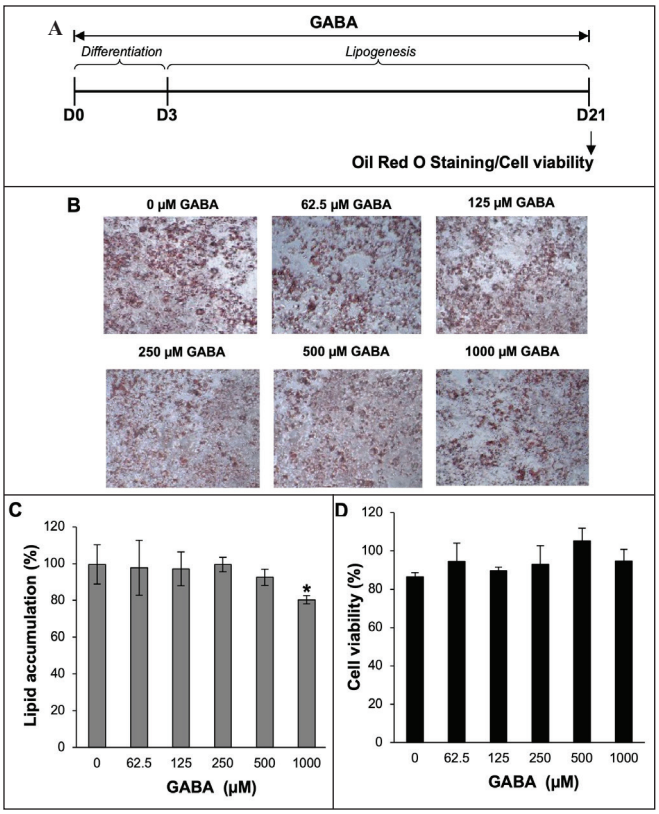

Figure 1. Effects of GABA on Lipid Accumulation and Cell Viability in 3T3-L1 Adipocytes. (A) Schematic Outline of the Experimental Setup: Following Differentiation (D0–D3), Adipocytes Were Maintained in Medium with GABA, Refreshed Every 3 Days Until Day 21. (B) Lipid Accumulations were Determined by Oil Red O Staining and Examined Under a Microscope (40×) and (C) Quantitatively Analyzed by Dissolving Lipid Droplets with Isopropanol and Measuring the Absorbance at 510 nm. (D) Cell Viabilities were Determined by Mitochondrial Enzyme Activity (MTT) of 3T3-L1 Adipocytes After 21-day Treatment. Data are Expressed as Mean ± SD from Six Experiments, *$p \leq .05$, Compared with Control (GABA 0 μM).

(Figure 2B). IL-6 release was reduced in adipocytes cultured with GABA at 500 and 1000 μM (Figure 3B). Fully differentiated (21 days in culture) cells were selected for subsequent experiments to demonstrate the anti-inflammatory effect of GABA. GABA suppressed IL-6 secretion in a dose-dependent manner, with significant inhibition observed at 500 and 1000 μM (Figure 4B). In contrast, TNF-α secretion was not significantly affected by GABA at any concentration (Figure 4B). These findings indicate that fully mature adipocytes exhibit an inflammatory stage characterized by elevated IL-6 secretion, which can be attenuated by GABA.

Differentiation Phase is Critical for GABA-mediated Inhibitory Effects

To investigate the stage-specific effects of GABA, adipocytes were treated during either the differentiation phase (D0–D3),

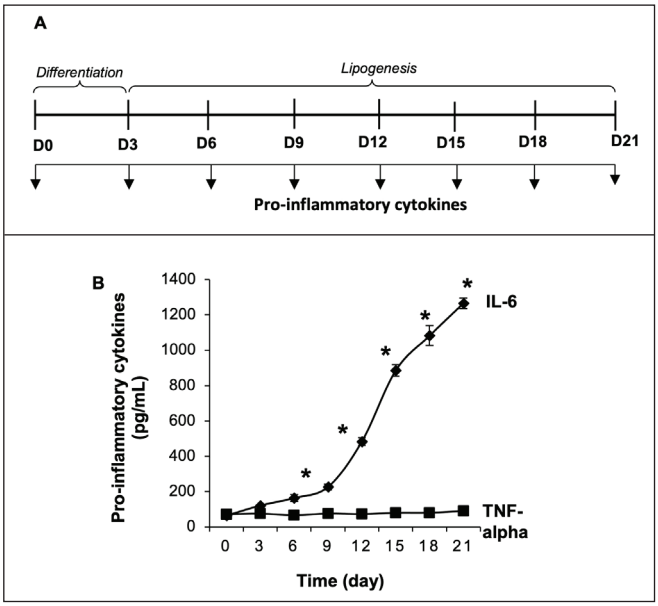

Figure 2. The Release of Pro-inflammatory Cytokines by 3T3-L1 Adipocytes Over 21 Days of Culture. (A) Schematic Outline of the Experimental Setup: After Differentiation, 3T3-L1 Adipocytes Were Cultured in Maintenance Media With Media Refreshed Every 3 Days. (B) IL-6 and TNF-α Were Measured From the Removed Media. Values are Mean ± SD from Three Experiments, $*p \leq .05$ Compared With D0.

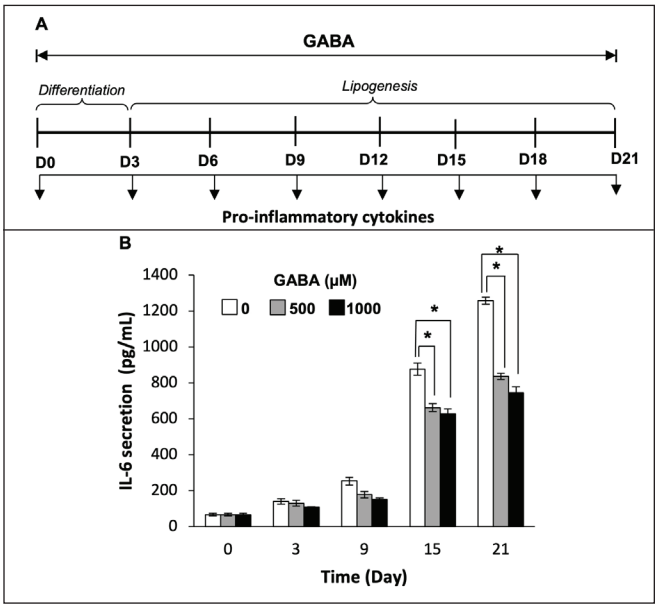

Figure 3. GABA Suppressed IL-6 Secretion in 3T3-L1 Adipocytes at Different Stages in Culture. (A) Schematic Outline of the Experimental Setup: After Differentiation, 3T3-L1 Adipocytes Were Cultured in Maintenance Media in the Absence and Presence of 500 and 1000 μM GABA, with Media Refreshed Every 3 Days. (B) IL-6 was Measured at Day 0, 3, 9, 15, and 21 From the Removed Media. Values are Mean ± SD From Three Experiments, $*p \leq .05$ Compared With Control (GABA 0 μM) on the Same Day.

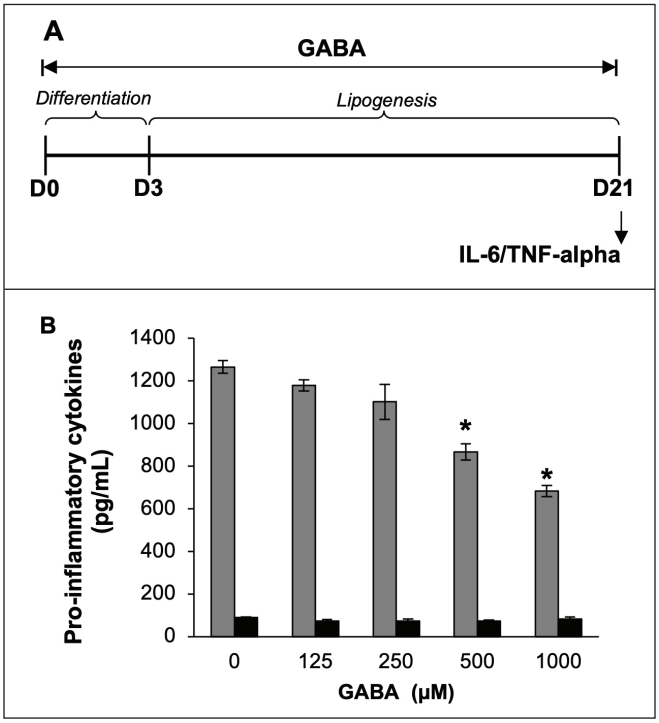

Figure 4. The Effect of GABA on IL-6 and TNF-α Release in Mature Adipocytes. (A) Schematic Outline of the Experimental Setup: After Differentiation, 3T3-L1 Adipocytes Were Cultured in Maintenance Media in the Presence of Various Concentrations of GABA for 21 Days, with Media Refreshed Every 3 Days. (B) IL-6 and TNF-α Levels in Culture Medium at Day 21 Media Were Quantified Using ELISA Kits. Values are Mean ± SD from Three Experiments, $*p \leq .05$ Compared With Control (GABA 0 μM).

the lipogenesis phase (D3–D21), or the entire adipogenesis period (D0–D21) (Figure 5). GABA treatment during the differentiation period (D0–D3) inhibited lipid accumulation to a similar extent as treatment throughout adipogenesis (D0–D21) (Figure 5B). In contrast, GABA treatment during the lipogenesis phase (D3–D21) resulted in a less pronounced reduction in lipid accumulation. The pattern of IL-6 suppression paralleled these effects, with the greatest inhibition observed when GABA exposure included the differentiation stage. These results indicate that the early stage or differentiation phase is critical for GABA-mediated inhibition of both lipid accumulation and pro-inflammatory response in adipocytes.

Effect of GABA on Glucose Uptake in Mature 3T3-L1 Adipocyte

Because adipocyte inflammation was closely associated with insulin resistance, glucose uptake was assessed as an

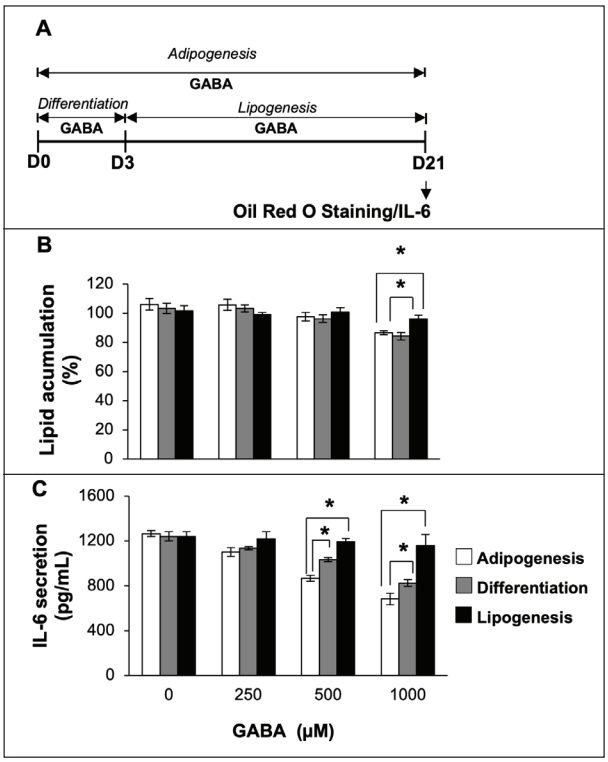

Figure 5. Lipid Accumulation and IL-6 Release in GABA-treated 3T3-L1 Adipocyte at Different Developmental Stages. (A) Schematic Illustration of the 3T3-L1 Treatment Protocols. (B) Lipid Accumulation and (C) IL-6 Release in 3T3-L1 Adipocyte Following GABA Treatment at Differentiation (D0–D3), Lipogenesis (D3–D21), or Adipogenesis (D0–D21) Stages. Values are Mean ± SD, From Three Experiments, *$p \leq .05$ Compared Between Groups.

indicator of insulin responsiveness. In 21-day-cultured adipocytes, glucose uptake did not increase in response to insulin, indicating an insulin-resistant state (Tables 1 and 2). Long-term GABA treatment reduced basal glucose uptake in a dose-dependent manner, with significant decreases observed at 500 and 1000 μM (Table 1). Under insulin-stimulated conditions, however, GABA enhanced insulin sensitivity, increasing glucose uptake by 18% and 27% at 500 and 1000 μM, respectively (Table 1). It should be noted that the uptake of 2-NBDG (fluorescence glucose analog) was performed in the absence of GABA, indicating that these effects reflect cellular adaptation induced by the 21-day GABA treatment.

The direct effects of GABA on glucose uptake were also examined. Mature 3T3-L1 adipocytes were cultured for 21 days without GABA, and glucose uptake assays were subsequently conducted in the presence of GABA. GABA tended to reduce basal glucose uptake while enhancing insulin responsiveness in mature adipocytes (Table 2). Under insulin-stimulated conditions, GABA increased glucose uptake in a dose-dependent manner, with increases of 10% and 18% observed at 500 and 1000 μM, respectively (Table 2). These results suggest that GABA treatment was associated with improved insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes, indicating its ability to modulate insulin responsiveness under the experimental conditions. GABA can also directly improve functional insulin responsiveness by promoting glucose uptake in mature 3T3-L1 adipocytes.

Table 1. Glucose Uptake in Adipocytes Following 21-day GABA Treatment.

	Fluorescence Intensity		
GABA (μM)	Without Insulin	With Insulin	Effect of Insulin (% Increase)
Control	1469.3 ± 46.2	1409.3 ± 76.1	−4.1 ± 3.1
125	1440.0 ± 58.9	1450.7 ± 37.8	0.9 ± 5.7
250	1354.7 ± 62.0	1430.7 ± 26.6	5.7 ± 4.5
500	1298.7 ± 45.5#	1540.0 ± 62.5*#	18.6 ± 1.6#
1000	1266.0 ± 50.7#	1610.7 ± 31.1*#	27.3 ± 2.7#

Notes: The glucose uptake assay was performed in adipocytes cultured with GABA for 21 days. Values are mean ± SD from six experiments, *$p \leq .05$ compared between no insulin and insulin, #$p \leq .05$ compared between control (GABA 0 μM) and GABA-treated cells.

Table 2. Direct Effect of GABA on the Glucose Uptake in Adipocytes.

	Fluorescent Intensity		
GABA (μM)	Without Insulin	With Insulin	Effect of Insulin (% Increase)
Control	1437 ± 36	1425 ± 29	−0.78 ± 3.95
125	1389 ± 55	1413 ± 83	1.69 ± 3.16
250	1429 ± 34	1469 ± 44	2.79 ± 0.67
500	1389 ± 18#	1536 ± 52*#	10.59 ± 4.98#
1000	1304 ± 42#	1541 ± 64*#	18.19 ± 2.68#

Notes: Adipocytes were cultured for 21 days without GABA.
After this, the glucose uptake assay was performed in the presence of GABA.
Values are mean ± SD from six experiments.
*$p \leq .05$ compared between no insulin and insulin, #$p \leq .05$ compared between control (GABA 0 μM) and GABA.

Discussion

We employed a prolonged 21-day adipocyte culture model to evaluate lipid accumulation, inflammatory responses, and insulin sensitivity in response to GABA. Unlike conventional 7–8-day models, this system revealed a time-dependent increase in IL-6, becoming significant after Day 9, thereby better reflecting chronic low-grade inflammation. Within this context, GABA was associated with reduced lipid accumulation, decreased IL-6 production, and improved insulin responsiveness. Collectively, these findings suggest that GABA modulates adipogenic, inflammatory, and metabolic features in adipocytes, supporting its potential relevance to obesity-related metabolic dysfunction in vitro.

Our findings are consistent with previous studies showing that hypertrophic, lipid-laden adipocytes develop inflammatory and insulin-resistant phenotypes. In line with this, the prolonged culture of mature adipocytes in our study resulted in increased IL-6 secretion and impaired insulin responsiveness. Previous reports have demonstrated beneficial metabolic effects of GABA, including reduced lipid accumulation, enhanced lipolysis, anti-inflammatory actions via GABA-B signaling, and suppression of adipogenic transcription factors.[14,15,17] Consistent with these observations, our results show that GABA suppresses IL-6 secretion and improves insulin responsiveness in mature adipocytes.

Prolonged adipocyte culture was associated with chronic low-grade inflammation and metabolic dysfunction, consistent with obesity-related alterations in adipokine profiles and pro-inflammatory cytokines.[18,19] In our model, IL-6 was the predominant cytokine, showing a time-dependent increase during adipocyte maturation, whereas TNF-α remained unchanged, suggesting differential regulation of cytokine secretion. These findings support a stronger association of IL-6 with chronic inflammatory features in mature adipocytes, consistent with previous reports in long-term culture[20] and obesity.[20–23] Although TNF-α is elevated in adipose tissue, its systemic contribution may be limited due to predominant local production by macrophages.[8] While multiple markers contribute to chronic adipocyte inflammation, our analysis was limited to IL-6 and TNF-α, which are widely used indicators in 3T3-L1 models. Among these, IL-6 serves as a representative marker due to its clear time-dependent increase during adipocyte maturation. However, inclusion of additional inflammatory and signaling markers would provide a more comprehensive understanding of adipocyte dysfunction.

In addition, our study identifies the early differentiation phase (D0–D3) as the critical window where GABA acts as a preventive metabolic protector. This provides a new perspective compared to studies focusing on treating mature cells, as we demonstrate that intervening during this specific stage "programs" adipocytes to resist lipid accumulation and inflammation throughout their 21-day maturation. This highlights GABA's role in prevention and protection during development rather than just a curative treatment.

Elevated IL-6 levels are associated with impaired insulin responsiveness and alterations in key signaling components, including the insulin receptor and GLUT4 in hepatocytes[24,25] and adipocytes.[26] Consistent with this, prolonged culture of adipocytes in our study increased IL-6 secretion and reduced insulin-stimulated glucose uptake. Given the central role of GLUT4 in glucose transport, its regulation in long-term–cultured adipocytes warrants further investigation as a potential link between inflammation and insulin resistance.

In our model, GABA treatment reduced IL-6 production and improved insulin responsiveness, suggesting a modulatory role in inflammation-related metabolic dysfunction. Improvements in glucose uptake were observed in both preventive and treatment settings. These findings are consistent with prior studies linking GABA[3,15,27] and GABA-enriched germinated brown/waxy black rice extracts to reduced inflammation and modulation of adipose tissue function in animal models.[27,28] Although the GABA concentrations used may exceed physiological levels, they provide insight into underlying mechanisms, potentially involving specific receptor subtypes. Future studies should explore more potent GABA receptor agonists.

Previous studies suggest that GABA receptor systems contribute to inflammatory and metabolic regulation, with GABA-A receptors expressed in adipose and immune cells.[4,14,29–31] Both GABA-A and GABA-B receptors have also been implicated in adipogenic regulation, and GABA has been linked to lipolysis and potential interactions with β-adrenergic signaling in adipocytes.[14,32] However, the crosstalk between GABAergic and adrenergic pathways remains poorly understood due to limited evidence. This highlights a complex regulatory role of GABA receptors and underscores the need for further studies to clarify their interactions in metabolic regulation. Overall, these findings indicate that GABA treatment is associated with reduced adipogenic and inflammatory features, as well as improved insulin responsiveness, in adipocytes.

Conclusion

Maturing 3T3-L1 adipocytes exhibit increased IL-6 secretion, enhanced lipid accumulation, and insulin resistance. GABA demonstrates a protective effect against model-induced adipocyte dysfunction by suppressing lipid accumulation and IL-6 secretion, thereby maintaining functional insulin responsiveness in vitro.

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Authors' Contribution

All authors made substantial contributions to conception and design, acquisition of data, or analysis, and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave

final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be authors as per the International Committee of Medical Journal Editors' requirements/guidelines.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Data Availability Statement

All the data is available with the authors and shall be provided upon request.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study does not involve experiments on animals or human subjects.

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Informed Consent

Not applicable

Use of Artificial Intelligence-assisted Tools

The authors declare that they have not used artificial intelligence (AI) tools for writing and editing of the manuscript, and no images were manipulated using AI.

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