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Research Article

The effect of high-intensity interval training and spirulina supplementation on the levels of Pannexin-1 and NLRP-1 proteins in hippocampal tissue in male rats with type 1 diabetes

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Abstract

The purpose of this research is to investigate the effect of High-intensity interval training and spirulina supplementation on the levels of Pannexin-1(PANX-1) and NLRP-1 proteins in hippocampal tissue in male rats with type 1 diabetes. In this experimental study, 30 Wistar rats, aged 10 weeks and weighing 180-260 grams, were randomly divided into 5 groups of 6 each: exercise group, supplement group, exercise+supplement group, control group, 5 healthy group. After inducing diabetes and implementing the protocol, hippocampal tissue from the rats was extracted, and the levels of Pannexin -1 and NLRP-1 proteins were measured using the western blot method. Statistical analyses and data processing were conducted using SPSS version 26 software, with significance set at $p \leq 0.05$. The results showed a significant increase in Pannexin-1 and NLRP-1 proteins in diabetic rats ($p<0.05$). There was a noticeable decrease in protein expression after 6 weeks of rigorous intermittent exercise and spirulina supplements in the exercise, supplement, and exercise+supplement groups compared to the diabetic group. This reduction was mostly due to the combined effects of exercise and supplementation rather than either alone. Our research has verified the hypoglycemic effects of intense interval training and spirulina supplementation, along with their impact on reducing PANX-1 and NLRP-1 protein expression. Consequently, it appears that this form of physical activity and herbal supplement could significantly enhance the management of neurodegenerative disorders in individuals with type 1 diabetes.

Key Words: HIIT, Spirulina supplement, Hippocampus, Diabetes, NLRP-1, PANX-1

Introduction

Diabetes mellitus (DM) is widely regarded as one of the most common chronic and expensive metabolic diseases. It is caused by either absolute or relative insulin deficiency, resulting in a dysfunction in pancreatic beta cells' secretion of this hormone (Ceci et al., 2014; Gleeson et al., 2011). One of its primary symptoms is hyperglycemia (Rand et al., 2004). As diabetes progresses, hyperglycemia causes dysfunction in various bodily systems, including the cardiovascular system, kidneys, retina, eye lens, skin, and central and peripheral nervous systems (Martinon et al., 2002).

In simpler terms, the hippocampus is a crucial center for memory and learning functions that may be adversely impacted by high sugar levels, rendering its neurons more prone to type 1 diabetes (Martínez-Tellez et al., 2005; Reagan, 2007). Research has shown that individuals with diabetes tend to exhibit a reduced hippocampal volume in comparison to those without the condition, potentially due to damage to nerve cells in this area resulting from diabetes (den Heijer et al., 2003). However, the exact mechanisms by which diabetes triggers the deterioration of neuronal cells in the hippocampus remain incompletely understood.

It is crucial to understand the physiological and pathological roles of certain factors, such as the levels of Pannexin-1 and NLRP-1 proteins. The importance of comprehending the role of Pannexin-1, present abundantly in the CNS and various cell types including microglia, astrocytes, oligodendrocytes, and neurons, lies in its unique properties. This channel can activate certain ligand-gated CNS receptors under pathological conditions such as neuroinflammation, oxygen depolarization, stroke, cell death, and seizures, and it plays a significant role in cellular processes that contribute to chronic inflammation, cell death, and diseases (Isakson & Thompson, 2014; Thompson et al., 2006). On the other hand, studies have indicated that the hyperglycemic state associated with diabetes mellitus leads to

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persistent inflammation, potentially resulting in neuronal death (LaFerla et al., 2007). In 2006, Thomson and colleagues demonstrated that PANX-1 becomes activated in isolated hippocampal neurons in response to oxygen and glucose deprivation (ischemic conditions), generating a strong secondary current that depolarizes the membrane (oxygen depolarization), ultimately leading to neuronal death (Thompson et al., 2006).

The most well-known inflammasomes are NLRP3-1 and NLRP3. The NLRP3-1 inflammasome is primarily found in neurons (de Rivero Vaccari et al., 2014). Studies have demonstrated that the expression of NLRP-1 is elevated in the central nervous system (CNS) of diabetic mice, leading to neuroinflammation triggered by high glucose levels (Meng et al., 2014).

According to research, physical activity and exercise, when combined with medication and diet, seem to effectively control diabetes and lessen its complications. Increasing physical fitness is directly linked to lowering mortality rates from diabetes and its complications. Therefore, it is crucial to engage in sports activities as they are widely accepted, cost-effective, and easily accessible (Riahy, 2024). Recent studies have indicated that oxidative damage in the hippocampus decreases during submaximal-intensity activity, and regular exercise can enhance memory function through its antioxidant properties (Bertram et al., 2016). While the connection between diabetes and central nervous system disorders, along with its damaging effects on neural tissues, has been partially documented, the underlying mechanism remains unclear (Meek & Morton, 2012). Additionally, in recent years, dietary supplements have played a significant role in maintaining a healthy diet for various chronic conditions, including diabetes.

Spirulina is one of these dietary supplements, which has proven cholesterol-regulating and antioxidant effects, and also has immune-regulating effects. In patients who require insulin, because the sugar in spirulina is absorbed with minimal insulin and minimal pressure on the pancreas, and because spirulina reduces a person's desire to eat, it causes weight loss and reduces the need for insulin (Mridha et al., 2010). In this regard, research has shown that treatment with Spirulina-enriched diets leads to increased cerebellar glutathione (GSH) levels, decreased malondialdehyde (MDA) levels, decreased proinflammatory cytokines, and improved spatial and motor learning in aged mice (Abdelkhalek et al., 2015). Currently, a small number of studies have examined the effects of Spirulina supplementation in people with type 1 diabetes and its effect on the central nervous system. Therefore, the aim of this study was to investigate the interactive effect of Spirulina supplementation and high-intensity interval training on memory, Pannexin-1 and NLRP-1 protein levels, and hippocampal tissue histology in male rats with type 1 diabetes.

Materials and methods

Animals

The current study was an experimental, laboratory-based study with a test-post-test design involving a control group. To experiment, thirty male Wistar rats, aged 10 weeks and weighing between 180-260 grams, were selected and acquired as research samples from the Research Production Complex of the Pasteur Institute of Iran. Following a one-week adaptation period in the animal house of Qom University of Medical Sciences, where the rats were exposed to a new environment maintained at a temperature of 20-23°C, a 12-hour light-dark cycle (with light starting at 6 am and darkness starting at 6 pm), and provided with free access to water and food, the rats were induced to diabetes through an intraperitoneal injection of STZ (at a dose of 55 mg/kg in citrate buffer with a pH of 4.5) (glucose levels above 250 mg/dL were indicative of diabetes) (Shirwaikar et al., 2006).

After diet induction, the animals were divided into five groups: 1) Group 1 consisted of 6 streptozotocin-induced diabetic mice that were trained 5 days a week between 3:00 PM and 6:00 PM; 2) Group 2 consisted of 6 streptozotocin-induced diabetic mice that received Spirulina supplementation at 500 mg/kg of body weight daily for 8 weeks; 3) Group 3 consisted of 6 streptozotocin-induced diabetic mice that received Spirulina supplementation at 500 mg/kg of body weight daily + HIIT five days a week between; 4) Group 4 consisted of 6- streptozotocin-induced diabetic mice; 5) Group 5 consisted of 6 healthy rat.

HIIT protocol

Prior to initiating the main High-Intensity Interval Training (HIIT) program, a maximum speed test was conducted on a pilot group approximately one week ahead of the main training group to calibrate and control the speed of the main group's rats. The pilot group rats began running at a speed of 5 meters per minute, with the treadmill speed increasing by 5 meters per minute every three minutes until the rats reached exhaustion. Exhaustion was defined as the rats adhering to the end of the treadmill. The speed at which the rats reached exhaustion was recorded as their maximum speed (Alizadeh Palavani et al., 2023).

The HIIT training group underwent a 6-week program, with 4 sessions per week. For the HIIT protocol, the training rats warmed up at the start of each session at a speed of approximately 10–12 meters per minute for 6 minutes. The training program then consisted of 5 bouts of 4-minute high-intensity intervals at 85–95% of maximum speed, interspersed

with 3-minute active recovery periods at 50–60% of maximum speed. At the end of each session, the rats cooled down at a speed of approximately 10–12 meters per minute for 6 minutes. The total running time for the rats on the treadmill per session was 44 minutes. The treadmill incline was maintained at zero degrees and remained unchanged throughout the 6 weeks (Khanjani & Esmaelzadeh Toloee, 2021).

Spirulina was added to the drinking water of rats in the spirulina supplement groups (Groups B and D) at a dose of 500 mg/kg/day, starting 24 hours before the study and continued daily until the end of the eighth week (Eidizadeh et al., 2024). The exercise protocol is outlined in Table 1.

Blood variables

Biochemical indices were measured in the blood collected 48 hours after the rats' last training session. The rats were anesthetized by intraperitoneal injection using a combination of ketamine (70 mg/kg) and xylazine (53 mg/kg). After decapitation using a guillotine under sterile conditions, their hippocampal tissue was isolated and immediately transferred to a -80°C freezer. Pannexin-1 and NLRP-1 proteins were assessed through Western blotting. Initially, upon removal from the -80°C freezer, some tissue was placed on ice. Subsequently, 200 µl of Lysis Buffer was added to each sample, thoroughly homogenized, and left on ice for one hour to ensure complete disruption by the lysis buffer. The samples were then centrifuged at 12,000 rpm for 20 minutes at 4°C. Following this, the supernatant was transferred to a new 1 cc microtube, the samples were placed back in the -80°C freezer, and the precipitated material was discarded (0.5 µl of supernatant was transferred to a 2.5 microtube to determine the protein concentration).

Pannexin -1 and NLRP-1 expression

The expression levels of Pannexin-1 and NLRP-1 proteins were evaluated using Western blot analysis. Hippocampal tissue samples were homogenized in lysis buffer containing 50 mM Tris-HCl (0.3g), 0.1% Triton X-100 (0.02g), 0.25% sodium deoxycholate (0.05g), 150 mM NaCl (0.43g), 0.1% SDS (0.02 g), and 5.84 g EDTA, dissolved in 20 mL distilled water, adjusted to pH 7.4. Homogenization was performed at 16,000 rpm for 20 minutes at 4°C. For every 10 mL of lysis buffer (10X), one protease inhibitor cocktail tablet was added. The protein concentration of the supernatant was determined using the Bradford assay kit. Proteins were separated by electrophoresis on a 10% SDS-PAGE gel, initially at 60 V for 15 minutes, followed by 100 V for 1 hour. Subsequently, proteins were transferred onto a nitrocellulose membrane over 105 minutes. The membrane was incubated with primary monoclonal antibodies against Pannexin-1 (Human/Mouse/Rat Pannexin-1 Antibody, Rat, Human Anti-), NLRP-1 (MAB7097, R&D Systems; NALP1 antibody, ab3683, Abcam, 100 µg), and β-actin (beta Actin antibody, mAbcam 8226) at a dilution of 1:2000 in PBS. The membrane was blocked overnight with 5% skim milk. A secondary antibody (AS09 618 Goat anti-Rat IgG (H&L), HRP-conjugated, Agrisera, Sweden) was applied for 1 hour to bind the primary antibodies. Protein bands were visualized using an ECL kit on a Bio-Rad Gel Doc system. Finally, the protein bands were quantified using ImageJ software.

Statistical analysis

In this study, descriptive and inferential statistical methods were utilized for analysis. Initially, data obtained from laboratory analysis of the variables under study were presented using central tendency indicators such as mean, dispersion, and standard deviation. Following data collection, the Kolmogorov-Smirnov test was employed to confirm normal distribution, and the Levine test was used to assess the homogeneity of variances. Subsequently, a one-way analysis of variance was conducted to test research hypotheses and Bonferroni's post hoc test was utilized to identify differences within groups. Also, the significance level was considered to be 0.05. In addition, SPSS version 26 statistical software was used to perform statistical tests.

Results

Figures 1 and 2 depict the variations in body weight and blood glucose levels of rats across various experimental groups throughout the training period. As illustrated in Figure 1, there was no notable variance in the initial weight index among the study groups ($p>0.05$). However, significant alterations and distinctions in final weight were observed in certain groups ($p<0.05$). Also shown in Figure 2, at the beginning of the training program, blood glucose levels significantly increased 48 hours after induction of diabetes by streptozotocin in mice in the diabetic groups ($p<0.05$). The study results revealed a significant increase in the level of PANX-1 in the diabetic group compared to the healthy group. However, this level significantly decreased in the diabetic exercise, diabetic supplement, and exercise+ diabetic supplement groups compared to the diabetic group.

Tale 1. Exercise protocol.

Exercise component	Warm-up	The main parts of interval training Low intensity interval / High intensity interval		Cool-Down
Practice time	5min	1min	30s	5min
Exercise intensity	50%	30%	90%	20%

Furthermore, there was an elevation in NLRP-1 in the diabetic groups compared to the healthy group, whereas the level of this variable in the diabetic exercise, diabetic supplement, and exercise+diabetic supplement groups exhibited a significant decrease compared to the diabetic group ($p<0.05$).

Discussion

This study aimed to assess the impact of high-intensity interval training and Spirulina supplementation on Pannexin-1 and NLRP-1 protein levels in the hippocampal tissue of male rats with type 1 diabetes. The results revealed that six weeks of high-intensity interval training, either alone or in combination with Spirulina supplementation, significantly decreased PANX-1 levels in the hippocampal tissue of rats with type 1 diabetes when compared to the diabetic group. PANX-1 levels were lower in the exercise + supplement group than in the exercise+diabetic supplement group, indicating a more pronounced effect on PANX-1 protein levels when exercise is combined with supplementation. However, no significant difference was observed between the exercise-only and supplement-only groups.

These findings align with Rami et al, (2020) which explored the impact of six weeks of endurance exercise on hippocampal PANX-1 and NLRP-1 protein levels in male Wistar rats with experimental diabetes. The researchers observed a notable increase in PANX-1 and NLRP-1 protein expression in the diabetic rats (Rami et al., 2020). Additionally, the study indicated a significant reduction in these protein levels, moving them closer to normal levels, following endurance activity and Spirulina supplementation. These results are consistent with the findings of a study by Rezazadeh et al. (2023), who investigated alterations in NMDA glutamate receptor protein and Pannexin-1 channel expression in the gastric antrum tissue of rats with type 2 diabetes undergoing insulin treatment (Rezazadeh Mehrizi et al., 2023).

The latest findings suggest important alterations in the protein levels of NMDA receptors and PANX-1 channels, indicating their potential involvement in the onset of sensorimotor and secretory impairments linked to diabetes. The study reveals a significant reduction in PANX-1 levels in the stomach of type 2 diabetic mice. Evidence shows that endurance training diminishes hippocampal PANX-1 levels in diabetic mice, implying a protective function against neurodegenerative conditions. Additionally, it is suggested that PANX-1 channels play a role in ATP release mediation, participating in inflammation and cell signaling processes. Notably, Spirulina, which is rich in antioxidants and anti-inflammatory agents, could influence PANX-1 activity indirectly by modulating inflammatory responses. Nevertheless, further investigation is warranted in this area.

On the contrary, in relation to the NLRP-1 protein, a noteworthy reduction in this indicator was observed after six weeks of rigorous interval training and Spirulina supplementation compare

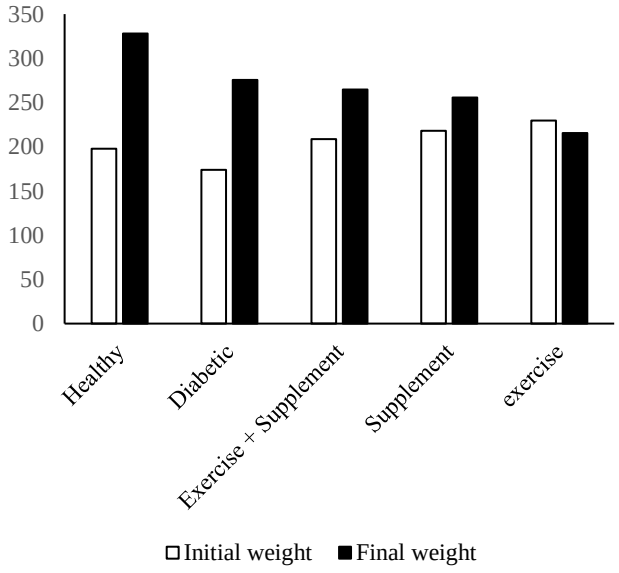

Figure 1. Average weight in different groups.

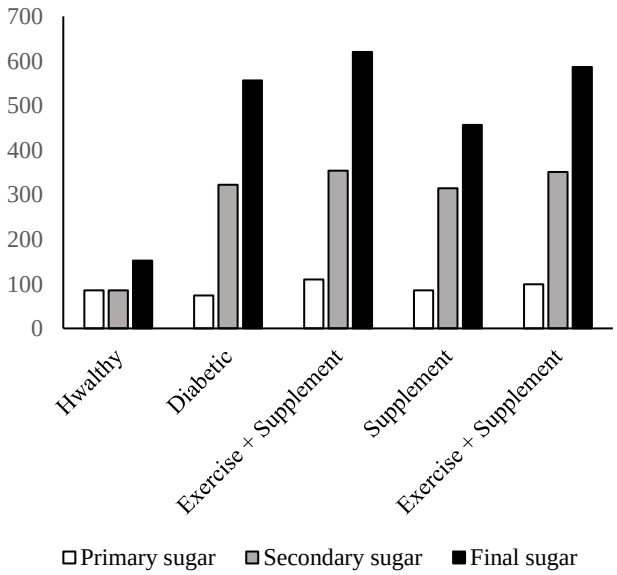

Figure 2. Average blood sugar in different groups

Tale 2. Changes in the levels of variables of different groups after implementing the research protocol.

Index	Exercise	Supplement	Exercise + Supplement	Diabetic	Healthy
PANX-1	*1.45±0.07	#*1.78±0.38	*1.37±0.10	#2.65±0.09	1.13±0.03
NLRP-1	*1.74±0.11	#*1.81±0.14	*1.55±0.09	#2.94±0.12	1.24±0.06

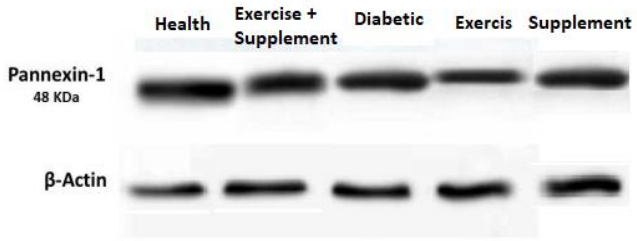

Figure 3. Western blot bands of Pannexin-1(PANX-1) in hippocampal tissues of five groups of diabetic rats.

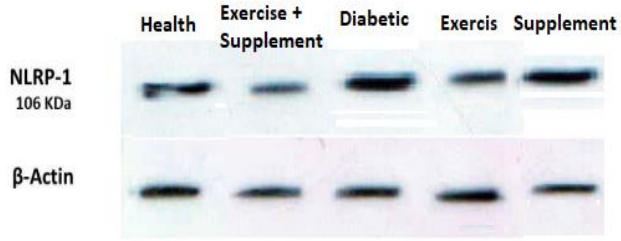

Figure 4. Western blot bands of NLRP 1 in hippocampal tissues of five groups of diabetic rats

to the diabetic group. This decrease was more prominent in the group that combined exercise with diabetic supplementation than in the groups that only engaged in exercise or received the supplement individually. Although both Spirulina supplementation and exercise alone led to a decrease in NLRP-1 levels, these changes did not reach statistical significance. These results align with a study by Ringsis et al. (2015) that explored the impact of endurance and resistance training on inflammasomes. The authors reported that a 10-week regimen of endurance and resistance training resulted in decreased expression of the NLRP-3 inflammasome in obese mice. Furthermore, their research indicated that six weeks of endurance training reduced the levels of hippocampal NLRP-1 protein in diabetic mice compared to the untrained diabetic control group (Ringseis et al., 2015). It has been suggested that exercise primarily influences NLRP-1 activation through its anti-inflammatory effects and modulation of signaling pathways.

Research has shown that regular exercise reduces the levels of inflammatory cytokines such as IL-1β and IL-18, which are products of inflammasome activation, including NLRP-1, which in general, can be said to act as a powerful modulator of inflammasome activity, including NLRP-1, through various biological mechanisms (Rami et al., 2020). Spirulina also prevents activation of the NLRP-3 inflammasome by suppressing the regulation of inflammatory cytokines such as IL-1β and IL-18 in macrophages by oligosaccharide (LPS), suggesting that spirulina may have potential as an anti-inflammatory nutrient by modulating inflammatory activities (Mullenix et al., 2021; Quagliariello et al., 2022). However, further research is needed to clarify the potential modulatory effects of spirulina on the inflammatory pathway of this inflammasome.

Several limitations should be acknowledged when interpreting the findings of this study. First, the absence of cognitive or behavioral assessments, such as memory tests or sensorimotor evaluations, limits the ability to establish a direct link between the observed reductions in PANX-1 and NLRP-1 protein levels and functional outcomes in the hippocampal tissue of diabetic rats. This gap weakens the capacity to infer whether the molecular changes translate into measurable improvements in cognitive or behavioral performance, which is critical for assessing the therapeutic relevance of the interventions. Second, the study was conducted exclusively on male rats, potentially limiting the generalizability of the findings to female rats or other species, including humans, due to possible sex-specific or species-specific differences in protein expression and response to interventions.

Third, the sample size, while sufficient for detecting significant changes in protein levels, may not have provided adequate statistical power to detect subtler differences, particularly in the comparisons between exercise-only and supplement-only groups where no significant differences were observed. Fourth, the study did not account for potential confounding factors, such as variations in baseline inflammatory status, dietary intake beyond Spirulina supplementation, or the severity of diabetes, which could influence PANX-1 and NLRP-1 expression. These limitations underscore the need for future studies incorporating cognitive and behavioral assessments, diverse cohorts, larger sample sizes, and longitudinal designs to better elucidate the functional and clinical implications of high-intensity interval training and Spirulina supplementation in type 1 diabetes.

Conclusion

In conclusion, this study demonstrates that six weeks of HIIT combined with Spirulina supplementation significantly reduced PANX-1 and NLRP-1 protein levels in the hippocampal tissue of male rats with type 1 diabetes, with greater effects observed in the combined exercise and supplementation group compared to exercise or supplementation alone. These findings highlight the potential of HIIT and Spirulina supplementation as adjunctive therapeutic strategies for mitigating neurodegenerative processes in type 1 diabetes by modulating hyperglycemia and inflammation-related protein expression. Patients with type 1 diabetes may benefit from incorporating HIIT and Spirulina supplementation into their management plan under medical supervision to improve neurodegenerative outcomes. Further research is warranted to validate these findings and explore the underlying molecular mechanisms.

What is already known on this subject?

Diabetes mellitus (DM) is widely regarded as one of the most common chronic and expensive metabolic diseases.

What this study adds?

These findings highlight the potential of HIIT and Spirulina supplementation as adjunctive therapeutic strategies for mitigating neurodegenerative processes in type 1 diabetes by modulating hyperglycemia and inflammation-related protein expression.

Organ Cross-Talk Tips:

- Diabetes (a metabolic disorder) directly caused harmful changes in the brain (hippocampus), increasing proteins linked to neuroinflammation (Pannexin-1, NLRP-1).
- High-intensity exercise and oral spirulina supplementation were able to reverse the brain-specific damage. This demonstrates how signaling from peripheral organs (muscle, gut) can positively influence brain biochemistry.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest in the present research.

Ethical approval The study was approved by the Ethics Committee of the University of Qom, Qom, Iran under protocol number IR.QOM.REC.1402.011.

Informed consent Animal study.

Author contributions

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

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