International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2022.856.863

Research Article
Beneficial Effects of Tofacitinib in Long-Standing Diabetes-Induced Cognitive Impairment in Rats through BDNF-TNF-α-Nrf2 Signalling Pathway

[1]Suobing Fan and [2]Rui Song

[1]Department of Endocrinology, Fufeng County People's Hospital, Baoji 722200, China
[2]Department of Critical Care Medicine, Xi'an No. 3 Hospital, Xi'an 710082, China

Abstract

Background and Objective: Tofacitinib is a Janus kinase inhibitor and it improves memory in an experimental model of Alzheimer disease. It is hypothesized that tofacitinib may also prevent diabetes-induced cognitive decline. The study was aimed to investigate the beneficial effects of tofacitinib in diabetes-induced cognitive impairment and explore the signalling pathway involved in its beneficial effects. **Materials and Methods:** Diabetes was induced by a single injection of streptozotocin (60 mg kg^{-1}) and rats were kept for 10 weeks for the development of cognitive dysfunction. The comparison of escape latency time (ELT) of day 1 with ELT of day 4 on the Morris Water Maze test was made to measure learning, while the time spent in the target quadrant (TSTQ) on the 5th day assessed memory. Tofacitinib (15 and 30 mg kg^{-1}) was administered for the last fourteen days of the experimental protocol. The levels of Brain-Derived Neurotrophic Factor (BDNF), Nrf2, reduced glutathione and TNF-α were measured in the brain. The role of BDNF in tofacitinib-mediated effects was explored by co-administering ANA-12, a TrkB antagonist, along with tofacitinib. **Results:** Tofacitinib significantly attenuated the diabetes-induced increase in day 4 ELT and decrease in day 5 TSTQ suggesting the improvement in learning and memory. It also increased BDNF, reduced glutathione, Nrf2 and decreased TNF-α. Co-administration of ANA-12 abolished the effects of tofacitinib on memory and biochemical parameters suggesting that the effects of tofacitinib are mediated through BDNF. **Conclusion:** Tofacitinib may be effective in diabetes-induced cognitive dysfunction, which may involve the BDNF-TNF-α-Nrf2 signalling pathway.

Key words: Learning, memory, inflammation, oxidative stress, diabetes, tofacitinib, brain homogenates, BDNF

Citation: Fan S. and R. Song, 2022. Beneficial effects of tofacitinib in long-standing diabetes-induced cognitive impairment in rats through BDNF-TNF-α-Nrf2 signalling pathway. Int. J. Pharmacol., 18: 856-863.

Corresponding Author: Rui Song, Department of Critical Care Medicine, Xi'an No. 3 Hospital, Xi'an 710082, China Tel: + 86 18082613742

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus is becoming a very common lifestyle disease, which is characterized by impairment in glucose metabolism. Apart from the short term symptoms of diabetes, long-standing diabetes is associated with several complications including diabetic neuropathy, nephropathy, retinopathy and cognitive changes[1,2]. The decline in cognitive functions is increasingly documented in diabetic patients and possesses a significant burden on the healthcare system[3,4]. There is a need to explore new pharmacological entities to abrogate or prevent cognitive impairment in long-standing diabetes.

Janus Kinase (JAK) is an important intracellular signalling pathway and its activation is essential to elicit important physiological functions in the body. Tofacitinib is a selective JAK inhibitor and it produces beneficial effects in different diseases including liver injury, asthma, vascular injury, atherosclerosis, psoriasis and other inflammatory diseases[5-7]. Its beneficial effects in attenuating ischemia-reperfusion-induced cerebral injury have been reported[8]. It has been shown to ameliorate memory dysfunction in an experimental model of Alzheimer disease in rats[9]. Based on these reports showing the neuroprotective properties of tofacitinib, it was hypothesized that tofacitinib may also be useful in preventing cognitive decline in long-standing diabetes in rats.

Brain-Derived Neurotrophic Factor (BDNF) is an important member of the neurotrophin family and it has been shown to produce beneficial effects in memory disorders of diverse aetiology[10]. There have been studies showing the decline in the levels of BDNF in diabetes[11] and this decline may contribute to cognitive impairment[12]. Neuroinflammation and oxidative stress are also important factors contributing to memory decline in diabetes-induced memory decline[13,14].

The present study was designed to explore the role of tofacitinib in long-standing diabetes-induced cognitive impairment in rats along with the possible involvement of BDNF, neuroinflammation and oxidative stress.

MATERIALS AND METHODS

Study area: All experiments were performed in Fufeng County People's Hospital, China from January to June, 2021.

Methodology: Sixty Wistar Albino rats (250-280 g) were used in this study. The rats were kept in Departmental's Animal House and animals were provided standard laboratory conditions. The experimental protocol was approved by the Ethics Committee of Fufeng County People's Hospital Ethical Committee, Approval Number: ffxrm0323.

Induction of diabetes mellitus: The injection of streptozotocin (60 mg kg^{-1}) was made in rats to induce diabetes mellitus[15,16]. Thereafter, these rats were kept for 10 weeks to develop learning and memory deficits. The levels of glucose in the plasma were assessed in fasting condition, before STZ injection and at the end of the 10th week. The glucose levels were measure using the glucose oxidase method.

Assessment of learning and memory: The learning and memory were assessed during the last (10th) week using 5 days trials using the Morris Water Maze test[17]. In the first 4 days, the escape latency time (ELT) was assessed to compare the difference in day 1-4 ELT. The decrease in ELT on day 4 described that the rats were able to learn. The trial on the 5th day was used to assess memory, which was quantified in terms of time spent in the target quadrant. The increase in time spent in the target quadrant described the acquisition of memory.

Assessment of biochemical parameters in the brain homogenate: The rats were sacrificed to isolate the brain, which was homogenized in the phosphate buffer saline (PBS, pH: 7.4). Thereafter, it was centrifuged at 6000 g for 20 min at 4°C to obtain the clear supernatant solution. The supernatant was used to quantify the levels of BDNF, TNF-α and reduced glutathione. The levels of BDNF and TNF-α were estimated using commercially available ELISA kits, while the levels of reduced glutathione were estimated using commercially available colourimetric kits. The levels of protein were quantified using the Folin Lowery method. To estimate the nuclear : cytoplasmic ratios of Nrf2, the nuclear and cytoplasmic fractions were separated using an extraction kit. Thereafter, the levels of Nrf2 were assessed in the nuclear and cytoplasmic fractions using commercially available ELISA kits.

Design of experimental study: Six experimental groups were employed and each group comprised of 10 rats.

- **Group I:** Non-diabetic animals were kept for 10 weeks. In the last 5 days of the 10th week, rats were subjected to five consecutive day trials on the Morris Water Maze test to assess learning and memory. Afterwards, animals were sacrificed to remove the brain, which was homogenized to measure biochemical parameters
- **Group II:** The STZ was injected into rats and were kept for 10 weeks. The rest of the protocol was the same as in group I

- **Groups III and IV:** Tofacitinib (15 and 30 mg kg^{-1}) was administered in diabetic animals for the last 14 days of protocol i.e., from week 8th-10th in groups III and IV, respectively
- **Groups V and VI:** The ANA-12 (0.25 and 0.5 mg kg^{-1}) was co-administered was tofacitinib (30 mg kg^{-1}) in diabetic animals for the last 14 days of protocol i.e., from week 8th-10th in groups V and VI, respectively

Statistical analysis: The Graphpad Prism version 8 was employed for statistical analysis. The data of the present study were represented as Mean±S.D. The two way ANOVA was used to analyse the data of ELT and glucose levels. The results of other parameters were analysed using one-way ANOVA. The *post hoc* analysis was done using Tukey's test for multiple comparisons. $p<0.05$ was considered to be statistically significant.

RESULTS

Effects of different pharmacological agents on the plasma glucose levels: There was no significant increase in the basal glucose levels in all experimental animals. However, there was a significant rise in the plasma glucose levels in STZ-injected rats in diabetic rats in comparison to non-diabetic rats, which was noted on the 10th week of STZ-injection. Treatment of STZ-injected rats with tofacitinib (15 and 30 mg kg^{-1}) or ANA-12 (0.25 and 0.50 mg kg^{-1}) did not alter the plasma glucose levels, assessed at the end of the 10th week (Fig. 1).

Effects of different pharmacological agents on learning and memory: In nondiabetic rats, there was a marked decline in day 4 ELT in comparison to day 1 ELT and this decrease in ELT on the fourth day of trial suggests the learning ability of rats. In STZ-injected rats, a decrease in day 4 ELT was not marked as compared to non-diabetic rats. The failure to markedly reduce the day 4 ELT in STZ-injected rats suggests the inability of rats to learn. Treatment with tofacitinib (15 and 30 mg kg^{-1}) in STZ-injected rats significantly decreased the day 4 ELT suggesting the restoration of the learning ability of rats. However, co-administration of ANA-12 (0.25 and 0.5 mg kg^{-1}) abolished the effects of tofacitinib on day 4 ELT suggesting that ANA-12 abolished the learning restoring effects of tofacitinib (Table 1).

Similar effects were produced on the day 5 trial in which the trials were done to study the effects on retrieval of information i.e., memory. The day 5 TSTQ was significantly reduced in STZ-injected rats in comparison to non-diabetic rats, which suggests the decrease in memory in STZ-injected rats. Treatment with tofacitinib (15 and 30 mg kg^{-1}) significantly increased the day 5 TSTQ in STZ-injected rats suggesting the improvement in memory in diabetic rats. However, the memory improving actions of tofacitinib in STZ-injected rats were significantly abolished on co-administration of ANA-12 (0.25 and 0.50 mg kg^{-1}) with tofacitinib (Fig. 2).

Effects of different interventions on biochemical levels: In STZ-injected rats, there was a significant decrease in the brain BDNF levels in comparison to non-diabetic rats, which were quantified in the brain homogenates. However, treatment with tofacitinib (15 and 30 mg kg^{-1}) significantly restored the brain BDNF in STZ-injected rats suggesting the possible association of tofacitinib with BDNF. Co-administration of BDNF receptor antagonist, ANA-12 (0.25 and 0.5 mg kg^{-1}) did not modulate the tofacitinib-induced increase in BDNF levels in STZ-injected rats (Fig. 3).

In STZ-injected rats, there was a significant increase in the brain TNF-α levels (Fig. 4), a decrease in reduced glutathione levels (Fig. 5) and a reduction in nuclear:cytoplasmic ratio of Nrf2 (Fig. 6). It suggests that long diabetes led to an increase in neuroinflammation (increase in TNF-α) and decrease in antioxidative activity (decrease in reduced glutathione and nuclear : cytoplasmic ratio of Nrf2). However, treatment with tofacitinib (15 and 30 mg kg^{-1}) significantly ameliorated

Table 1: Effect of tofacitinib and ANA-12 on escape latency time (ELT) in Morris Water Maze test in STZ-injected rats

Groups	Day 1 ELT (s)	Day 4 ELT (s)
Non-diabetic	84.5±3.1	31.4±2.2[a]
Diabetic	99.2±4.1	78.9±2.7[b]
Tofacitinib (15 mg kg^{-1}) in diabetic	87.2±2.9	52.1±1.9[c]
Tofacitinib (3 mg kg^{-1}) in diabetic	86.1±2.2	41.5±2.7[c]
ANA-12 (0.25 mg kg^{-1}) and tofacitinib (30 mg kg^{-1}) in diabetic	89.2±2.4	52.3±2.9[d]
ANA-12 (0.50 mg kg^{-1}) and tofacitinib (30 mg kg^{-1}) in diabetic	93.2±2.6	70.9±3.9[d]

[a]$p<0.05$ vs. day 1 ELT of non-diabetic, [b]$p<0.05$ vs. day 4 ELT of non-diabetic, [c]$p<0.05$ vs. day 4 ELT of diabetic, [d]$p<0.05$ vs. day 4 ELT of diabetic and [e]$p<0.05$ vs. day 4 ELT of tofacitinib (30 mg kg^{-1}) in diabetic

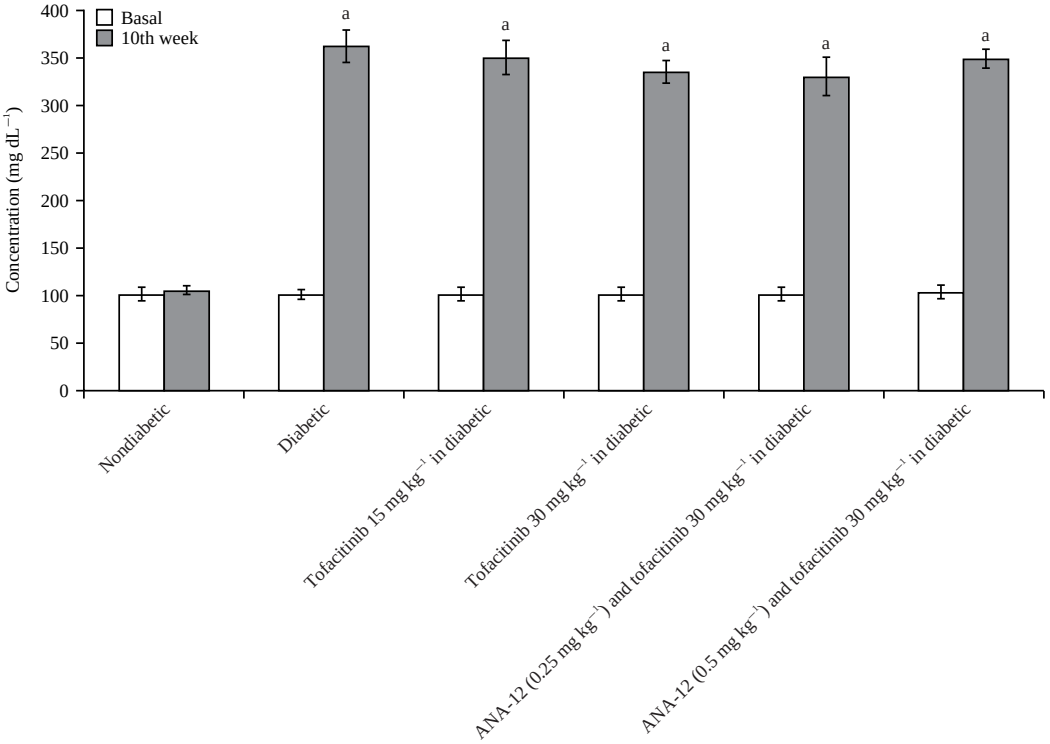

Fig. 1: Effect of tofacitinib and ANA-12 on the plasma glucose levels, measured at the start of the experiment (basal) and the end of the experiment (10th week)

Values are expressed as Mean±SD, the values on Y-axis are expressed on mg dL^{-1} and $^{a}p<0.05$ vs. corresponding groups at basal

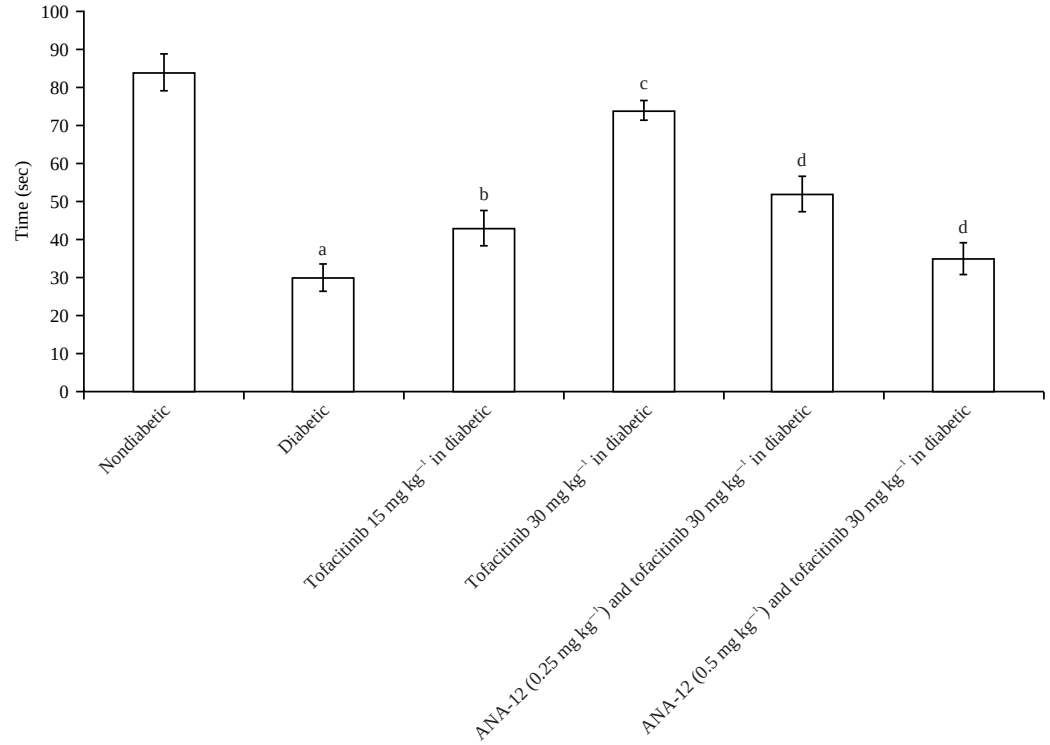

Fig. 2: Effect of tofacitinib and ANA-12 on the time spent in the target quadrant (TSTQ), measured on the 5th day in the Morris Water Maze test

Values are expressed as Mean±SD, $^{a}p<0.05$ vs. non-diabetic and $^{b}p<0.05$ vs. diabetic

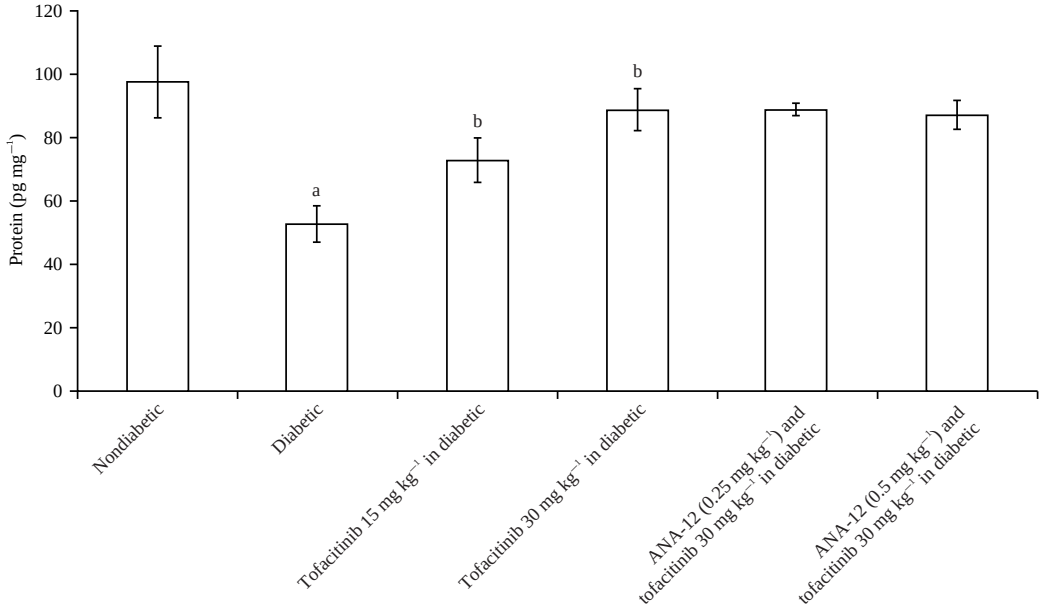

Fig. 3: Effect of tofacitinib and ANA-12 on the BDNF levels in the brain homogenate in STZ-injected rats
Values are expressed as Mean±SD, [a]p<0.05 vs. non-diabetic and [b]p<0.05 vs. diabetic

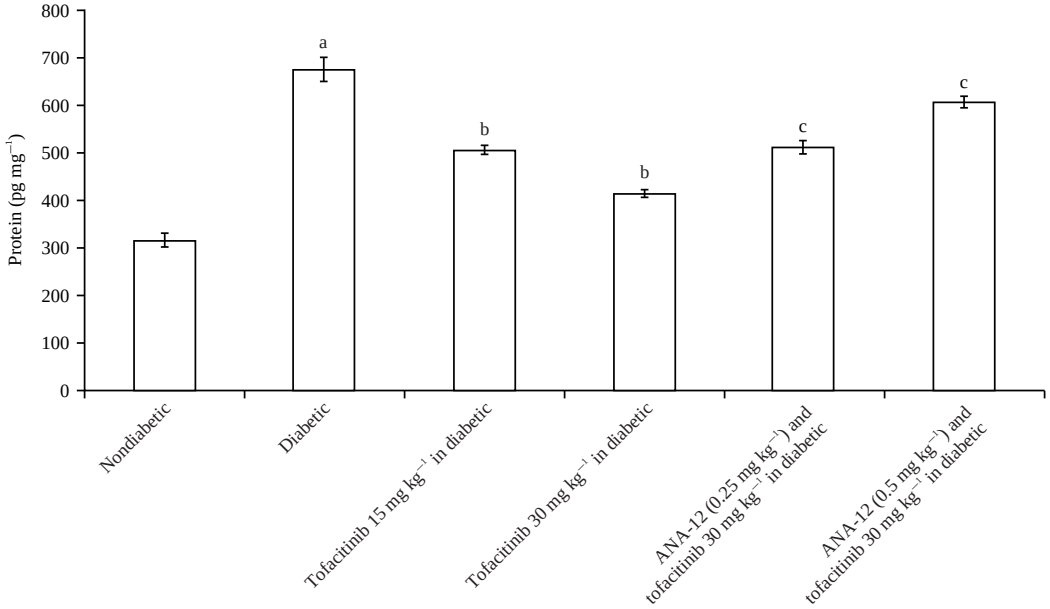

Fig. 4: Effect of tofacitinib and ANA-12 on the TNF-α levels in the brain homogenate in STZ-injected rats
Values are expressed as Mean±SD, [a]p<0.05 vs. non-diabetic, [b]p<0.05 vs. diabetic and [c]p<0.05 vs. tofacitinib (30 mg kg^{-1}) in diabetic

the deleterious effects of long-standing diabetes on neuroinflammation and anti-oxidant activities. Indeed, in tofacitinib-treated rats, there was a significant decrease in TNF-α levels (Fig. 4), an increase in the reduced glutathione levels (Fig. 5) along with an increase in the nuclear: cytoplasmic ratio of Nrf2 (Fig. 6). However, these beneficial effects of tofacitinib were significantly abolished on co-administration of ANA-12 (0.25 and 0.50 mg). In ANA-12 co-administered rats, there was a significant rise in TNF-α levels (Fig. 4), a decrease in the reduced glutathione levels (Fig. 5) along with a decrease in the nuclear: cytoplasmic ratio of Nrf2 (Fig. 6).

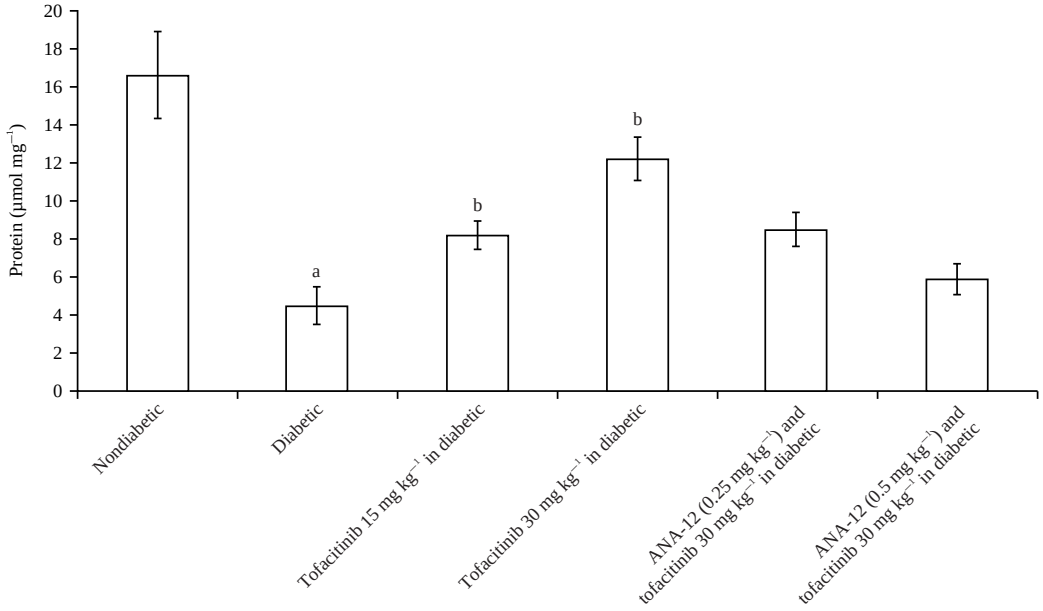

Fig. 5: Effect of tofacitinib and ANA-12 on the reduced glutathione levels in the brain homogenate in STZ-injected rats
Values are expressed as Mean±SD, [a]p<0.05 vs. non-diabetic, [b]p<0.05 vs. diabetic and [c]p<0.05 vs. tofacitinib (30 mg kg^{-1}) in diabetic

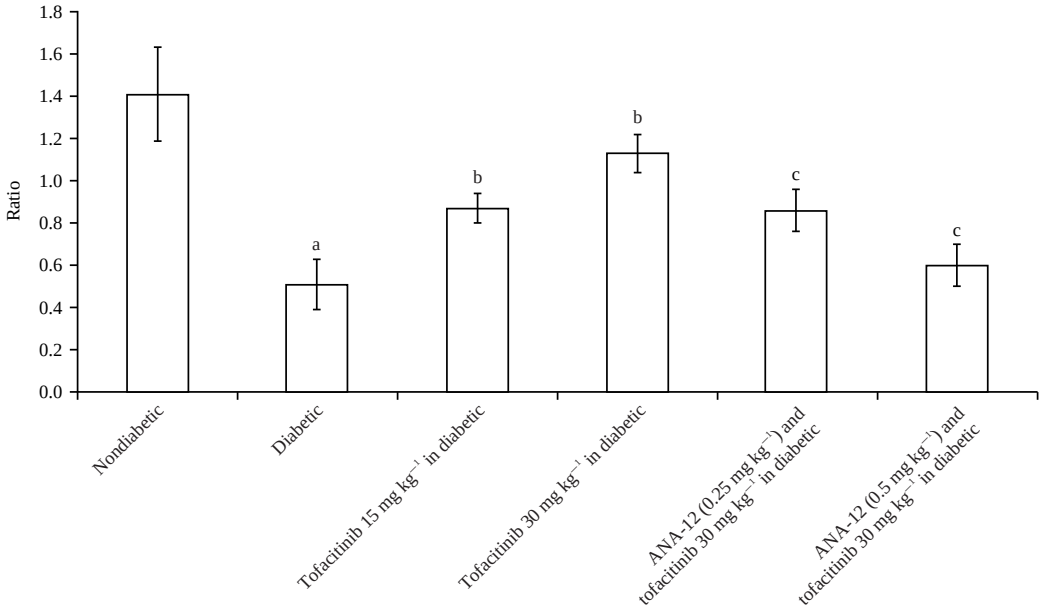

Fig. 6: Effect of tofacitinib and ANA-12 on the nuclear : cytoplasmic Nrf2 ratio in the brain homogenate in STZ-injected rats
Values are expressed as Mean±SD, [a]p<0.05 vs. non-diabetic, [b]p<0.05 vs. diabetic, [c]p<0.05 vs. tofacitinib (30 mg kg^{-1}) in diabetic

DISCUSSION

In this study, STZ injection led to the induction of diabetes mellitus and there was a significant increase in plasma glucose levels. Moreover, in long-standing diabetic rats, there was significant impairment in cognitive functions, which were assessed in the form of impairment in learning (no significant decrease in day 4 ELT) and memory (significant decrease in day 5 TSTQ). The present study results showing the impairment in cognitive functions are following the previous studies showing the decrease in learning and memory in STZ-injected rats[18,19].

In this current investigation, treatment of STZ-injected rats with tofacitinib (15 and 30 mg kg^{-1}) significantly improved the cognitive functions as assessed by a significant decrease in day 4 ELT (increase in learning) and increase in day 5 TSTQ (increase in memory). Tofacitinib is a JAK inhibitor and it has been shown to attenuate neurological deficits in ischemia-reperfusion injury in rats[8]. Moreover, it has also been reported to ameliorate beta-amyloid-induced memory impairment of Alzheimer's type in rats[9]. However, it is the first report suggesting the beneficial role of tofacitinib in long-diabetes-induced impairment in learning and memory in rats.

In this current investigation, along with the impairment in learning and memory, there were significant alterations in biochemical parameters in the brains of long-standing diabetic rats. There was a significant decrease in the levels of BDNF levels in STZ-injected rats suggesting that a decrease in BDNF may contribute to the impairment of memory. The BDNF is a neurotrophic factor and its beneficial role in learning and memory has been well documented[20]. It has also been shown that long-standing diabetes reduces the expression of BDNF in the brain[21]. However, treatment with tofacitinib (15 and 30 mg kg^{-1}) significantly restored the expression of BDNF in the brains of diabetic rats suggesting that the beneficial effects of tofacitinib in diabetes-induced impairment in cognitive functions may be secondary to an increase in BDNF levels. This contention was supported by the results of the present study showing that the blocker of BDNF i.e., ANA-12 significantly abolished the beneficial effects of tofacitinib on learning and memory. To the best of our knowledge, it is the first report suggesting that tofacitinib has the potential to increase the expression of BDNF to produce beneficial effects. However, further studies shall be done to explore the mechanisms that may be involved in the tofacitinib-mediated increase in the expression of BDNF.

In this investigation, more biochemical changes were noted in the brains of long-standing diabetic rats including an increase in neuroinflammation (increase in TNF-α) and a decrease in antioxidative activity (decrease in reduced glutathione and nuclear : cytoplasmic ratio of Nrf2). Treatment with tofacitinib (15 and 30 mg kg^{-1}) significantly abolished diabetes-induced neuroinflammatory and oxidative changes in the brain. There have been studies on the deleterious effects of neuroinflammation[22] and oxidative changes[23] on cognitive functions in diabetic rats. Accordingly, it may be hypothesized that a decrease in neuroinflammation and an increase in anti-oxidative activities of tofacitinib may contribute to restoring the cognitive functions in diabetic rats. This contention was supported by the results of this study showing that ANA-12 abolished the effects of tofacitinib on neuroinflammation and oxidative parameters. Since the pharmacological blocker of BDNF (ANA-12) abolished the anti-inflammatory and anti-oxidative actions of tofacitinib, therefore, it is possible to suggest that tofacitinib may have increased the expression of BDNF, which may have contributed to decreasing neuroinflammation and increasing anti-oxidative activities. The previous studies showing the decrease in neuroinflammation[24] and increase in anti-oxidative actions[25] in the presence of BDNF supports this hypothesis. Based on these, it may be proposed that tofacitinib may restore the cognitive functions in long-standing diabetic rats possibly through an increase in BDNF expression, which may contribute to decreasing neuroinflammation and increase in anti-oxidative activities.

CONCLUSION

Long-standing diabetes induces cognitive impairment in rats, which is manifested in the form of learning and memory deficits. Tofacitinib, a JAK inhibitor, has the potential to attenuate long-standing diabetes-induced learning and memory impairment. Its potential usefulness in diabetes-induced cognitive dysfunction may be attributed to the activation of the BDNF-TNF-α-Nrf2 signalling pathway.

SIGNIFICANCE STATEMENT

The present study discovers the potential of JAK inhibitor, tofacitinib, in mitigating the learning and memory deficits in long-standing diabetes-induced cognitive dysfunction. Many researchers were not able to explore its effectiveness in cognitive dysfunction. Thus, a new potential therapy may be employed to prevent memory decline in diabetic patients.

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