INTRODUCTION

Mounting evidence indicates that systemic inflammation has a significant role in the pathogenesis of brain diseases such as depression and anxiety (Miller & Raison, 2015) and memory failure (Sankowski et al., 2015; Skelly et al., 2019). In chronic inflammation, memory impairment may be present even after cessation of the initial stimulus of systemic inflammation (Salmani et al., 2021). Systemic bacterial endotoxin lipopolysaccharide (LPS) injection as a well-characterized model of inflammation is commonly used to investigate the effects of peripheral inflammation on brain function (Brown, 2019). It has been reported that long-term treatment of mice with LPS causes cognitive impairment, which persists beyond the acute effects of LPS injection (Lee et al., 2015; Salmani et al., 2021). In this study, repeated injections of LPS were used as a chronic model of systemic inflammation.
In the mammalian brain, long-term potentiation (LTP) is the main accepted cellular mechanism underlying learning and memory (Bliss & Collingridge, 1993). Systemic inflammation has been reported to suppress LTP in the hippocampal CA1 area of experimental animals (Anaéigoudari et al., 2016; Chapman et al., 2010; Liu et al., 2012). While inflammatory cytokines in physiological levels have a pivotal role in healthy brain function, including learning and memory and LTP (Prieto & Cotman, 2017), in pathological conditions, inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β can directly inhibit LTP in the hippocampus (Cunningham et al., 1996; Murray & Lynch, 1998; Prieto et al., 2019; Vereker et al., 2016; Chapman et al., 2010; Liu et al., 2012). While the protective effects of ARBs in inflammation-induced cognitive impairment have been reported in previous studies (Salmani et al., 2020; Singh et al., 2017; Sun et al., 2015). In addition, in a mouse model of Alzheimer’s disease, treatment with losartan has been reported to improve cerebrovascular function (Papadopoulos et al., 2017). While the protective effects of ARBs in inflammation-induced memory impairment have been frequently reported, their effect on inflammation-induced LTP suppression has been rarely investigated. In the present study, the protective effect of losartan on the inflammation-induced LTP suppression resulting from repeated LPS injection was investigated.

## MATERIALS AND METHODS

### 2.1 Reagents

Lipopolysaccharide (E. coli; serotype O55:B5) was purchased from Sigma Aldrich Chemical Co. Losartan (Batch NO: LOS(04)-16, Alborz Bulk pharmaceutical manufacturer) was a kind gift from PourSina Pharmaceutical Company.

### 2.2 Animals

The experiment was performed on 8–10 weeks old male Wistar rats (weighing 220–250 g) obtained from the animal house of Mashhad University of Medical Sciences. A week before starting the experiment, the animals were brought to the housing room to acclimatize to the new environment, and they were handled two min each day. The housing room had standard temperature conditions (23 ± 2°C) and light/dark cycle (12:12 h), and the animals had free access to rodent chow and water. The experimental procedure was approved by the Ethical Committee on Animal Research of Mashhad University of Medical Sciences (IR.MUMS. fm.REC.1394.562). All efforts were made to minimize the pain or discomfort of the animals.

### 2.3 Experimental design

An illustration of the experimental design is shown in Figure 1. Briefly, 22 rats were divided into three groups, including control (n = 8), LPS (n = 7), and LPS-Losartan (n = 7). Rats received intraperitoneal (ip) injections of LPS (250 μg kg⁻¹ day⁻¹) or endotoxin-free saline for seven consecutive days. LPS was dissolved in sterile saline at a concentration of 0.25 mg/ml and injected into the rats based on their weights. The dose of LPS and duration of injection

![FIGURE 1 Experimental design. Rats received intraperitoneal injections of losartan (3 mg/kg) from day 3 until day 6 (10 days). LPS injections (250 μg/kg/day) were started from day 0 and continued until day 6 (7 days). Three days after the last LPS injection (day 9), rats were anesthetized and used for the electrophysiological experiment. LPS, lipopolysaccharide](image-url)
were selected based on previous reports indicating that in this paradigm, LPS induces mild and chronic systemic inflammation (Lee et al., 2012; Salmani et al., 2021). Chronic treatment with losartan (ip, 3 mg kg\(^{-1}\) day\(^{-1}\)) or its vehicle (sterile saline, 1 ml/kg) was started 3 days before the LPS injection and continued during the LPS injections. On each day, losartan was injected 30 min before the LPS injection. Losartan was dissolved in pathogen-free saline and stored at 4°C. The dose and duration of treatment with losartan were selected based on previous studies (Koh et al., 2013; Salmani et al., 2018). At 72 h after the last LPS injection, rats were anesthetized and used for the electrophysiological experiment. This time point (72 h after the LPS injection) was chosen since the acute effects of LPS have been shown to diminish at this time point (Godbout et al., 2008; Muccigrosso et al., 2016),

2.4 | Electrophysiology

2.4.1 | Surgery

Monosynaptic field excitatory postsynaptic potentials (fEPSP) evoked by Schaffer collateral pathway stimulation were recorded in the CA1 area of the hippocampus. Schaffer collateral pathway-CA1 synapses were used to study LTP since previous studies have reported that LPS injection suppresses the LTP induction in this area (Abareshi et al., 2016; Anaeigoudari et al., 2016; Strehl et al., 2014). Rats were anesthetized with urethane injection (ip; 1.6 g/kg), and their head was fixed in a stereotaxic frame. Then the animal skull was exposed, and CA1 and Schaffer collateral coordinates were determined on the skull according to the atlas of Paxinos and Watson (2007). The recording electrode was lowered from the left side of the skull and positioned in the right CA1 stratum radiatum (coordinates; AP = −3.4 mm, ML = 1.5, DV = 4.4–5.1, at an angle of 52.5°) and a bipolar stimulating electrode was positioned in the ipsilateral Schaffer collateral pathway (coordinates; AP = −4.2 mm, ML = −3.8 mm, DV = 2.7–3.8 mm; Figure 2; Sadeghi et al., 2017). The electrodes were made of 125 μm Teflon-coated stainless steel wire (A-M systems). A test recording procedure was conducted to determine the final position of the electrodes in which a reliable fEPSP with typical characteristics in the stratum radiatum layer of the hippocampal CA1 (Manahan-Vaughan, 2018; Sweatt, 2008) was recorded.

2.4.2 | Stimulating and recording procedure

A two-channel Electromodule amplifier (R12, ScienceBeam) was used to record the extracellular fEPSPs. The signals from the recording electrode were amplified (1000x), low-pass filtered (1 Hz–3 kHz), digitized, and analyzed using the Electromodule R12 amplifier and eProbe software (Science Beam). Input–output (I/O) curves were constructed using stepwise increases of presynaptic fiber stimulation until the fEPSP amplitude was saturated. Then, for each animal, the stimulation strength was adjusted to give an fEPSP amplitude of 50% of the maximum response and kept constant at this level throughout the experiment. Before inducing LTP, stable baseline synaptic responses were recorded for 30 min, and then a high-frequency stimulus (HFS; 100 pulses delivered at 100 Hz) was used to induce LTP. Synaptic responses were
recorded 90 min following LTP induction (Anaeigoudari et al., 2016; Atabaki et al., 2020).

2.4.3 | Data analysis

The eProbe software (Science Beam Institute) was used for the off-line analysis of fEPSP slope and amplitude. LTP was assessed as the increase in the amplitude and slope of the fEPSP (i.e., the 10%–90% rise time of the slope automatically calculated by the software) over the 90 min post-tetanus period. Data were averaged over 5-min intervals and expressed as the percentage change from baseline (mean ± SEM). Statistical analyses of data were done using the SPSS 26.0 software (SPSS Inc.). Paired sample t-test or mixed-design ANOVA (with treatment as between-subjects factors) followed by Bonferroni post hoc test were used for statistical analyses of data. p-values < 0.05 were considered as a significant difference between the mean values.

3 | RESULTS

To examine the influence of losartan treatment on synaptic transmission in the LPS-treated rats, fEPSP was recorded at CA1 str. radiatum in response to stimulation of the Schaffer-collaterals pathway (Figure 2). To measure LTP, the averaged fEPSP amplitude and fEPSP slope during the final 15 min of pre-tetanus baseline recording was compared with 20–40 min post-tetanus recording. As expected, in the control group, the comparison of fEPSP amplitude (150 ± 9.95, paired sample t-test, $t(7) = -4.89, p < 0.01$) and slope (169.64 ± 13.1, paired sample t-test, $t(7) = -4.97, p < 0.01$) showed that LTP was successfully induced (Figure 3b). Interestingly, in the LPS group, LTP was not induced, as no significant differences were observed in fEPSP amplitude (122.42 ± 12.92, paired sample t-test, $t(6) = -1.71, p = 0.138$) and slope (114.7 ± 10.9, paired sample t-test, $t(6) = -1.47, p = 0.190$) between the pre-tetanus and post-tetanus recording. Pretreatment with losartan restored the post-tetanus fEPSP amplitude (141.75 ± 15.7, paired sample t-test, $t(6) = -2.61$, $p < 0.05$).
p < 0.05) and slope (175.7 ± 15.52, paired sample t-test, \( t_{(65)} = -4.679, p < 0.01 \)) to the control level (Figure 3a,b).

To investigate the effect of losartan pretreatment on the magnitude of LTP in the LPS-treated rats, fEPSP amplitude and slope were compared between the groups (Figure 3c,d). Analyzing data with mixed-design ANOVA revealed significant main effect of time \( (F_{(23,437)} = 25.45, p < 0.001) \), treatment \( (F_{(2,19)} = 7.29, p < 0.01) \), and time × treatment interaction \( (F_{(46,437)} = 3.4, p < 0.001) \) on fEPSP slope. There was a significant main effect of time \( (F_{(23,437)} = 18.84, p < 0.001) \) on fEPSP amplitude, but no significant effects of treatment \( (F_{(2,19)} = 0.831, p = 0.451) \) or time × treatment interaction \( (F_{(46,437)} = 0.951, p = 0.565) \). Further analysis of slope data with Bonferroni post hoc test showed that in the LPS group, fEPSP slope significantly decreased compared to the control rats \( (p < 0.05) \) and pretreatment with losartan restored the fEPSP slope to the control level \( (p < 0.01; \) Figure 3c,d).

4 | DISCUSSION

It has been well known that inflammation impairs synaptic plasticity in various synapses of the CNS. Previous reports indicated that systemic inflammation induces a mirror inflammation in the brain and subsequently impairs multiple aspects of brain function, including hippocampal synaptic plasticity (Anaeigoudari et al., 2016; Di Filippo et al., 2013; Strehl et al., 2014). Although we did not evaluate cognitive function in this study, previous studies reported that repeated LPS injection induces spatial memory, recognition memory, and fear memory impairment (Lee et al., 2012; Salmani et al., 2021). In this study, we measured the protective effects of losartan on hippocampal LTP impairment induced by repeated LPS injection. Our findings indicated that LTP impairment in the Schaffer collateral-CA1 synapses persisted beyond the acute effects of LPS injection. Consistent with these findings, it has been previously reported that tetanic stimulation of the Schaffer collateral pathway was not able to induce LTP in the Schaffer collateral-CA1 synapses in LPS-treated animals (Anaeigoudari et al., 2016; Di Filippo et al., 2013). On the other hand, it has been reported that multiple systemic LPS injections (twice a week for 1 month) impaired hippocampal LTP in Complete Freund’s Adjuvant-injected mice but not in normal mice (Maggio et al., 2013).

Our previous studies showed that IL-1β and TNF-α levels in the brain tissue of repeated LPS-injected mice were significantly higher than the control animals even 2 weeks after LPS withdrawal (Salmani et al., 2020, 2021). In physiological concentrations, IL-1β enhances hippocampal LTP and memory function, whereas, in pathological concentrations, it suppresses LTP and induces memory impairment (Goshen et al., 2007; Ross et al., 2003). Inflammatory cytokines have been reported to suppress LTP in hippocampal slices directly. Most importantly, two cytokines, including IL-1β and TNF-α, have been reported to impair LTP and cognitive function in experimental animals (Cunningham et al., 1996; Murray & Lynch, 1998; Vereker et al., 2000). However, cytokines start complex downstream events by inducing microglial activation, producing multiple inflammatory mediators, and altering regulatory proteins such as neurotrophins. For instance, it has been reported that while IL-1β and TNF-α directly suppress hippocampal LTP at synapses, IL-18 impairs LTP by indirect mechanisms (Prieto et al., 2019). Indeed, studies suggested that IL-1β is the final effector for most cytokines modulating LTP and memory (Prieto & Cotman, 2017). In this study, we did not evaluate the inflammatory cytokines in the brain tissue; however, based on previous reports, elevated pro-inflammatory cytokines may be the reason for LTP suppression.

In our previous studies, we have shown that pretreatment with losartan prevented brain inflammation and cognitive impairment in LPS-treated mice (Salmani et al., 2020) and rats (Salmani et al., 2018). In the present study, we further investigated the protective effect of losartan on hippocampal LTP following repeated systemic inflammation. Our results showed that pretreatment with losartan reversed hippocampal LTP impairment induced by systemic inflammation. There is considerable evidence regarding the effects of AT1R activation in suppressing LTP (Denny et al., 1991; von Bohlen und Halbach and Albrecht, 1998; Wright & Harding, 2004; Wright et al., 2002); however, the protective actions of ARBs on synaptic plasticity in pathological conditions like inflammation have been rarely investigated (Takeda et al., 2009). Strong evidence indicates that Ang II suppresses LTP, while Ang IV facilitates LTP (Wright et al., 2002). In addition, Ang II, through AT1R activation, contributes to the peripheral immune system and CNS communication. Previous studies have shown that AT1R blockade following systemic inflammation ameliorates brain inflammation (Benicky et al., 2011; Saavedra, 2012). Our previous study also showed that losartan prevented brain inflammation by reducing the inflammatory cytokines IL-1β and TNF-α in hippocampal tissues (Salmani et al., 2020). Both of these cytokines are highly expressed in a diseased brain, and both of them have been reported to directly suppress hippocampal LTP (Prieto et al., 2019). Therefore, losartan maybe by reducing the brain inflammation, was able to improve LTP. Moreover, it has been suggested that the blocking of AT1R leads to the conversion of excess endogenous Ang II to Ang IV in the brain, which in turn activates AT4R (Wright & Harding, 2013). It has been shown that Ang IV facilitates memory and LTP (Wright et al., 2002). However, more investigations are needed to be done to find the exact mechanism(s).

As a limitation of the study, we did not measure inflammatory mediators in the brain or periphery to attribute the beneficial effects of losartan to its anti-inflammatory effects. The second limitation of the study was that the control group treated with losartan was not included in the experiment to examine the impact of losartan on LTP in normal conditions.
5 | CONCLUSION

In conclusion, the findings of the present study demonstrate that repeated LPS injections suppress hippocampal LTP, and AT1R blockade by losartan can prevent LTP suppression resulting from prolonged systemic inflammation.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

Mahmoud Hosseini: Conceptualization, Methodology, Validation, Resources, Data curation, Writing – review and editing, Supervision, Project administration, Funding acquisition. Hossein Salmani: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. Yousef Baghcheghi: Writing – review and editing, Investigation.

ORCID

Hossein Salmani © https://orcid.org/0000-0002-0643-1392

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