RESEARCH PAPER

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The effects of PPARγ agonists on long-term potentiation and apoptosis in the hippocampus area of juvenile hypothyroid rats

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The aim of the present study was to evaluate the effect of rosiglitazone (RSG) or pioglitazone (POG) on the synaptic plasticity, neuronal apoptosis, brain-derived neurotrophic factor (BDNF), and nitric oxide (NO) metabolites in the hippocampus of juvenile hypothyroid rats. The animals were divided into four groups: control; propylthiouracil (PTU), 0.05% dose in drinking water for 42 days; PTU–POG; and PTU–RSG. The POG (20 mg/kg) and the RSG (4 mg/kg) were administered by IP injection. We conducted long-term potentiation (LTP) in the cornu ammonis 1 area of the hippocampus using high-frequency stimulation of the Schaffer collateral pathway. Then, the hippocampal tissues were collected to determine BDNF and NO levels and the degree of apoptosis. PTU administration decreased the slope (10–90%) and amplitude of the fEPSPs compared to control. Injection of RSG or POG increased the slope, slope (10–90%), and amplitude of the fEPSP in the PTU-POG or PTU-RSG groups compared to the PTU group. TUNEL-positive neurons and NO metabolites in the hippocampus of the PTU group were higher than those of the control group. RSG or POG increased BDNF content in PTU–POG or PTU–RSG groups. Treatment of the rats with POG or RSG decreased apoptotic neurons and NO metabolites in the hippocampus of PTU–POG or PTU–RSG groups, respectively, compared to the PTU group. This study's results revealed that POG or RSG normalized LTP impairment, neuronal apoptosis, and improved BDNF content in the hippocampal tissue of juvenile hypothyroid rats.

Key words: apoptosis, BDNF, hypothyroid, LTP, pioglitazone, rosiglitazone

INTRODUCTION

Impaired brain development due to thyroid hormone deficiency results in structural damage in brain areas, including the hippocampus (Desouza et al., 2005). Hypothyroidism also interferes with learning and memory by reducing the density of dendritic spines, enhancing apoptosis, and impairing synaptic network connectivity (Rivas & Naranjo, 2007; Sala-Roca et al., 2008; Shibutani et al., 2009; Gong et al., 2010). The hippocampus is highly vulnerable to a deficit in thy-

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roid hormones, which indicates that thyroid hormones play a pivotal role in normal hippocampal development and function (Gong et al., 2010). It has been reported that hypothyroidism is connected with impairments in synaptogenesis, neuronal migration, myelination, proliferation, and differentiation of neuronal cells (Oppenheimer & Schwartz, 1997; Thompson & Potter, 2000; Zoeller et al., 2002; Bernal et al., 2003; Huang et al., 2008). It has also been suggested that hypothyroidism results in injury to the brain by enhancing mitochondrial disorders, increasing the pro-apoptotic protein Bax, and reducing anti-apoptotic proteins, including Bcl-2 and Bcl-xL (Porterfield & Hendrich, 1993; Muller et al., 1995; Xiao & Nikodem, 1998; Singh et al., 2003).

The inability to induce long-term potentiation (LTP) in the hippocampal neurons of hypothyroid rats and the observed effects of thyroid hormones on proteins involved in LTP indicate that thyroid hormones are pivotal to normal LTP induction or synaptic processes (Calzà et al., 1996; Niemi et al., 1996). It has also been reported that induction of hypothyroidism impairs LTP induction in hippocampal slices from newborn rats (Niemi et al., 1996). This makes LTP in the CA1 area of the hippocampus a well-recognized learning and memory mechanism (Vara et al., 2003).

Peroxisome proliferator-activated receptor γ (PPARγ)

It has been clearly documented that PPARγ activation plays a positive role in the modulation of the inflammatory response, oxidative damage, LTP impairment, and reduction of apoptosis (Fuenzalida et al., 2007; Yi et al., 2008; Fong et al., 2010). PPARγ is also expressed in the brain, including hippocampal and cortex tissues (Kainu et al., 1994; Berger & Moller, 2002). Through *in vitro* and *in vivo* studies, it was found that PPARγ is expressed in neurons and glial cells (Bernardo et al., 2003; Moreno et al., 2004; Park et al., 2004; Cristiano et al., 2005; Inestrosa et al., 2005). Previous studies have revealed that PPARγ agonists, including pioglitazone (POG) and rosiglitazone (RSG), improve brain damage induced by ischemia and spinal cord injury (Sundararajan et al., 2005; Zhao et al., 2005). Beneficial effects of POG and RSG have been observed in different central nervous system (CNS) disorders, including Alzheimer's and Parkinson's diseases and amyotrophic lateral sclerosis (Breidert et al., 2002; Schütz et al., 2005; Pedersen et al., 2006). It was observed that administration of RSG resulted in a decrease in the death of neuronal cells and improved LTP impairment in the hippocampal area (Pedersen et al., 2006; Gensch et al., 2007). Furthermore, beneficial effects of PPARγ agonists on ischemia/reperfusion injury have been shown for different parts of the body, including the kidney (Gensch et al., 2007), heart (Cowley et al., 2012), intestine (Wayman et al., 2002; Sivarajah et al., 2003), lung (et al., 2002), and CNS (Dehmer et al., 2004; Gray et al., 2012).

Hypothyroidism can cause serious damage to a number of brain areas, including the hippocampal area (Rami et al., 1986). On the other hand, previous studies have revealed that the hippocampal areas, including the CA1 pyramidal cells and the granular and polymorphic layers of the dentate gyrus, have a high density of PPARγ (Moreno et al., 2004). Considering this cumulative evidence, the present study aimed to investigate the effects of POG and RSG on apoptosis, brain-derived neurotrophic factor (BDNF) level, and LTP impairment in hypothyroid rats.

METHODS

Animals and drugs

In this study, 52 male Wistar rats, aged three weeks and weighing 60 ± 5 g, were randomly selected from the animal center at Mashhad University of Medical Sciences, Mashhad, Iran. All animals were housed in standard conditions that included a temperature of 22 ± 2°C, a period of 12 h of light/dark, and free access to water and food. In all experiments, we followed the guidelines provided by the National Institute for Health Guide for the Care and Use of Laboratory Animals and approved by Mashhad University's Committee on Animal Research (IR.MUMS.REC.1394.158). Animals were randomly assigned to four groups: control, PTU, PTU-POG, and PTU-RSG. A dose of 0.05% PTU (Iran Hormone Company, Tehran, Iran) was given to the animals in the PTU, PTU-POG, and PTU-RSG groups (0.5 g of PTU was added to 1,000 ml in drinking water) for six weeks. The POG and RSG (Iran Hormone Company, Tehran, Iran), or the same volume of vehicle, were administered intraperitoneally to rats at doses of 20 mg/kg and 4 mg/kg, respectively, for six weeks. The electrophysiological studies were conducted on 32 animals (n=8 in each group). The brains of these animals were ablated to determine the contents of BDNF and nitric oxide (NO) metabolites. Additionally, twenty animals were treated for histological experiments (n=5 in each group).

Electrophysiological study

In our study investigating the effects of PPARγ agonists on LTP and apoptosis in the hippocampal area of juvenile hypothyroid rats, we utilized a specific

high-frequency protocol to induce LTP. Here, we provide a comprehensive description of the methodology employed in our experiments (Saadati et al., 2014; Baghcheghi et al., 2019).

Following the administration of urethane anesthesia at a dose of 1.6 g/kg, rats were placed in a stereotaxic apparatus for head fixation. The CA1 area of the skull was surgically exposed using coordinates (ML=3 mm; AP=4.1 mm) to allow targeted electrode placement.

Utilizing the Paxinos and Watson atlas as a reference, the Schafer collateral pathway within the hippocampus was located relative to specific coordinates (ML=3.5 mm; DV=2.8–3 mm; AP=3 mm).

Field potentials in the hippocampal region were recorded using established electrode placements within the Schafer collateral pathway. The recording setup was based on protocols previously described in our published studies to ensure consistency and reproducibility.

The high-frequency stimulation (HFS) protocol involved the application of a specific pattern of high-frequency electrical stimulations to induce LTP in the hippocampal CA1 region. Parameters such as pulse duration, intensity, and frequency were optimized based on standard protocols for LTP induction in rodent models.

Field potential measurement and analysis

Following the application of HFS, field potentials in the CA1 region were measured and analyzed for changes in response characteristics, including amplitude and slope. These measurements were conducted with meticulous attention to temporal dynamics to capture immediate synaptic plasticity alterations.

Strict experimental controls were implemented to minimize variability and ensure accurate data interpretation. Replication of the high-frequency protocol across experimental groups allowed for robust comparisons of LTP induction efficacy.

Recorded field potentials were analyzed to determine the impact of PPARγ agonist treatments on LTP induction and synaptic plasticity in juvenile hypothyroid rats. Statistical analyses were performed to validate the significance of observed changes and correlations with treatment conditions.

Measurement of nitric oxide metabolites and BDNF levels

After the LTP recordings, the rats were sacrificed, and their hippocampus was removed for further analysis. The levels of NO metabolites (NO2/NO3) were determined using the Griess reagent method following the manufacturer's instructions. In brief, hippocampal tissues were homogenized in lysis buffer and centrifuged to obtain the supernatant. Then, the supernatant was mixed with the Griess reagents (sulfanilamide and NED) and incubated at room temperature for 10 min. The absorbance was measured at 540 nm using a spectrophotometer, and the NO2/NO3 levels were calculated based on a standard curve.

BDNF levels were determined using a rat ELISA Kit from MyBioSource Company. The hippocampal tissues were homogenized in a lysis buffer provided in the kit and centrifuged to collect the supernatant. The supernatant was then added to the pre-coated ELISA plate and incubated for a specific period as instructed by the manufacturer. After washing the plate, a detection antibody was added, followed by a substrate solution for color development. The absorbance was measured at 450 nm using a microplate reader, and the BDNF levels were calculated based on a standard curve provided in the kit (Baghcheghi et al., 2021).

Histological studies

Histological studies were carried out on 20 animals (n=5 in each group). Deep anesthesia was accomplished by injecting a high dose of urethane. In the following steps, the rats were transcardially perfused with saline, followed by 100 ml of glutaraldehyde 1.25% plus paraformaldehyde 1% (in buffer phosphate saline [PBS]; 0.2 molar, pH 7.4) as a fixative. Then, serial coronal sections (5 µm) were prepared from the paraffin blocks. By using systematic randomized sampling, ten brain sections, including the hippocampus, were selected randomly from each animal. For TUNEL staining, the poly-L-lysine slides were used. The TUNEL method was performed according to the instructions provided in the TUNEL kit (manufacturer's instructions). In brief, the sections were deparaffinized and rehydrated, followed by proteinase K digestion. The TUNEL reaction mixture was then added to the sections, and they were covered with a coverslip. The sections were incubated in a humidified chamber for the appropriate amount of time at 37°C. After the incubation, the sections were washed with PBS and counterstained with DAPI for nuclear visualization. The slides were examined under a fluorescent microscope, and the number of apoptotic cells in four areas of the hippocampus (CA1, CA2, CA3, and DG) was estimated as per the TUNEL kit instructions. All counting was performed by a blinded observer to ensure unbiased results (Ebrahimzadeh Bideskan et al., 2017).

Determination of serum T4 content

Blood samples were obtained from the hearts of anesthetized rats following the manufacturer's protocol for the Daisource T4-RIA-CT radioimmunoassay kit for measuring serum thyroxin levels. The blood samples were collected in tubes containing an anticoagulant and were centrifuged at 3,000 rpm for 10 minutes to separate the serum from the cells. The serum samples were then aliquoted into separate tubes for analysis. The T4-RIA-CT kit utilizes a competitive binding assay in which a fixed amount of radiolabeled thyroxin competes with the T4 in the serum samples for binding to specific antibodies. The amount of radiolabeled T4 bound to the antibodies is inversely proportional to the concentration of T4 in the sample. The serum samples and the radiolabeled T4 were incubated together in the presence of the antibody for a specific period of time at a controlled temperature. After the incubation, the unbound radiolabeled T4 was separated from the antibody-bound T4 using a separation method recommended by the manufacturer. The radioactivity of the bound T4 was then measured using a gamma counter, and the concentration of T4 in the serum samples was calculated based on a standard curve generated from known concentrations of T4 (Baghcheghi et al., 2019).

The data are presented as mean ± SEM. Repeated measures analysis of variance (ANOVA), one-way ANOVA, and Tukey's *post hoc* test were used to analyze the data. Statistically significant differences were defined as $P<0.05$.

RESULTS

Electrophysiological results

The repeated measures ANOVA results showed that treatment ($F_{(3,648)}=186.9$, $P<0.001$) and time ($F_{(23,648)}=11.46$, $P<0.001$) had an effect on the 10–90% slope. There was also an interaction between treatment and time ($F_{(69,648)}=2.951$, $P<0.001$). Higher 10–90% slopes for the fEPSP were observed when HFS was applied in the control group (Fig. 1A). Following the application of HFS, the 10–90% percent slope of the PTU group was lower than that of the control group ($P<0.001$, Fig. 1B). Compared to the PTU group, the PTU-POG and PTU-RSG groups with POG or RSG injections had a greater fEPSP 10–90% slope ($P<0.001$ for all, Fig. 1B). The results also showed that after the application of HFS, the 10-90% slope of the fEPSP in the Control, PTU-POG, and PTU-RSG groups was higher than before the application of HFS in the same groups ($P<0.001$ for all; Fig. 1B), except for the PTU group, in which there was no significant difference before and after HFS (Fig. 1B).

BDNF and NO metabolite levels

The ANOVA results showed that treatment was effective on BDNF levels in the hippocampus ($F_{(3,27)}=18.57$, $P<0.001$). The results also showed that PTU-induced hypothyroidism led to a decrease in hippocampal tissue BDNF levels in the PTU group compared to the control level ($P<0.01$). Treatment of the animals with POG or RSG for six weeks in the PTU-POG and PTU-RSG groups increased BDNF concentration in the hippocampal tissues compared to the PTU group ($P<0.001$) (Fig. 2A).

The ANOVA results showed that the treatment had an effect on NO metabolite levels in the hippocampus ($F_{(3,24)}=9.61$, $P<0.001$). Higher levels of NO metabolites were detected in the hippocampal tissue of the PTU group than those of the control group ($P<0.001$). The PTU-POG and PTU-RSG groups had lower levels of NO metabolites in their hippocampal tissues compared to the PTU group ($P<0.001$, Fig. 2B).

Histological results obtained from the hippocampus

The ANOVA results showed that there was an effect of treatment on TUNEL-positive cells in the CA1 area ($F_{(3,16)}=36.21$, $P<0.001$). The results also revealed that the PTU group had greater TUNEL-positive cells in the CA1 area compared to the control group ($P<0.001$, Fig. 3A). The number of TUNEL-positive cells generated in the PTU-POG and PTU-RSG groups was less than the number generated in the PTU group ($P<0.001$, Fig. 3A). Moreover, there were more TUNEL-positive cells in the CA1 area of the PTU-RSG group compared to the control group ($P<0.01$, Fig. 3A).

The ANOVA results showed that treatment had an effect on TUNEL-positive cells in the CA2 area ($F_{(3,16)}=37.78$, $P<0.001$). The results also revealed that the PTU group had more TUNEL-positive cells than the control group in the CA2 area ($P<0.001$, Fig. 3B). The PTU-POG and PTU-RSG groups had lower TUNEL-positive cells than the PTU group in the CA2 area ($P<0.001$, Fig. 3B). Nevertheless, the TUNEL-positive cells generated by the control group were also less than those generated by the PTU-RSG group in the CA2 area ($P<0.05$; Fig. 3B).

The ANOVA results showed an effect of treatment on TUNEL-positive cells in the CA3 area ($F_{(3,16)}=78.08$, $P<0.001$). A higher number of TUNEL-positive cells were found in the CA3 area of the PTU group com-

pared to the control group (P<0.001, Fig. 3C). Additionally, the PTU-POG and PTU-RSG groups generated fewer TUNEL-positive cells than the PTU group (P<0.001, Fig. 3C). The PTU-RSG group generated more TUNEL-positive cells than the control and PTU-POG groups (P<0.001 and P<0.05, respectively; Fig. 3B). Moreover, the number of TUNEL-positive cells in the control and PTU-POG groups did not differ significantly (Fig. 3C).

The ANOVA results showed an effect of treatment on TUNEL-positive cells in the CA3 area ($F_{(3,16)}$=62.25, P<0.001). The results also revealed that the control group had fewer TUNEL-positive cells in the DG compared to the PTU group (P<0.001, Fig. 3D). The PTU-POG and PTU-RSG groups generated significantly fewer TUNEL-positive cells than those in the PTU group (P<0.001, Fig. 3D). Moreover, the PTU-RSG group had more TUNEL-positive cells than the control and PTU-POG groups (P<0.001 and P<0.01, respectively; Fig. 3D).

Serum T4 level

The ANOVA results showed that there was a significant difference among the groups in serum thy-

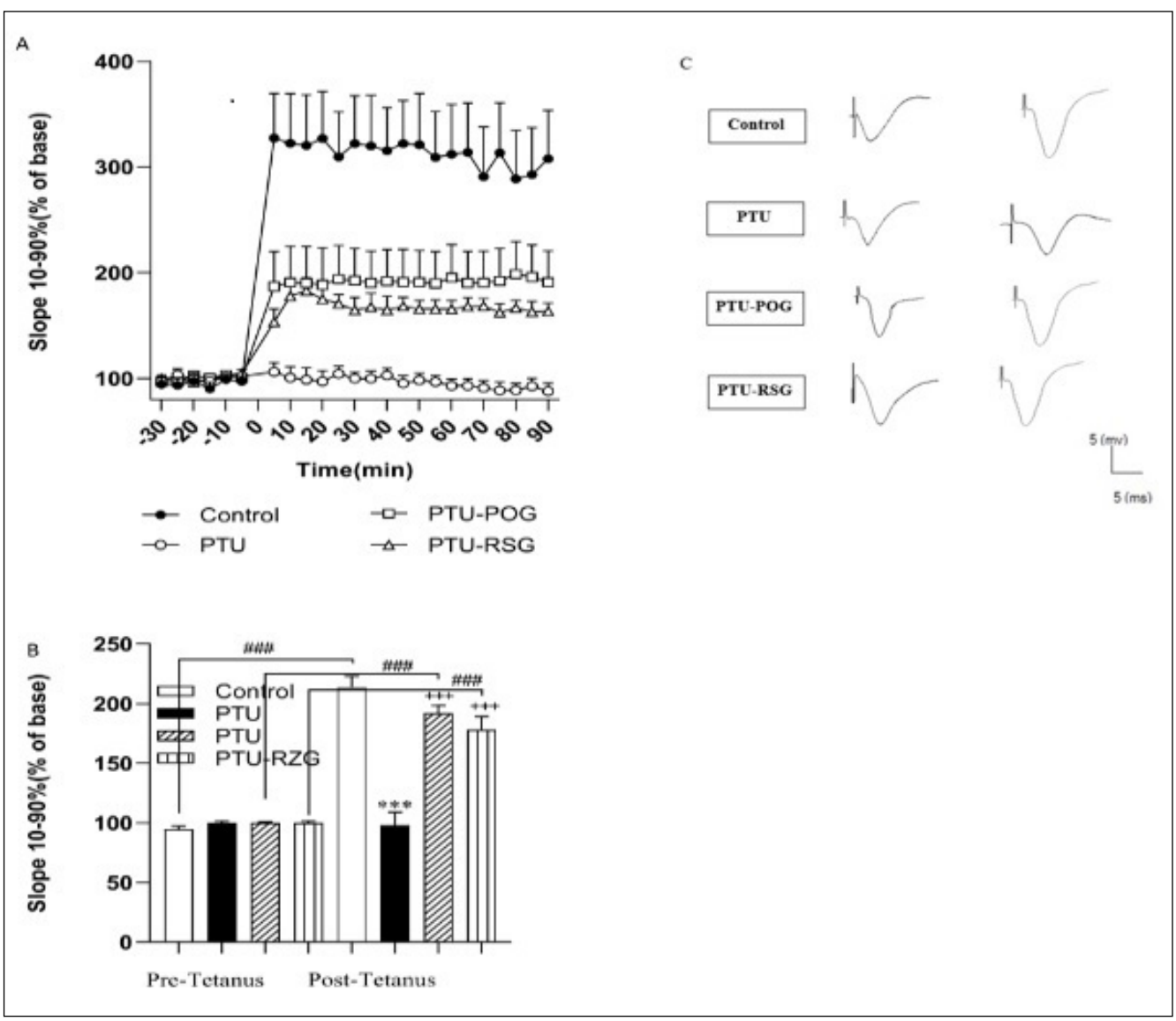

Fig. 1 (A, B) The effects of pioglitazone (POG) and rosiglitazone (RSG) on the 10–90% slope of the fEPSP in the CA1 area of the hippocampus of hypothyroid rats are shown (n=8) (C) The sample original traces for field excitatory postsynaptic potentials for each group are shown. ***P<0.001 compared to the control group, $^{+++}$P<0.001 compared to the PTU group, $^{###}$P<0.001 compared to before high-frequency stimulation in each group.

roxine level ($F_{(3,32)}$=11.80, P<0.001). The results of the experiments revealed that PTU treatment of juvenile rats led to a hypothyroid state, which was reflected by a decreased level of serum thyroxine compared to the control group (P<0.001). Interestingly, the PTU-RSG group had a higher serum thyroxin level than the PTU group (P<0.001). Nonetheless, the thyroxin level in the PTU-POG group was lower than in the control group (P<0.05, Fig. 4).

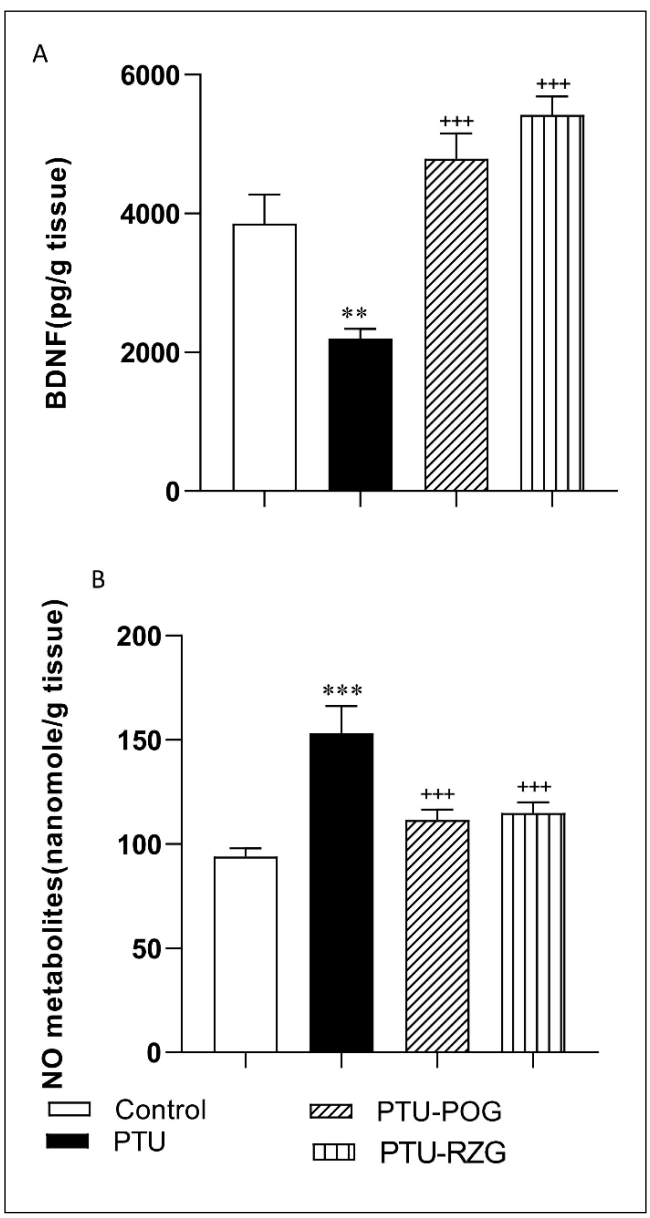

Fig. 2. The effects of POG and RZG on the BDNF and NO metabolite concentrations in the hippocampus of hypothyroid rats are shown (n=6–8). ***P<0.001 *vs.* control group. $^{+++}$P<0.001 *vs.* PTU group.

DISCUSSION

In this study, we attempted to determine how PPARγ agonists (POG and RSG) can improve LTP impairment and neuronal apoptosis in the hippocampal tissue of juvenile hypothyroid rats.

This study found that hypothyroidism led to LTP impairment in the CA1 area and increased apoptosis in the hippocampal tissue. Our results also showed that hypothyroidism induction for six weeks increased NO levels and decreased BDNF levels in the hippocampal tissue. The results of the present study also showed that PPARγ agonists (POG and RSG) significantly decreased the number of apoptotic neurons in hippocampal tissue and restored hippocampal LTP impairment in juvenile hypothyroid rats. Furthermore, our findings revealed that the administration of POG or RSG for six weeks normalized the BDNF and NO levels in hippocampal tissue.

In the present study, the number of apoptotic cells in the hypothyroid rats was higher than in the healthy rats. Moreover, the administration of POG or RSG decreased the number of apoptotic cells in the different hippocampus areas. The results of our study are in line with the findings of previous studies that demonstrated that the administration of PPARγ agonists decreased the number of apoptotic cells in the endothelial progenitor cells. It has also been suggested that RSG prevents neuronal apoptosis caused by traumatic brain injury (Yao et al., 2015).

Bcl-2 and Bcl-xL are anti-apoptotic proteins, and Bax, Bak, Bid, and Bad are pro-apoptotic proteins (Cory & Adams, 2002). In fact, the response of mitochondria to pro-apoptotic proteins depends on the balance between anti-apoptotic proteins (especially Bcl-2) and pro-apoptotic proteins (especially Bax), and the ratio of Bax to Bcl-2 plays a critical role in pulling the cellular trigger to undergo apoptosis (Upadhyay et al., 2003). Previous studies have shown that hypothyroidism results in an increase in Bax expression while leading to a decrease in Bcl-2 expression in the developing brain (Singh et al., 2003). Administration of thyroid hormones inhibits apoptosis induced by hypothyroidism *via* an increase in the Bcl-2 level in the hippocampal neurons (Huang et al., 2008). Furthermore, previous studies showed that induction of hypothyroidism in juvenile rats enhanced the pro-apoptotic Bax protein while decreasing the anti-apoptotic Bcl-2 protein in the hippocampus of juvenile rats (Zhang et al., 2009).

In this regard, previous studies have demonstrated that administration of RSG improved Bcl-2 and p-Bad protein concentrations in brain tissue, which were reduced by early brain injury (Gu et al., 2015). These beneficial effects of PPARγ agonists on anti-apoptot-

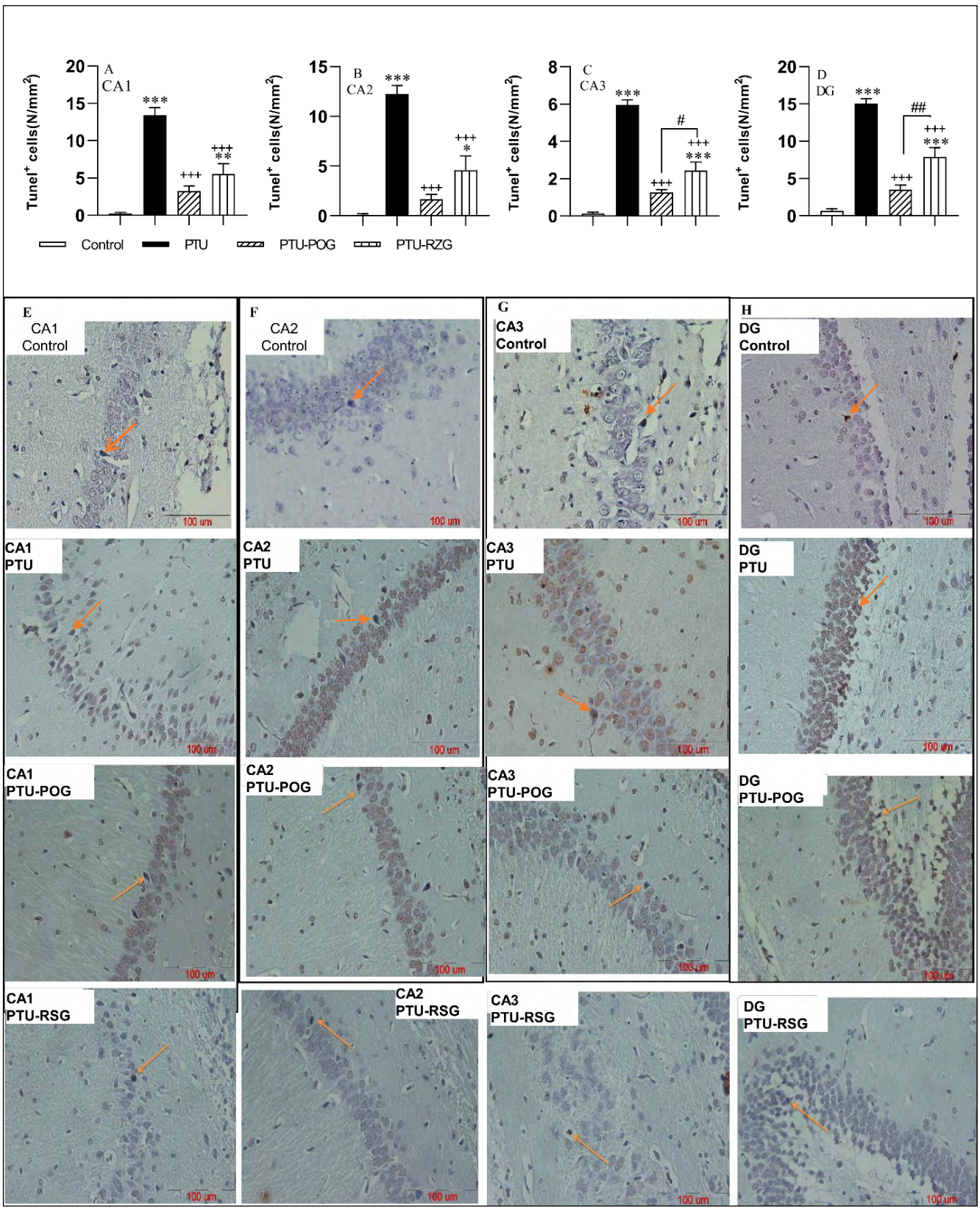

Fig. 3. TUNEL-positive cell number per area in the CA1 (A), CA2 (B), CA3 (C), and DG (D) areas (n=5). *P<0.05, **P<0.001, and ***P<0.001 *vs.* control group. $^{+++}$P<0.001 *vs.* PTU group, $^{\#}$P<0.05 and $^{\#\#}$P<0.01 *vs.* PTU-POG group. CA1 (E), CA2 (F), CA3 (G), and DG (H) areas of the hippocampus after TUNEL immunohistochemistry for the detection of apoptotic cells.

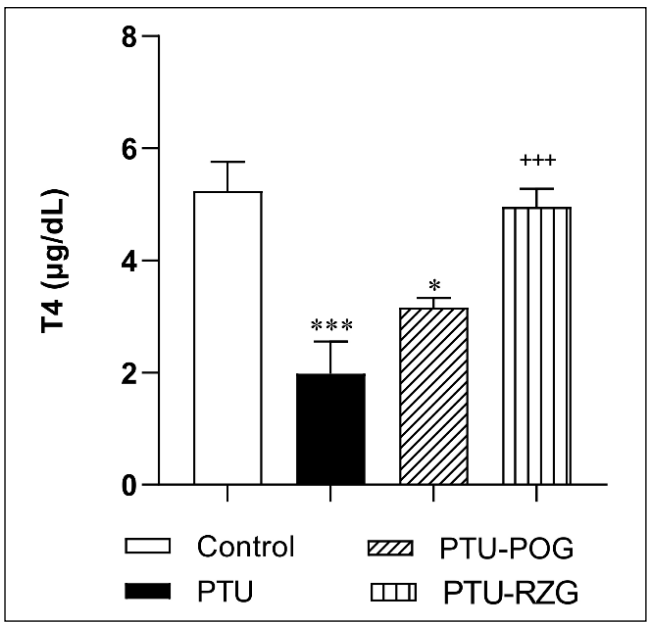

Fig. 4. Serum T4 level (n=8–10). *P<0.05, and ***P<0.001 *vs.* control group. $^{+++}$P<0.001 *vs.* PTU group.

ic proteins were abolished by the administration of PPARγ antagonists, which indicated that these effects are PPARγ dependent (Fuenzalida et al., 2007; Wu et al., 2009a). Previous studies have also shown that POG or RSG normalized caspase-3 in brain tissues, which were reduced by subarachnoid hemorrhage or administration of D-galactose (Fuenzalida et al., 2007; Gu et al., 2015). Therefore, the results of the present study and previous studies suggest that normalization of the levels of anti-apoptotic proteins in hippocampal tissues might be a mechanism through which PPARγ agonists improve the damage induced by hypothyroidism.

Translocation of Bad and its binding with Bcl-2 and Bcl-xl results in the inactivation of anti-apoptotic proteins such as Bcl2 and Bcl-xl (Wu et al., 2009b). These events lead to a change in the balance between anti-apoptotic and pro-apoptotic proteins, promoting apoptosis (Gu et al., 2015). On the other hand, it has been reported that phosphorylated AKT can phosphorylate Bad and prevent Bad translocation (Wu et al., 2009b). In line with these data, it has been reported that activation of PPARγ leads to phosphorylation of AKT, and then, activation of AKT can deactivate Bad. Finally, these cascading events result in a shift toward inhibition of apoptosis by preventing the binding of Bad to Bcl-2 and Bcl-xl (Fong et al., 2010). Moreover, activation of the PI-3K/Akt pathway is not the only way that PPARγ agonists cause a reduction in the level of apoptosis. It has also been reported that administration of RSG enhanced the level of 14-3-3ε (a protein involved in apoptosis) and enhanced the level of 14-3-3ε, which subsequently resulted in dephosphorylation of p-Bad and, ultimately, dephosphorylation of p-Bad reduced the level of apoptosis (Datta et al., 1997).

Based on the findings of the present study, PTU-induced hypothyroidism was accompanied by LTP impairment in the Schaffer collateral CA1 synapses. Results from previous studies showed that hypothyroidism led to impairment of early and late phases of LTP and short- and long-term memory (Gerges et al., 2004; Wu et al., 2009a). Moreover, administration of thyroxine to hypothyroid rats normalized impaired LTP in the Schaffer collateral CA1 synapses of the hippocampus area (Gerges et al., 2004). Synaptic plasticity caused by LTP occurs at excitatory synapses, and it is an activity-dependent and long-lasting process (Gerges et al., 2004). Memory formation is influenced by synaptic and cellular events; in this regard, LTP is considered to be a model for evaluating memory impairment (Alzoubi et al., 2009). LTP has been studied in different areas of the hippocampus, including CA1 (Subramaniyan et al., 2015), CA3 (Bliss & Lømo, 1973), and DG (Dumas & Foster, 1995; Izquierdo et al., 2008). Moreover, in the present study, it was found that treating rats with POG or RSG improved hypothyroidism-associated LTP impairment in hippocampal areas. The results of our study are in line with the findings of previous studies, which demonstrated that the administration of PPARγ agonists improved LTP in aged rats. These results are also consistent with previous studies that found administration of RSG or POG improved LTP in aged rats, AD transgenic mice, and Aβ-induced LTP impairment (Irvine et al., 2006; Talaei & Salami, 2013; Chen et al., 2015).

A considerable body of evidence exists supporting the fact that enhancing NO levels to above-normal levels results in oxidative damage in different parts of the body. In fact, under pathological conditions, NO can induce oxidative stress *via* the creation of highly reactive metabolite peroxynitrite (Cowley et al., 2012; Xu et al., 2014; Baghcheghi et al., 2019; 2020). Interestingly, our results showed that hypothyroidism enhanced the level of NO in hippocampal tissue. These results are in line with previous studies that reported hypothyroidism was followed by increased levels of NO in the hippocampal tissue (Cano-Europa et al., 2008; Baghcheghi et al., 2016; Memarpour et al., 2020; Baghcheghi et al., 2021). Moreover, it has been reported that NO synthase gene expression in the brain is related to thyroid hormone concentration (Cano-Europa et al., 2008; Baghcheghi et al., 2019). Hypothyroidism enhances nNOS activity or nNOS expression in the hippocampus and amygdala areas (Cano-Europa et al., 2008). On the other hand, under oxidative stress conditions, increased levels of NO are followed by a reaction between NO and super-

oxide and generates peroxynitrite, which is a powerful oxidant able to damage many biological compounds and tissues (Chabrier et al., 1999; Cano-Europa et al., 2008; Sinha et al., 2008). Furthermore, increasing NO levels led to damage to complexes I-III, II-III, and cytochrome c oxidase of the respiratory chain, resulting in more generated oxidative radicals (Jonnala & Buccafusco, 2001; Radi et al., 2002). Based on the results of the present study, we also found that treating animals with POG or RSG led to a decrease in NO levels in the hippocampal tissue, which can be considered as one of the possible mechanisms underlying the positive effects of PPARγ activation. These results are in agreement with our previous studies, which showed that POG or RSG decreased NO levels in brain tissues (Franco et al., 2006; Venditti & Di Meo, 2006; Baghcheghi et al., 2021). Therefore, in the present study, we can imply that POG or RSG, probably by diminishing NO, prevents apoptosis and LTP impairment in the hippocampal tissue of hypothyroid rats.

The results of our study also revealed that the content of BDNF was reduced in the hippocampal tissue of hypothyroid rats. These results are in agreement with previous studies that reported hypothyroidism results in a reduction of BDNF content in brain tissues (Zhang et al., 2009; Sui & Li, 2010; Baghcheghi et al., 2019). Furthermore, our findings revealed that the administration of POG or RSG normalized the BDNF level of hippocampal tissue in hypothyroid rats. Results from previous studies support these results, reporting that treating mice with RSG resulted in an increased level of BDNF in the hippocampal tissue (Lasley & Gilbert, 2011). BDNF belongs to the family of neurotrophic factors and plays a critical role in the survival and growth of nerve cells (Chakraborty et al., 2012). Moreover, BDNF plays a crucial role in the differentiation, proliferation, and protection of the cells, as well as synaptic plasticity in the CNS (Kariharan et al., 2015). The normal neural plasticity, including learning and memory, apoptosis, LTP, and mood change, depends on BDNF (Mattson et al., 2004).

In connection to the effect of BDNF on neural apoptosis, it has been demonstrated that the inhibitory effect of BDNF on apoptosis is mediated *via* intracellular signaling cascades such as tropomyosin-related kinase B (TrkB) (Numakawa et al., 2010). Previous studies have suggested that there is a connection between BDNF and oxidative stress conditions. For instance, administration of BDNF to rats reduced oxidative stress and neuronal death in substantia nigra in a dopaminergic neuronal damage model induced by 6-hydroxydopamine (Yamada et al., 2002). In addition, BDNF decreased cell death through inhibition of the MAPK pathway in NMDA- or H_2O_2-exposed cultured cortical neurons (Numakawa et al., 2010). Conversely, oxidative stress conditions caused a reduction in BDNF content and then impairment in neuroplasticity and cognition (Altar et al., 1994). The beneficial effect of BDNF in neuronal synaptic plasticity seems to be mediated *via* energy metabolism, so the disorder in energy homeostasis can result in impairment in cognitive function and synaptic plasticity (Wu et al., 2004; Boutahar et al., 2010). Considering these results and the results of previous studies, the beneficial effects of POG or RSG on apoptosis and LTP impairment in hypothyroid rats, at least in part, can be explained by normalizing the BDNF level.

Moreover, the intriguing results presented in Fig. 4 of our study shed light on potential differences in the effects of RSG and POG on T4 levels in juvenile hypothyroid rats. These findings prompt a deeper exploration of the indirect effects of these PPARγ agonists through the restoration of thyroid hormone levels in the hippocampus area. While the discussion in the present study focused on the direct actions of RSG and POG on synaptic plasticity, apoptosis, BDNF, and NO levels, it is essential to consider the possibility that the observed effects on these parameters may, in part, be mediated by the restoration (full and/or partial) of T4 levels. Thyroid hormones play a crucial role in modulating neuronal processes, including synaptic plasticity and neurotrophic factor expression. Therefore, it is plausible that the effects of RSG and POG on these neurobiological outcomes could be secondary to their actions on thyroid hormone regulation. Further studies are warranted to elucidate the complex interplay between PPARγ agonists, thyroid hormone signaling, and hippocampal function in hypothyroid conditions, offering potential insights into novel therapeutic strategies for neurological disorders associated with thyroid dysfunction.

CONCLUSION

Treating rats with PPARγ agonists (POG and RSG) decreased apoptotic cells and improved LTP through normalizing NO and BDNF levels in hippocampal tissue of hypothyroid rats. Therefore, according to our results, POG or RSG might be a potent therapeutic agent for improving LTP and decreasing apoptosis in juvenile hypothyroid rats.

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