Research Article

Neuroprotective effects of intense training and thyme honey on hippocampal cognitive pathways in diabetic rats

Shadi Jalalian[1], Hossein Abednatanzi[1*], Mandana Gholami[1], Farshad Ghazalian[1]

Abstract

Unmanaged Type 2 Diabetes (DM2) is a known risk factor for cognitive decline, dementia, and Alzheimer's disease (DM3). This study explores the combined effects of high-intensity interval training (HIIT) and thyme honey on the expression of genes involved in memory-related signaling pathways (BDNF-TrkB-CREB), which are compromised in both DM2 and DM3. This experimental study involved 36 young male Wistar rats, divided into four groups: control (C), HIIT (T), thyme honey (H), and HIIT-thyme honey (TH). The T and TH groups underwent 40 training sessions over two months, with progressively increasing intervals (from 2 to 8) and intensity (from 80% to 95% of maximum running speed). Concurrently, the H and TH groups were administered 3 g/kg of thyme honey 5 days a week. Changes in BDNF, TrkB, and CREB gene expression were assessed using RT-PCR. The data were analyzed through one-way ANOVA, Bonferroni post hoc test, and Univariate analysis using SPSS-22 software. A significant increase in BDNF and CREB expression in the interactive intervention group and the expression of the TrkB gene in honey intervention groups were observed compared to diabetic control ($P \geq 0.001$). The interactive intervention with HIIT exercises and thyme honey has a synergistic effect on increasing gene expression in memory-related pathways. The highest effect size was observed for HIIT training on BDNF (EF=0.667) and CREB (EF=0.540), while the honey intervention showed a significant effect size on TrkB (EF=0.666).

Key Words: **HIIT, Honey, Antioxidant, Diabetes, BDNF, Memory, Hippocampus**

1. Department of Physical Education and Sport Science, Science and Research Branch, Islamic Azad University, Tehran, Iran.

*Author for correspondence: abednazari@gmail.com

SH J: 0000-0003-3210-4245; H A: 0000-0001-6638-1131; M GH: 0000-0001-8960-4123; F GH: 0000-0002-7315-1382

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Introduction

Unmanaged Type 2 diabetes (DM2), recognized as a risk factor for mild cognitive impairment, accelerates the progression of dementia and Alzheimer's disease. In some literature, this cognitive decline is referred to as Type 3 diabetes (DM3), due to its association with disrupted insulin signaling in the brain, leading to memory-related deficits and neurodegenerative changes (Kang et al., 2019). The hippocampus, known for its critical role in learning and memory, is one of the first regions to be affected or damaged during DM3 (Annita et al., 2024).

Moreover, it is notably influenced by brain-derived neurotrophic factor (BDNF), which plays a key role in neurogenesis and synaptic plasticity in this region. BDNF and its receptor TrkB are highly expressed in the hippocampus and cerebral cortex. This highlights their importance in memory formation, learning, and other cognitive functions. BDNF exerts its effects through the cyclic AMP response element-binding protein (CREB) in these regions (Hashemi & Ahmadi, 2023).

Emerging evidence from the literature highlights the disruption of the BDNF-TrkB-CREB pathway as a critical factor in cognitive decline in diabetic conditions (Sumbul-Sekerci et al., 2023). This pathway has also been identified as a potential therapeutic target for enhancing neuroplasticity and cognitive resilience in diabetes-related cognitive impairment. Further studies have demonstrated that the metabolic role of BDNF in DM2 includes regulation of energy balance, glucose metabolism, and neuronal health. Although findings have been somewhat contradictory, a correlation between BDNF levels and glycemic parameters has been reported (Fujinami et al., 2008). For example, in a study conducted as part of a larger mega project, a significant reduction in blood sugar levels was observed in the intervention groups compared to the control group (Jalalian et al., 2023). Notably, a decline in BDNF serum levels has been directly correlated with the duration of diabetes (Rozanska et al., 2020). However, some studies have reported increased BDNF levels, which may be influenced by the use of antidiabetic drugs (Sumbul-Sekerci et al., 2023). Impaired

BDNF-TrkB-CREB signaling has also been observed in the brains of diabetic rats. For instance, Han et al. demonstrated that increasing BDNF expression in the hippocampus of diabetic rats could suppress inflammatory and apoptotic factors, thereby mitigating hyperglycemia-induced brain damage (Han et al., 2019).

The cross-talk between the brain and muscles is well-established, with evidence showing that the release of certain exerkines, such as irisin and cathepsin B, their crossing of the blood-brain barrier, and subsequent accumulation in the hippocampus (Panahzadeh & Sabzevari Rad, 2023)—a region responsible for memory and particularly sensitive to exercise (dos Santos et al., 2020; Suzuki et al., 2022; Zhou et al., 2022)—activates signaling pathways that induce BDNF expression. This process promotes neurogenesis, increases brain volume, and reduces neuronal death. Numerous studies have reported elevated serum levels or increased expression of BDNF in the brain following various exercise protocols in both human and animal subjects, suggesting that these effects are related to exercise intensity, with intermittent exercises proving more effective than continuous ones (Bayrakdaroğlu et al., 2022; Jalalian & Ghazalian, 2022; Tang et al., 2017; Wu et al., 2020). For example, 12 weeks of training (30 minutes/5 times per week) in Streptozotocin (STZ)-induced diabetic rats successfully reversed short-term memory loss and impaired spatial learning. Several mechanisms have been proposed to explain the increase in BDNF expression in both neurons and glial cells. Increased Wnt3 expression and decreased GSK-3β expression have been linked to enhanced neurogenesis in the dentate gyrus and improved brain glucose metabolism (Kim et al., 2016; Yi et al., 2012). In addition, the AMPK-PGC-1α-FNDC5 pathway, activated by high-intensity exercise, is known to enhance irisin release and support BDNF signaling, linking peripheral muscle activity to central neuroplasticity processes (Azimi et al., 2018; Bayrakdaroğlu et al., 2022).

Additionally, studies have highlighted the potential of honey and thyme in managing diabetes complications, improving memory function, and preventing DM3, primarily due to their antioxidant properties (Aameri et al., 2022; Fadzil et al., 2023; Lafraxo et al., 2021; Terzo et al., 2022). The high concentrations of flavonoids, phenols, and amino acids in thyme honey are crucial for the dimerization, phosphorylation, and synthesis necessary for TRKB and CREB activation (Conte et al., 1998; Mijanur Rahman et al., 2014; Yang & Zhu, 2022; Zulkifli et al., 2022). Long-term honey intervention has been shown to reduce neuroinflammation and prevent the decline of BDNF levels in the brains of obese mice (Terzo et al., 2022). Moreover, a single dose of thyme honey has been associated with improved memory in rat models of Alzheimer's disease (Aameri et al., 2022). Additionally, thymol an active compound in thyme, has been shown to increase CREB and BDNF expression in the brains of rats (Ogaly et al., 2022).

While various studies have explored exercise and natural interventions separately for their potential to enhance neurogenesis and delay memory loss in diabetic models, few have combined these strategies to assess their interactive effects. The combined effect of a modified form of high-intensity interval training (HIIT) and thyme honey on the expression of genes related to memory-associated signaling pathways in diabetic models has yet to be investigated. This study seeks to fill this gap and encourage further research in this field.

Materials and Methods

Study design overview

This experimental study was conducted using 36 young male Wistar rats weighing 110 ± 10 grams, purchased from the Royan Institute. In accordance with the Helsinki ethical guidelines (Helsinki, 2023), and after obtaining the ethics code IR.IAU.SRB.REC.1401.155, the rats were transferred to the Razi Laboratory Animal House at the Science and Research Branch of Islamic Azad University, Tehran, Iran. The rats were housed in transparent, autoclave-capable polycarbonate containers, maintained at a temperature of 20 to 24°C with relative humidity between 30% and 60%. The lighting in the hall was electronically controlled, alternating every 12 hours. The rats were given two weeks to acclimate to the environment with unlimited access to food and water.

Induction of obesity and diabetes

To induce obesity, the rats were placed on a high-fat diet (HFD) after reaching an average weight of 197.70 ± 19.46 grams. The HFD consisted of 45% fat for twelve weeks, followed by 60% fat for eight weeks. An average weight of 402.75 ± 51.69 grams was used as the criterion for selecting obese rats. To induce diabetes, 25 mg of Streptozotocin (STZ) was injected intraperitoneally. One week after the injection, random blood samples were taken from the tail to measure fasting blood sugar (FBS) (363 ± 124.5), fasting insulin (FI) (3.92 ± 0.49), and the homeostatic model assessment of insulin resistance (HOMA-IR) (3.56 ± 1.43) to confirm the diabetic status of the rats (Gheibi et al., 2016; Ma et al., 2014).

Experimental groups

The rats with similar average weights were divided into the following groups: control (C, n=8), high-intensity interval training (T, n=10), thyme honey (H, n=8), and high-intensity interval training with thyme honey (TH, n=8).

HIIT protocol

The training groups underwent an 8-week HIIT program, with 5 sessions per week. The intensity was progressively increased every two weeks, with high-intensity intervals ranging from 32 to 38 meters per minute (80–95% of maximum speed) and rest intervals from 16 to 22 meters per minute (50–56% of maximum speed), lasting 16 to 34 minutes per session, according to the Akbarzadeh et al. protocol (Akbarzadeh & Fattahi bafghi, 2018) (Table 1).

To familiarize the rats with the treadmill, they were introduced to the device one week prior to the start of the protocol. During this time, they walked on the treadmill three times a week for 10, 12, and 15 minutes at a speed of 5 m/min with no incline. During the implementation of the protocol, the control group also walked on the treadmill under the same conditions.

Due to the lack of access to tools such as a breath gas analyzer, which directly calculates VO_{2max}, and given the high correlation between treadmill speed and VO_{2max} in rats ($P<0.05$, $r=0.94$-0.98), aerobic exercise intensity was estimated using the maximum running speed test (MERT). Every two weeks, during a training session, the rats warmed up for 5 minutes at 10 m/min, followed by a 2-minute run at 15 m/min. The speed was increased by 3 m/min every 3 minutes until the rats could no longer run and remained on the shocker. The speed at which the rats stopped was recorded as their maximum running speed (Rodrigues et al., 2007).

Honey administration

Five days a week, the H and TH groups were administered 3 g/kg of Shirazi thyme honey diluted with distilled water via gavage prior to training (Lafraxo et al., 2021). To prepare the extract, three kilograms of thyme plants were collected from the fields of Shiraz and placed in a shaker machine with a solution of distilled water and alcohol (30:70 ratio) for 48 hours. The mixture was filtered twice, and after evaporation at 35–38°C, it was reduced to a thick paste. This extract was then dissolved in water and fed to bees in the hives to produce pure thyme honey (Erejuwa O. Omotayo et al., 2013).

Table 1. Treadmill HIIT protocol.

Week	Warm-up intensity 5 m/min	Intense Intervals number	Intense Intervals time	Intense Intervals speed	Rest Intervals time	Intense Intervals speed	Cool down intensity 5 m/min	Session time
1&2	10 m/min	2	min 2	MERT 80% m/min 32	min 1	MERT 50% m/min 16	10 m/min	min 16
3&4	10 m/min	4	min 2	MERT 85% m/min 34	min 1	MERT 52% m/min 18	10 m/min	min 22
5&6	10 m/min	6	min 2	MERT 90% m/min 36	min 1	MERT 54% m/min 20	10 m/min	min 28
7&8	10 m/min	8	min 2	MERT 95% m/min 38	min 1	MERT 56% m/min 22	10 m/min	min 34

Table 2. Primer's information was used in the research related to BDNF, TrkB, and CREB genes

Gene type	Primer type	Sequence	Primer length bp
BDNF	Forward (5'->3')	GGCCCAACGAAGAAAACCAT	20
	Reverse (3'->5')	TTCCTCCAGCAGAAAGAGCA	20
TrkB	Forward (5'->3')	CCGGCTTAAAGTTTGTGGCT	20
	Reverse (3'->5')	CTGGAGAGTCTTGAGCCACA	20
CREB	Forward (5'->3')	TGGAGTTGTTATGGCGTCCT	20
	Reverse (3'->5')	CTCTTGCTGCTTCCCTGTTC	20

Preparation and tissue collection

Forty-eight hours after the interventions concluded, the remaining rats (8 from the T and TH groups, and 6 from the H and C groups) were sacrificed following a 12-hour fasting period. The hippocampus was carefully removed from the rats' brains for gene expression analysis. After extraction, the tissue was placed in liquid nitrogen and subsequently stored in a freezer at -80°C.

Gene expression analysis

Gene expression was measured using real-time polymerase chain reaction (RT-PCR) with Corbett's Rotor-Gene 6000 Thermocycler. The $2^{-\Delta\Delta CT}$ method was employed for quantitative and relative analysis of gene expression (PCR data). Primers were designed using Primer Express software version 3 (Table 2). The hypoxanthine phosphoribosyl transferase (HPRT1) gene was used as a reference in this study. The final PCR products were analyzed by gel electrophoresis.

Statistical analysis

To assess the normality and homogeneity of variance in the dataset, the Shapiro-Wilk test and Levene's test were respectively applied. For comparing the average changes among groups, one-way ANOVA was employed in the inferential statistics section. The two-way ANOVA test was utilized to evaluate the influence of each intervention and determine the

groups. Statistical analysis was performed using SPSS-22, and a significance level of P≥0.05 was maintained for all measurements.

Results

One-way ANOVA showed that the interventions in obese diabetic samples resulted in significant differences in the expression of BDNF (F=52.303, P=0.001), TrkB (F=24.7, P=0.0001), and CREB (F=34.43, P=0.0001) genes.

Univariate analysis revealed a significant increase in the expression of BDNF and CREB genes in the T and TH groups, alongside a significant decrease in the H group compared to the C group (Figure 1&3). The exercise intervention had the largest effect size (Table 3). Although all intervention groups showed an increase in TrkB gene expression (Figure 2), this increase was not significant in the TH group, with the honey intervention demonstrating the greatest effect size for this outcome (Table 3).

According to the Bonferroni post hoc test, the increase in BDNF and CREB gene expression due to the combined intervention (TH) was significant compared to all other groups (P = 0.0001). However, the changes in gene expression in the T and H groups, while trending upwards and downwards respectively, were not statistically significant when compared to the C group. A significant increase in TrkB gene expression was observed in the TH group compared to the T and C groups (P = 0.0001), and also compared to the H group (P = 0.002). Additionally, the thyme honey intervention led to a significant increase in TrkB expression compared to the C group (P = 0.011), whereas the increase in the T group was not statistically significant compared to the C group.

Discussion

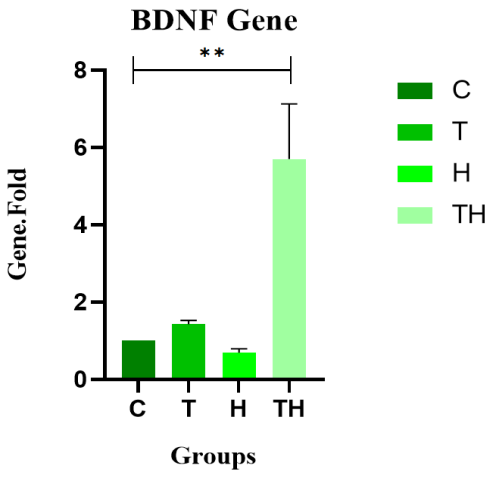

Figure 1. BDNF genes expression changes and significance between groups according to Bonferroni (*P≤ 0.05, **P ≤ 0.01)

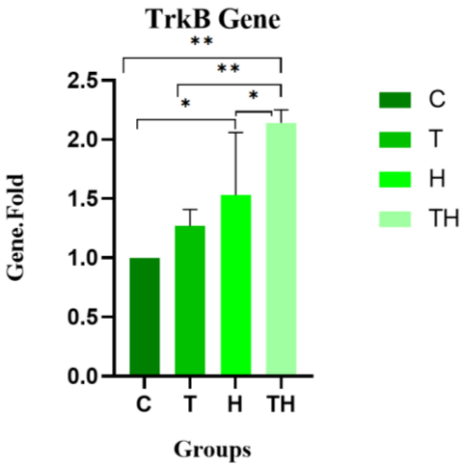

Figure 2. TrkB genes expression changes and significance between groups according to Bonferroni (*P≤ 0.05, **P ≤ 0.01).

The increased expression of BDNF and CREB in the TH group compared to the C, T, and H groups suggests that the combined intervention of HIIT and thyme honey is more effective in enhancing memory-related signaling pathways than either intervention alone. This result highlights the synergistic effect of both interventions in promoting neurogenesis and synaptic plasticity. As demonstrated in our previous observation (Jalalian et al., 2023) the TH group also exhibited a significant reduction in blood glucose levels. This reduction in blood sugar could be linked to the enhanced cognitive and neuroprotective effects observed in the current study. Improved glycemic control might not only contribute to metabolic health but also play a role in the regulation of cognitive functions through BDNF signaling, supporting the idea that BDNF may serve as a bridge between metabolic and brain health.

BDNF-TrkB-CREB signaling is known to be crucial for memory

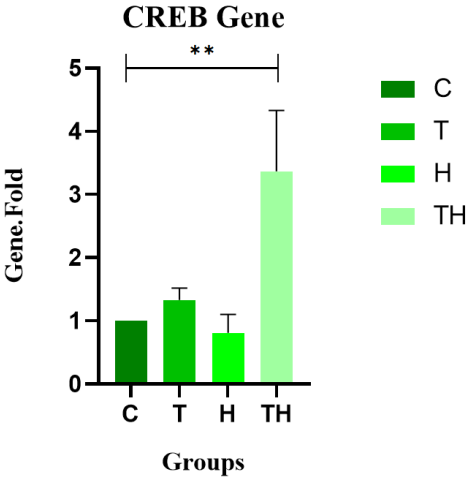

Figure 3. CREB genes expression changes and significance between groups according to Bonferroni (*P≤ 0.05, **P ≤ 0.01)

Table3. Statistical description and two-way ANOVA to determine the effects of interventions on changes in the expression of BDNF, TrkB, and CREB genes.

Groups	Outcomes	Gene fold Mean	F	P value
T	BDNF	1.43±0.1	59.916	0.0001
H		0.7±0.1	35.192	0.0001
TH		5.7±1.43	48.071	0.0001
C		1.00	-	-
T	TrkB	1.27±0.14	19.177	0.0001
H		1.53±0.53	47.864	0.0001
TH		2.14±0.11	2.694	0.114
C		1.00	-	-
T	CREB	1.33±0.19	47.798	0.0001
H		0.81±0.29	19.554	0.0001
TH		3.37±0.96	28.129	0.0001
C		1.00	-	-

formation and synaptic plasticity. Several studies have shown that both exercise and honey can positively influence this pathway (Ogaly et al., 2022; Zhou et al., 2022; Zulkifli et al., 2022).

For instance, Han et al. showed that BDNF overexpression in the hippocampus of STZ-induced diabetic models can reverse neuroinflammation and promote learning-dependent synapse formation through TrkB phosphorylation. In our study, the observed improvements in BDNF and TrkB signaling in the TH group may mirror these neuroprotective effects, suggesting potential cognitive benefits for diabetic rats (Han et al., 2019).

HIIT has been associated with several molecular mechanisms that enhance memory and learning. Previous studies (Kim et al., 2016; Yi et al., 2012) have shown that intermittent, high-intensity exercise leads to increased BDNF expression in both neurons and glial cells, reversing memory loss, as observed in DM2 or DM3, and improving brain plasticity. Furthermore, this type of exercise has been linked to increased Wnt3 and decreased GSK-3β expression, both of which contribute to neurogenesis in the dentate gyrus and improved brain glucose metabolism.

Additionally, key molecular factors activated by HIIT, such as AMPK, PGC-1α, FNDC5, and irisin, are known to support BDNF-TrkB-CREB signaling, further strengthening memory-related processes in the hippocampus. AMPK is a central regulator of cellular energy balance and is activated by HIIT, leading to increased mitochondrial biogenesis. PGC-1α, a downstream target of AMPK, promotes the expression of FNDC5, which is cleaved to produce irisin, an exerkine that crosses the blood-brain barrier. Irisin has been shown to increase BDNF expression in the hippocampus, thereby enhancing neurogenesis and synaptic plasticity (Azimi et al., 2018; Bayrakdaroğlu et al., 2022; Wu et al., 2020).

The neuroprotective effects of honey, specifically thyme honey, are also supported by various studies. A 35-day honey intervention was shown to enhance synaptogenesis and memory performance, primarily by upregulating neurotrophic factors such as BDNF (Mustafa et al., 2019). Similar results have been observed in obese rats, where honey consumption led to increased BDNF expression in both the brain and hippocampus (Terzo et al., 2022; Zulkifli et al., 2022). Thyme honey's rich composition of phenolic compounds, including quercetin, catechin, and gallic acid, has been shown to activate CREB via MAPK/ERK pathways, further promoting synaptic plasticity and cognitive function (Mijanur Rahman et al., 2014). In addition, flavonoids and amino acids such as phenylalanine and tyrosine, which have been reported in thyme honey, may play a role in the increased expression of TrkB observed in the H group (Conte et al., 1998; Yang & Zhu, 2022; Zulkifli et al., 2022). Additionally, thymol, a key active component in thyme, has been shown to enhance BDNF and CREB levels in the brain, thereby providing neuroprotection against various neurotoxic conditions (Ogaly et al., 2022). In line with these findings, the improvements in BDNF and CREB signaling in the TH group in our study may exhibit synergistic neuroprotective effects due to their complementary mechanisms.

Conclusion

Enhancement of BDNF-TRKB-CREB signaling through increased neurogenesis, synaptogenesis, synaptic plasticity, and maintenance of brain energy homeostasis may effectively delay memory impairment, cognitive dysfunction, and Alzheimer's disease, all of which are well-documented complications of unmanaged DM2. These effects were observed in the present experimental study following the simultaneous intervention of HIIT and thyme honey.

However, due to budget constraints, we could not assess memory function tests or protein levels of the mentioned genes. Further histochemical and clinical studies will be required to confirm and expand these findings. Additionally, the study was limited by an 8-week intervention and sample size constraints, which could affect the robustness of the results. Longer-term studies with larger sample sizes would be essential to fully understand the therapeutic potential of HIIT and thyme honey as a natural intervention to enhance cognitive function and improve glycemic control in diabetic patients.

What is already known on this subject?

The interactive intervention of HIIT and thyme honey has a synergistic effect on increasing BDNF and CREB gene expression.

What this study adds?

The combination of HIIT and thyme honey could serve as a natu-

-ral intervention to counteract the decrease in memory-related gene expression in the hippocampus of diabetic rat.

Organ Cross-Talk Tips:

- Exercise-induced molecules, such as irisin and cathepsin B, foster the release of neuroprotective factors that facilitate brain-muscle crosstalk, improving memory and cognition by stimulating the hippocampal BDNF-TrkB-CREB pathway.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval for this study was obtained from the Faculty of Medical Sciences and Technologies, Science and Research Branch, Islamic Azad University, with the ethics code IR.IAU.SRB.REC.1401.155.

Informed consent Not applicable

Author contributions

Conceptualization: Sh.J., H.A., M.Gh.; Methodology: Sh.J., H.A., F.Gh.; Software: H.A.; Validation: Sh.J., Formal analysis; Investigation: M.Gh., F.Gh.; Resources: Sh.J., H.A.; Data curation: Sh.J., H.A., M.Gh.; Writing - original draft: Sh.J.; Writing – review & editing: H.A.; Visualization: M.Gh.; Supervision: H.A. Project administration: H.A.; Funding acquisition: Sh.J.

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