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Full Length Article

Thyroid hormone treatment alleviates the impairments of neurogenesis, mitochondrial biogenesis and memory performance induced by methamphetamine

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ABSTRACT

Chronic use of methamphetamine (MA), a neurotoxic psychostimulant, leads to long-lasting cognitive dysfunctions in humans and animal models. Thyroid hormones (THs) have several physiological actions and are crucial for normal behavioral, intellectual and neurological development. Considering the importance of THs in the cognitive processes, the present study was designed to evaluate the therapeutic effects of THs on cognitive and neurological impairments induced by MA. Escalating doses of MA (1–10 mg/kg, IP) were injected twice daily for 10 consecutive days in rats and cognitive functions were evaluated using behavioral tests. The expression of factors involved in neurogenesis (NES and DCX), mitochondrial biogenesis (PGC-1α, NRF-1, and TFAM), neuroinflammation (GFAP, Iba-1, and COX-2) as well as Reelin and NT-3 (synaptic plasticity and neurotrophic factor, respectively) was measured in the hippocampus of MA-treated animals. The effects of three different doses of T4 (20, 40 or 80 μg/kg; intraperitoneally) or T3 (20, 40 or 80 μg/rat; 2.5 μl/nostril; intranasal) treatment, once a day for one week after MA cessation, were assessed in MA-treated rats. After the last behavioral test, serum T4 and T3 levels were measured using radioimmunoassay. The results revealed that repeated escalating regimen of MA impaired cognitive functions concomitant with neurogenesis and synaptic plasticity impairments, mitochondrial dysfunction, and neuroinflammation. T4 or T3 treatment partially decreased the alterations induced by MA. These findings suggest that THs can be considered as potential candidates for the reduction of MA abuse related neurocognitive disturbances.

1. Introduction

Methamphetamine (MA), an extremely addictive drug, exerts serious effects on the nervous system that may lead to long-lasting deficits in brain structure, chemistry and function (Sekine et al., 2008; North et al., 2013). Several neurocognitive impairments, such as disorders in episodic memory and executive functions, complex information processing speed and psychomotor functions (Kalechstein et al., 2009; Casaletto et al., 2014; Ghazvini et al., 2016) were observed in the long-term use MA, that may persist after MA discontinuation (Scott et al., 2007). The precise neural mechanisms responsible for MA-induced toxicity are poorly understood, but it has been reported that oxidative stress, excitotoxicity, neuroinflammation, and neurodegeneration play a major role in MA toxicity (Shin et al., 2014).

MA because of lipophilic properties can diffuse via the cell membranes of the intra cellular organelles, such as mitochondria (Yamamoto et al., 2010), and causes mitochondrial dysfunction (Brown et al., 2005). Dynamic properties of mitochondria including fusion, fission, mitophagy and mitochondrial biogenesis are essential for neuronal cell functions and survival (Chan, 2012; Chaturvedi and Beal, 2013). In the function of mitochondrial biogenesis, several transcription factors are involved. PGC-1α (peroxisome proliferator-activated receptor gamma coactivator-1 alpha) is a transcriptional co-activator that activates a broad range of transcription factors involved in mitochondrial biogenesis, such as TFAM (mitochondrial transcription factor A) and NRF-1 and 2 (nuclear respiratory factors) (Onyango et al.,

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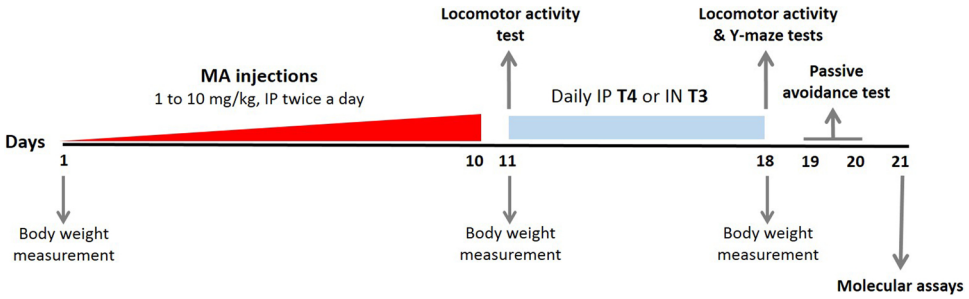

Fig. 1. The schematic of experimental design.

2010). The physiological importance of PGC1α is proved by the fact that inhibition of PGC-1α leads to abnormalities in mitochondrial function and also major neurodegenerative disorders such as Alzheimer's disease (AD) (Cui et al., 2006; Johri and Beal, 2012). Thus, transcriptional/pharmacologic activation of the PGC-1α pathway is expected to have neuroprotective effects in the central nervous system (CNS) disorders.

Thyroid hormones (THs; 3,5,3′-triiodothyronine (T3) and thyroxine (T4)) have an established necessary role in the normal CNS developmental and physiological processes (Williams, 2008). In the brain, THs are essential for neurogenesis, neuroplasticity, glial and neuronal cells differentiation and myelination (Bernal, 2007; Mohan et al., 2012). Intense restrictions of THs attenuate developmental processes producing smaller animals with smaller brains along with specific sensibility in the hippocampus (Hasegawa et al., 2010). The hippocampus, the main structure for different forms of learning and memory (Burgess et al., 2002), is highly sensitive to the actions of THs because of a high expression of TH receptors (Cooke et al., 2014), and also involved in neurogenesis processes (Bond et al., 2015). Adult hippocampal neurogenesis is an important physiological process with extensive implications for neural plasticity, normal behaviors and cognitive functions (Yau et al., 2015; Lieberwirth et al., 2016), and can be regulated by THs (Montero-Pedrazuela et al., 2006). It has been reported that thyroid dysfunction is associated with psychiatric deficits such as depression, anxiety and even cognitive impairments (Williams, 2008; Accorroni et al., 2017). Fu et al. (2010) have indicated that TH treatment prevents cognitive deficits and improves the neurological functions by inhibiting the damage of free radicals, regulating cholinergic functions and enhancing the number of hippocampal neuronal cells in the brain of AD mice. Moreover, a recent study has shown deficits in hippocampal-dependent spatial learning and memory in adult rats with TH deficiency (Artis et al., 2012), which are accompanied by impairments in LTP (long-term potentiation) and neurotrophic factors expression in the hippocampus (Husson et al., 2004). Other experiments have also reported that THs by increasing of neurotrophic factors expression exert protective effects in the setting of brain injury, such as trauma and ischemia (Crupi et al., 2013; Genovese et al., 2013).

Currently, there is no definitive pharmacological treatment for MA neurotoxicity. Recent improvements in understanding the neurobiological toxicity of MA have led to the study of the potential beneficial effects of pharmacological approaches including the use of anti-oxidants, antagonists of excitatory receptors, anti-neuroiflammatory agents, neurotrophic agents and even immunotherapies (Beirami et al., 2018; Yang et al., 2018). However no success in clinical practice, necessitate further efforts to develop agents for the treatment of clinical MA abuse-related problems specially neurocognitive impairments. THs have recently gained attention for their potential therapeutic effects in the treatment of nervous system disorders. So, in the present study, we examined the effects of these hormones on neurocognitive and neurological deficits caused by repeated MA administration.

2. Materials and methods

2.1. Animals

All experiments were carried out based on the guide for the care and use of laboratory animals (National Institutes of Health Publication No. 80-23, revised 1996) and approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNS.REC.1395.61). Adult male Wistar rats, weighting 220–280 g, were maintained under the standard laboratory conditions (21 ± 2 °C, 12 h light/dark cycle) and in groups of four per cage with free access to food and water. All behavioral tests were performed between 9:00 and 16:00 h.

2.2. Experimental design

Methamphetamine hydrochloride (with 99.2% purity; synthesized by the laboratory of Medicinal Chemistry, Tehran University of Medical Sciences) was dissolved in 0.9% saline solution before the intraperitoneally (IP) injection of each increasing dose (1–10 mg/kg; twice daily (9:00 in the morning and 3:00 in the afternoon), for 10 consecutive days). MA administrations were started with 1 mg/kg in the first day, and gently enhanced, 1 mg/kg/day. These escalating doses were used in order to mimic human MA abuse. Control group received injections of saline, IP, at the same volume. From one week after MA cessation, the cognitive functions of MA and saline-treated rats were evaluated using Y-maze and passive avoidance (PA) tests. MA-treated rats in six experimental groups, received levothyroxine (T4; 20, 40 or 80 μg/kg, IP) or triiodothyronine (T3; 20, 40 or 80 μg/rat, 2.5 μl/nostril, intranasal (IN)), once a day for one week after MA cessation and then were assessed for behavioral and molecular alterations (Fig. 1). To assess the effect of T4 or T3 treatment in control animals, two groups of saline-received rats were treated with T4 or T3 at the selected doses based on the results of behavioral tests. T4 or T3 (Sigma Aldrich) was dissolved in 0.9% saline solution. Although, T3 is more potent than T4 (Hall, 2008), in the systemic administration due to the presence of THs transporter proteins in the blood-brain barrier with more tendency to T4, insufficient amounts of T3 can enter into the brain. However, IN T3 delivery provides a proper pathway of drug delivery into several regions of the brain including the hippocampus, without significant increase in the uptake into the peripheral blood flow and also without systemic side effects (Hanson and Frey, 2008). IN T3 delivery was performed under mild anesthesia by insertion of a polyethylene 10 tube attached to a Hamilton syringe into the nostrils of rat, while the animal was laid on his back and the head was maintained in a horizontal position (Bender et al., 2015). In the set of T3 treatments, all groups of MA and saline-received rats, were treated with IN T3 or its vehicle (saline) under the same schedule of mild anesthesia. Animals were not given any drugs on the test days. A day after last behavioral test, rats were sacrificed and the hippocampus tissues were immediately separated, frozen in liquid nitrogen and kept at −80 °C until western blot and quantitative polymerase chain reaction (qPCR) assays. Blood samples were also collected at the same time.

2.3. Locomotor activity

Locomotor activity was quantified as the total number of beam crossings by each rat in a box (40 × 40 × 40 cm) comprising horizontal infrared sensors inserted 2.5 cm above the floor (Zakharova et al., 2009). Rats were put in the box for a 5 min habituation, and then their horizontal activity was recorded for 5 min as an index of locomotor activity. This activity was recorded twice, first time, the day after the last injection of MA or saline and the second time, one week after last saline or MA administration (on days 11 and 18, respectively).

2.4. Y-maze test

Spontaneous alternation behavior, an indication of spatial working memory performance, was evaluated in a Y-maze apparatus (day 18). The maze was made of 3 arms (50 × 10 × 30 cm) and an equilateral triangular central region. Each rat was gently put at the end of one arm to explore the maze for 8 min. Two parameters were visually recorded, the sequence of arm entries and total number of arm entries, as an indicator of general activity. In this protocol, alternation was considered as three consecutive choices of three different arms. The percentage of alternation was quantified as the number of triads comprising entries into all arms divided by the maximum possible alternations (the total number of arm entries minus 2) × 100 (Holcomb et al., 1998).

2.5. Passive avoidance test (PA)

Passive avoidance performance was examined according to our previous study (Beirami et al., 2018). Passive avoidance apparatus consisted of dark and light chambers of the equal size (30 × 20 × 20 cm) separated by a guillotine door (10 × 20 cm). Briefly, on the training day (day 19) followed by 30 min after habituation trial, each rat was placed in the light chamber for 10 s. After this interval the guillotine door was raised and rat was allowed to enter the dark chamber. Then the door was closed and a foot-shock (50 Hz, 1 mA, and 2 s) was immediately delivered via electrified steel rods in the floor of the box. Next, the retention trial was carried out 24 h after training trail (days 20) to measure long-term memory. The retention trial was done in the same way as training trial, no foot shock was applied and step-through latency (latency into the dark chamber) was recorded in a period of 300 s as an index of memory retrieval.

2.6. RNA extraction and qPCR

Total RNA was isolated from the hippocampus using YTzol reagent (Yekta Tajhiz Azma, Tehran, Iran) according to the manufacturer's protocol. The concentration and purity of RNA samples were evaluated by spectroscopy method using Nano drop (Thermo Fisher Scientific, USA), and 1 µg of total RNA was then reverse transcribed to cDNA by Trans Script First-Strand cDNA Synthesis Kit (Pars toos, Tehran, Iran). RNA template, primer, and nuclease-free H_2O were mixed and incubated at 65 °C for 5 min and then RT-Premix 2X was added and incubated 10 min at 65 °C, 60 min at 50 °C, 10 min at 70 °C and held at −20 °C until further use. The expression levels of genes (Table 1) were quantitatively measured by qPCR. Assays were run on ABI System (Applied Biosystems, USA) using SYBR Green qPCR Master Mix (2X) (Ampliqon, Denmark) reagents. Threshold cycles (Ct) were used to quantify the mRNA levels of the target genes, and β-actin expression was considered as internal control. The $2^{-\Delta\Delta Ct}$ method was used to quantify mRNA levels of the target genes (Livak and Schmittgen, 2001).

2.7. Western blotting

Hippocampi were homogenized in a lysis buffer containing protease inhibitor. Using the BCA protein assay kit (Thermo Scientific, USA), protein concentration of samples was determined. Then proteins were separated using an SDS-PAGE gel (12%, polyacrylamide) and transferred to a PVDF (polyvinylidenefluoride) membranes (Millipore, Billercia, MA) and blocked with 2% non-fat milk for 1 h at room temperature (RT). Afterward, membranes were probed with the following primary antibodies: anti-NT-3 (1:1000, Abcam, ab6203), anti-GFAP (1:10000, Abcam, ab7260), anti-Iba-1 (1:1000, Abcam, ab5076) and anti−COX-2 (1:1000, Thermo Fisher Scientific, PA1-20955). HRP-linked antibody was used as the secondary antibody (1:12000, Abcam, ab97051). β-actin (1:750, Cell signaling, 4970) expression was used as an internal control for normalization of protein levels. Immunoreactive polypeptides were detected by chemiluminescence using electro-chemiluminescence kit (ECL, BioRad, USA). Eventually, the results were quantified by scan of X-ray films and analysis by the software of Image *J*.

2.8. Determination of thyroid hormone levels

Total serum THs (T4 and T3) concentrations were evaluated by commercial kits (ELISA-Pishtaz-Teb, Tehran-Iran). Blood samples were collected using cardiac puncture technique after the last behavioral test. Samples were allowed to clot at RT for 30 min and centrifuged at 2500 rpm at 4 °C for 15 min. Serum supernatants were stored at −80 °C until analysis. The sensitivity of the assay was 0.4 µg/dl for T4 and 0.1 ng/ml for T3.

2.9. Statistical analysis

Data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed in 16th version of SPSS using paired t-test, one-way and also repeated measures two-way ANOVA by LSD post hoc test. The level of significance was set at < 0.05.

3. Results

3.1. The effects of treatment with different doses of T4 on MA-induced behavioral impairments

Before the assessment of cognitive functions, the alterations in the body weight and locomotor activity were evaluated in all experimental groups. Repeated-measures two-way ANOVA indicated no significant differences between all groups in body weight ($F_{(5,\ 45)} = 1.626$, $P > 0.05$) that was measured before saline/MA administration (day 1)

Table 1
Primer sequences used for qPCR.

Gene	Forward primer (5'-3')	Reverse primer (5'-3')
Reelin	GTCGTCCTAGTAAGCACTCGC	ACCTTCGCCTTCGGTTGTAG
Nestin	GGAGCAGGAGAAGCAAGGTC	GAGTTCTCAGCCTCCAGCAG
Doublecortin	GGAAGGGGAAAGCTATGTCTG	TTGCTGCTAGCCAAGGACTG
PGC-1α	GTGCAGCCAAGACTCTGTATGG	GTCCAGGTCATTCACATCAAGTTC
TFAM	AGAGTTGTCATTGGGATTGG	CATTCAGTGGGCAGAAGTC
NRF-1	AAATTGGGCCACATTACAGGG	GTTGCATCTCCTGAGAAGCG
β-actin	TCTATCCTGGCCTCACTGTC	AACGCAGCTCAGTAACACTCC

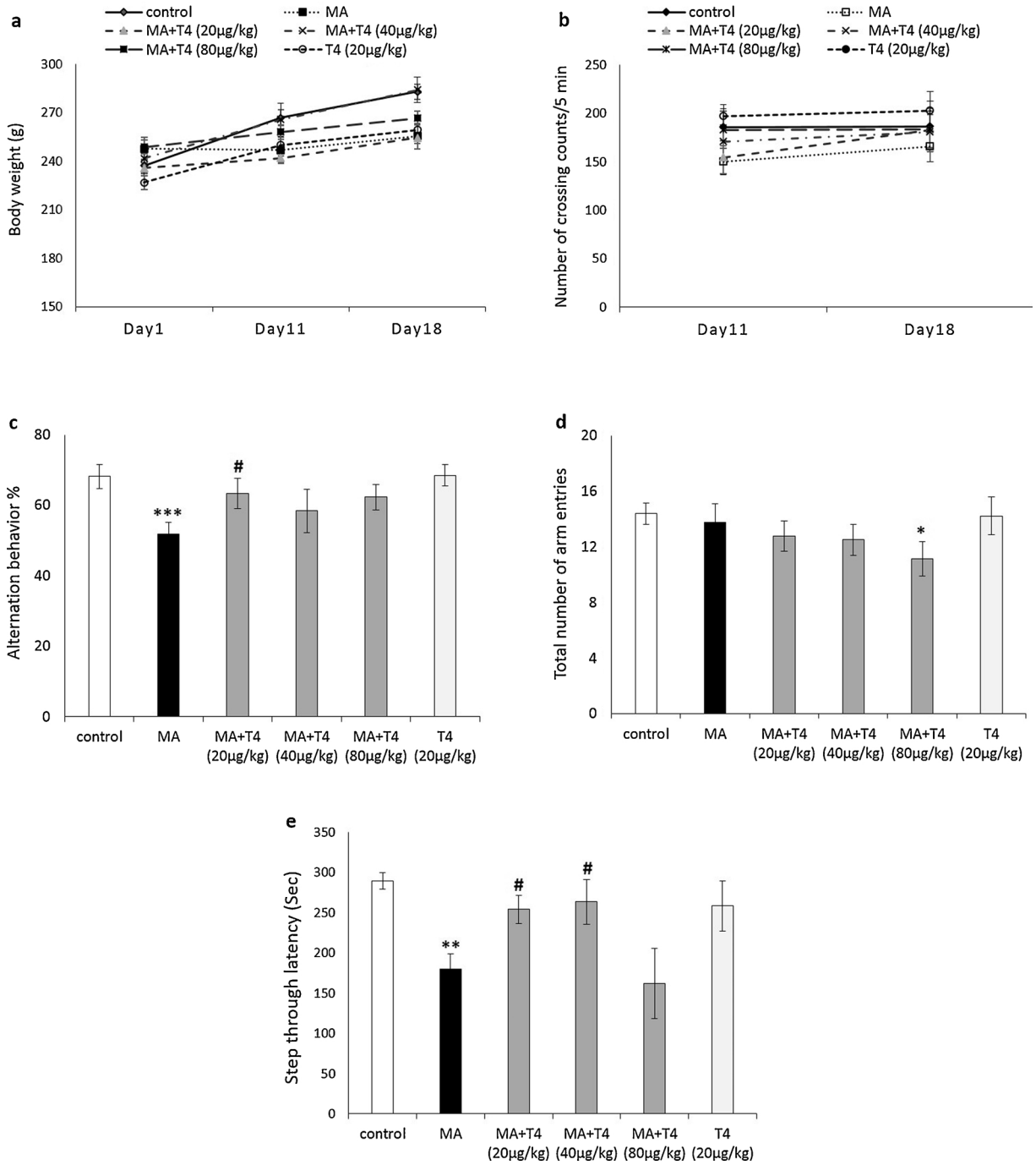

Fig. 2. The effects of escalating MA regimen (1–10 mg/kg, IP, twice daily, for 10 consecutive days) and different doses of T4 treatment (20, 40 or 80 μg/kg, IP, for one week after saline/MA cessation) on the body weight (a), locomotor activity index (b), Y-maze working memory (c and d), and passive avoidance memory (e). The differences between all experimental groups were revealed by ANOVA followed by LSD test. Data represent Mean ± SEM. *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ vs. control group; #$p < 0.05$ vs. MA-treated group, (n = 7–12).

and also one and seven days after saline/MA cessation (on days 11 and 18, respectively) (Fig. 2a).

Locomotor activity index was recorded as the total number of crossing during 5 min in the open field apparatus, one and seven days after saline/MA cessation (on days 11 and 18, respectively) (Fig. 2b). Repeated measures two-way ANOVA showed no significant differences between all groups ($F_{(5, 52)} = 1.078$, $P > 0.05$). These results indicate that long-term MA administration and also T4 treatment in different doses could not alter the body weight and locomotor activity.

To evaluate the effects of different doses of T4 treatment on working memory, the Y-maze test was used. One-way ANOVA analysis showed significant differences between groups ($F_{(5, 64)} = 2.968$, $p < 0.05$). As shown in (Fig. 2c), our data indicated that repeated MA injection significantly impaired spontaneous alternation compared with control group ($p < 0.001$), demonstrating spatial working memory deficit. Interestingly, it was revealed that T4 (20 μg/kg) could enhance spontaneous alternation compared with MA-treated group ($p < 0.05$). Indeed, this dose restored MA-induced working memory impairment while had no effect on total number of arm entries as a general locomotor activity index ($F_{(5, 64)} = 2.7$, $P > 0.05$) (Fig. 2d). T4 (40 μg/kg) had no effect on the mentioned parameters, but T4 (80 μg/kg) partially decreased total number of arm entries in this study.

Moreover, one-way ANOVA analysis showed significant differences between groups in the PA test ($F_{(5, 46)} = 3.731$, $p < 0.01$). As depicted in the (Fig. 2e), a significant reduction of the step-through latency was found in the MA-treated group compared to control animals ($p < 0.01$), indicating long-term memory impairments. But MA-injected rats that were intraperitoneally treated with 20 or 40 μg/kg dose of T4 exhibited a significant increase in the step-through latency compared with MA-treated group ($p < 0.05$). Animals that received only T4 (20 μg/kg) did not show any significant differences in spontaneous alternation, total number of arm entries and also step-through latency in comparison with control animals. According to the Y-maze and PA results, T4 (20 μg/kg) was selected for molecular assays. Because of T4 (40 μg/kg) could not increase spontaneous alternation compared with MA-treated animals and also T4 (80 μg/kg) partially decreased total number of arm entries, therefore these doses were not selected.

3.2. The effects of treatment with different doses of T3 on MA-induced behavioral impairments

Repeated-measures two-way ANOVA indicated no significant differences between all groups in body weight ($F_{(5, 43)} = 0.351$, $P > 0.05$) that was measured before saline/MA administration (day 1) and also one and seven days after saline/MA cessation (on days 11 and 18, respectively) (Fig. 3a).

Locomotor activity index was also recorded in all groups, one and seven days after saline/MA cessation (on days 11 and 18, respectively) (Fig. 3b). Repeated measures two-way ANOVA showed no significant differences between groups ($F_{(5, 52)} = 0.327$, $P > 0.05$). Indeed, repeated escalating doses of MA and also T3 treatment in different doses could not change the body weight and locomotor activity.

In the Y-maze test, one-way ANOVA analysis revealed significant differences between groups ($F_{(5, 66)} = 2.493$, $p < 0.05$). As shown in (Fig. 3c), repeated MA administration impaired spatial working memory compared with control group ($p < 0.001$). It was observed that T3 (40 μg/rat) could increase spontaneous alternation compared with MA-treated group ($p < 0.05$), but had no effect on total number of arm entries ($F_{(5, 66)} = 1.973$, $p > 0.05$) (Fig. 3d). T3 at doses of 20 and 80 μg/rat had no effects on the mentioned parameters.

About the PA test (Fig. 2e), one-way ANOVA analysis indicated significant differences between groups ($F_{(5, 51)} = 3.399$, $p < 0.01$). A significant decrease of the step-through latency was revealed in the MA group compared to control group ($p < 0.01$). But MA-injected rats that were intranasally treated with T3 (40 μg/rat) exhibited a significant increase in the step-through latency compared with MA-treated group ($p < 0.05$). Animals that received only T3 (40 μg/rat) did not show any significant differences in spontaneous alternation, total number of arm entries and also step-through latency in comparison with control animals. According to the Y-maze and PA results, T3 (40 μg/rat) was selected for molecular assays.

3.3. The increasing MA regimen and T4 or T3 administration did not affect the systemic levels of T4 and T3

Our study indicated that systemic levels of T4 and T3 were not significantly different between all experimental groups after T4 (20 μg/kg, IP) or T3 (40 μg/rat, IN) treatment ($F_{(5, 29)} = 0.002$, $p > 0.05$ and $F_{(5, 25)} = 0.008$, $p > 0.05$, one-way ANOVA, respectively) (Table 2). These findings show that MA and T4 or T3 treatment in the selected doses could not produce any disturbance in euthyroid state.

3.4. T3 or T4 treatment reversed the decreased levels of Nestin (NES) and Doublecortin (DCX) mRNA induced by repeated MA exposure

Relative quantification of the NES and DCX mRNA were performed using quantitative real-time PCR (qPCR) (table3). One-way ANOVA analysis revealed significant differences between groups in the mRNA levels of DCX ($F_{(5, 17)} = 4.407$, $p < 0.05$) and NES ($F_{(5, 17)} = 6.8$, $p < 0.01$). Post hoc LSD test showed that repeated MA administration reduced mRNA levels of NES ($p < 0.05$) and DCX ($p < 0.01$) compared to control group. In contrast, T3 or T4 treatment increased the expression of these neurogenesis markers compared with MA group. Indeed, THs treatment restored neurogenesis markers decrease caused by MA in the rat hippocampus. The increased expression of DCX by T3 treatment was not statistically significant ($P > 0.05$). Animals that received only T3 or T4 did not show a significant difference in the expression of these genes in comparison with control group.

3.5. T3 not T4 treatment reversed the reduced level of Reelin induced by repeated MA exposure

The effects of increasing doses of MA on the mRNA expression level of Reelin (synaptic plasticity factor) were evaluated using qPCR (Table 4). Statistical analysis revealed that repeated MA exposure decreased the mRNA level of Reelin ($F_{(5, 17)} = 4.413$, $p < 0.05$, one-way ANOVA) compared to control group. T3 but not T4 treatment increased the mRNA level of Reelin after repeated MA administration. Animals that received only T3 or T4 did not show a significant difference in the expression of this gene in comparison with control group.

3.6. T4 treatment enhanced the protein level of NT-3 in the hippocampus of MA-treated animals

Western blotting was used to examine the effects of T4 treatment on the protein level of NT-3 (neurotrophic factor) in the hippocampus of MA-treated animals (Fig. 4). One-way ANOVA showed significant difference between groups in NT3 level [$F_{(3, 17)} = 7.867$, $p < 0.05$]. LSD test for post-hoc comparison showed no significant difference between MA-treated animals compared with control group ($p > 0.05$). But T4 treatment increased the protein level of NT-3 following repeated MA administration compared to MA group ($p < 0.05$). Animals that received only T4 did not show a significant difference in the expression of this protein in comparison with control group. These results suggest that the upregulation of NT-3 expression by T4 treatment may be an important compensatory mechanism leading to the survival of neuronal cells in the hippocampus after MA exposure.

3.7. T4 or T3 treatment partially restored the expression of genes involved in mitochondrial biogenesis in MA-treated animals

Following repeated MA administration, the genes expression involved in mitochondrial biogenesis was measured by qPCR (Table 5). One-way ANOVA analysis indicated that MA administration reduced PGC-1α, NRF-1 and TFAM genes expression ($F_{(5, 17)} = 3.51$, $p < 0.05$; $F_{(5, 17)} = 46.311$, $p < 0.001$ and $F_{(5, 17)} = 3.642$, $p < 0.05$ respectively). Indeed, repeated MA administration led to a disturbance in mitochondrial biogenesis. T3 or T4 treatment could increase the expression of mitochondrial biogenesis factors in MA-treated animals, but only the increased expression of PGC-1α by T4 or T3 treatment was statistically significant ($P < 0.05$). Data analysis revealed no changes in the expression of these genes following only T3 or T4 administration compared to control group. But the expression of NRF-1 was higher than control in T3 treated group.

3.8. T4 treatment partially alleviated neuroinflammation induced by repeated MA exposure

Glial cells levels were assessed by measurement of GFAP, as a marker of astrocytes, and Iba-1, as a marker of microglia cells, by western blotting following repeated MA administration. One-way ANOVA revealed that significant differences between groups in the protein levels of Iba1 [$F_{(3, 8)} = 43.695$, $p < 0.01$], GFAP [$F_{(3,$

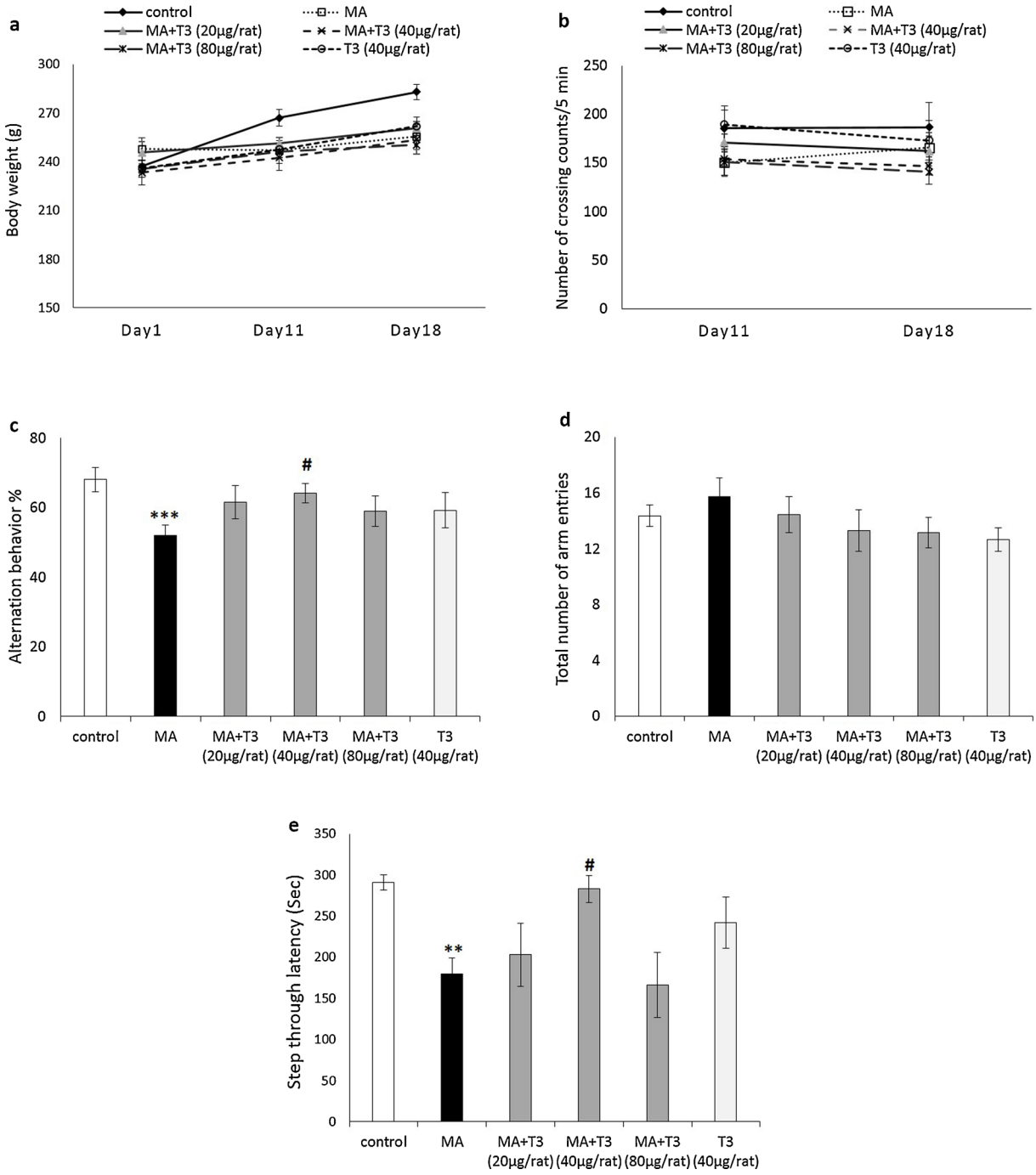

Fig. 3. The effects of escalating MA regimen (1–10 mg/kg, IP, twice daily, for 10 consecutive days) and different doses of T3 treatment (20, 40 or 80 μg/rat, IN, for one week after saline/MA cessation) on the body weight (a), locomotor activity index (b), Y-maze working memory (c and d), and passive avoidance memory (e). The differences between all experimental groups were revealed by ANOVA followed by LSD test. Data represent Mean ± SEM. **p < 0.01 and ***p < 0.001 vs. control group; #p < 0.05 vs. MA-treated group, (n = 7–12).

$_{8)}$ = 5.246, p < 0.05], and cyclooxygenase-2 (COX-2) levels [$F_{(3,}$ $_{8)}$ = 11.289, p < 0.05]. LSD Post-hoc analysis then demonstrated a significant increase in the protein levels of Iba-1 (p < 0.001), GFAP (p < 0.05) and also COX-2 (p < 0.01) in the hippocampus of MA-treated animals (Fig. 5). T4 treatment could decrease the levels of neuroinflammatory factors induced by repeated MA exposure. But it was not statistically significant in the case of Iba-1. Also, Iba-1 and GFAP levels in the T4-treated animals were higher than control group (p < 0.01, p < 0.05, respectively). These results indicate the effects of T4 on glial cells. In this case, it has been reported that THs aff ;ect morphological diff ;erentiation of glial sub-types such as microglia and astrocytes from progenitors to mature cells, while hypothyroidism decreases the number of matured glial cells in the several brain areas (Mohácsik et al., 2011; Mallat et al., 2002).

4. Discussion

4.1. Cognitive deficits

Several studies have indicated that chronic use of methamphetamine (MA) induces long-term neurocognitive disorders (North et al., 2013; Beirami et al., 2018; Tamijani et al., 2018). In this study, we

Table 2
The effects of MA (1–10 mg/kg, IP, twice daily, for 10 consecutive days) and THs administration [T4 (20 μg/kg, IP) or T3 (40 μg/rat, IN) for one week after MA cessation] on systemic levels of THs. The differences between groups were determined by one way ANOVA. Data represent Mean ± SEM, (n = 4–6).

Groups	T4 (μg/dl)	T3 (ng/dl)
Control	3.26 ± 0.57	110.15 ± 6.5
MA	3.36 ± 0.69	113.43 ± 9.3
MA + T4	3.29 ± 1.5	110.24 ± 4.18
MA + T3	3.29 ± 0.66	110.18 ± 1.89
T4	3.3 ± 0.7	110.35 ± 3.55
T3	3.27 ± 0.14	110.25 ± 5.22

Table 3
The effects of MA (1–10 mg/kg, IP, twice daily, for 10 consecutive days) and THs administration [T4 (20 μg/kg, IP) or T3 (40 μg/rat, IN) for one week after MA cessation] on mRNA levels of Doublecortin (DCX) and Nestin (NES). Relative values were normalized based on β-actin. The differences between all experimental groups were determined by ANOVA followed by LSD test. Data represent Mean ± SEM. *p < 0.05 and ** p < 0.01 vs. control group; ## p < 0.01 and ### p < 0.001 vs. MA-treated group, (n = 3–4).

	Fold changes	
Groups	NES	DCX
Control	1 ± 0.12	1.04 ± 0.28
MA	0.09 ± 0.01*	0.004 ± 0.0**
MA + T4	1.36 ± 0.24 ##	0.91 ± 0.2 ##
MA + T3	1.66 ± 0.33 ###	0.25 ± 0.07
T4	1.11 ± 0.55	0.74 ± 0.21
T3	0.97 ± 0.09	0.88 ± 0.14

Table 4
The effects of MA (1–10 mg/kg, IP, twice daily, for 10 consecutive days) and THs administration [T4 (20 μg/kg, IP) or T3 (40 μg/rat, IN) for one week after MA cessation] on mRNA level of Reelin. Relative values were normalized based on β-actin. The differences between all experimental groups were revealed by ANOVA followed by LSD test. Data represent Mean ± SEM.*p < 0.05 vs. control group; # p < 0.05 vs. MA-treated group, (n = 3–4).

Fold changes	
Groups	Reelin
Control	1 ± 0.03
MA	0.38 ± 0.21*
MA + T4	0.52 ± 0.03
MA + T3	0.88 ± 0.05#
T4	1.2 ± 0.08
T3	1.1 ± 0.25

observed repeated MA exposure impaired spatial working memory and passive avoidance memory, an indication of long-term memory (LeDoux, 1993), one week after MA cessation. In line with our findings, animal studies have demonstrated spatial working memory impairments and passive avoidance deficits after repeated MA exposure (Nagai et al., 2007; Lee et al., 2011; Mizoguchi et al., 2011; Murnane et al., 2012), which can be persisted after withdrawal of MA (Beirami et al., 2018; Mizoguchi et al., 2011). Extensive clinical experiments have also shown that MA abuse causes neurocognitive disorders (Kalechstein et al., 2009; Gonzalez et al., 2004; Hoffman et al., 2006), which are accompanied by disturbances in motor ability, learning and memory tests (Cherner et al., 2010). These impairments occur not only in individuals currently using MA (Simon et al., 2000) but can also

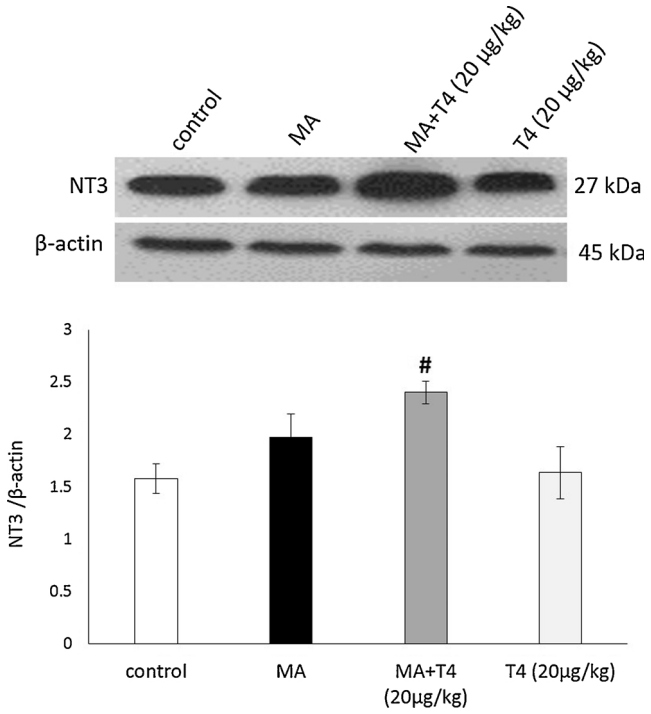

Fig. 4. The effects of MA (1–10 mg/kg, IP, twice daily, for 10 consecutive days) and T4 administration (20 μg/kg, IP, for one week after MA cessation) on the protein level of NT-3. The relative density was expressed as the NT-3/β-actin ratio. The differences between all experimental groups were revealed by ANOVA followed by LSD test. Data represent Mean ± SEM. #p < 0.05 vs. MA-treated group, (n = 3–4).

Table 5
The effects of MA (1–10 mg/kg, IP, twice daily, for 10 consecutive days) and THs administration [T4 (20 μg/kg, IP) or T3 (40 μg/rat, IN) for one week after MA cessation] on mRNA expression levels of PGC-1α, NRF-1, and TFAM. Relative values were normalized based on β-actin. The differences between all experimental groups were determined by ANOVA followed by LSD test. Data represent Mean ± SEM. *p < 0.05 and ***p < 0.001 vs. control group; #p < 0.05 vs. MA-treated group, (n = 3–4).

	Fold changes		
Groups	PGC-1α	NRF-1	TFAM
Control	1.03 ± 0.18	1 ± 0.12	1.1 ± 0.37
MA	0.08 ± 0.04*	0.07 ± 0.02***	0.08 ± 0.04*
MA + T4	0.75 ± 0.02#	0.1 ± 0.01	0.45 ± 0.16
MA + T3	0.76 ± 0.17#	0.12 ± 0.02	0.16 ± 0.01
T4	0.97 ± 0.05	0.67 ± 0.0	0.46 ± 0.03
T3	1.1 ± 0.63	0.11 ± 0.05*	0.45 ± 0.31

persist long after MA is discontinued (4 days to 7 months) (Kalechstein et al., 2009; Casaletto et al., 2014; Cherner et al., 2010). In our study, MA did not alter motor activity in locomotor activity test and the number of entries in Y-maze test. Indeed, the impairment of learning and memory observed in MA-treated animals was not due to changes in motivational functions induced by MA. Several studies have reported that single or multiple regimens of MA alters locomotor activity, but in the case of escalating doses of MA, there are controversial results (Ares-Santos et al., 2014; Yun, 2014; Grace et al., 2010). Indeed, exposure to lower doses of MA and then gradual increase of drug may provide a preconditioning effect against MA induced hyperlocomotor activity.

It has been indicated that thyroid hormones (THs) exert important effects on the functions of CNS and facilitate processes such as learning and memory (Raymaekers and Darras, 2017). In the present study, our results revealed the therapeutic effects of THs on MA-induced cognitive

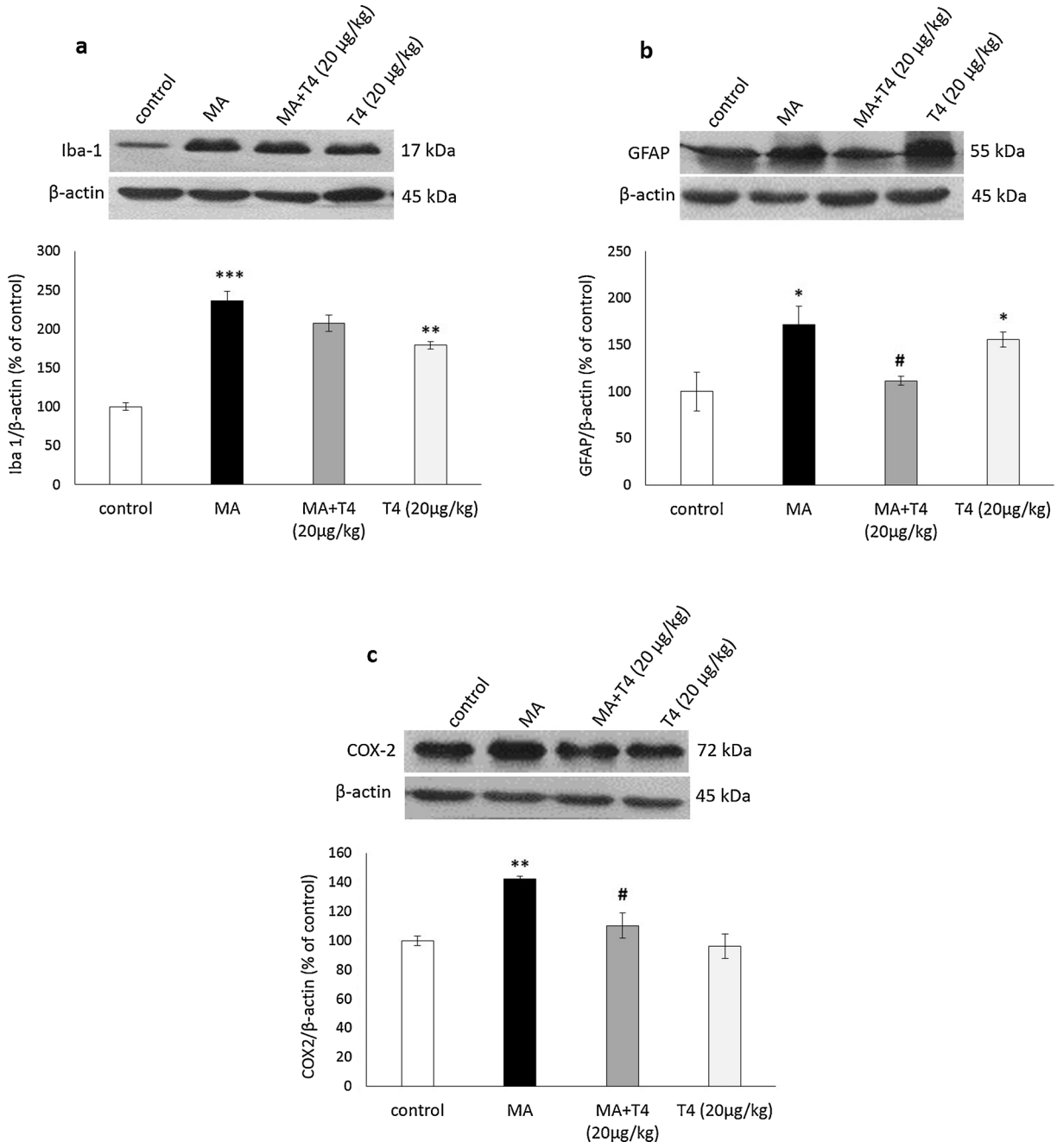

Fig. 5. The effects of MA (1–10 mg/kg, IP, twice daily, for 10 consecutive days) and T4 administration (20 µg/kg, IP, for one week after MA cessation) on protein levels of Iba-1 (a), GFAP (b) and COX-2 (c). The relative density was expressed as the ratio (Iba-1/β-actin, GFAP/β-actin, COX-2/β-actin). The differences between all experimental groups were determined by ANOVA followed by LSD test. Data represent Mean ± SEM. *p < 0.05, ** p < 0.01 and *** p < 0.01 vs. control group; #p < 0.05 vs. MA-treated group, (n = 3).

impairments, without any change in the euthyroid state. Some studies have reported an association between THs and neuropsychiatric disorders as well as cognitive dysfunctions in the patients with AD, even in a euthyroid state, and also shown the potential efficacy of adjunctive THs treatment in these patients (Choi et al., 2017; Chang et al., 2018). Another study has also found that central and peripheral administrations of T4 improves memory performance and amplifies brain electrical activity in the rat model of AD (Shabani et al., 2016). Biochemical and electrophysiological studies of thyroidectomized adult rats have also demonstrated that impaired memory due to hypothyroidism is associated with impairment of LTP in the hippocampus (Alzoubi et al., 2005), while T4 replacement therapy in these animals restores impaired LTP and cognitive deficits and also normalizes most of the molecular alterations (Gerges and Alkadhi, 2004). The exact mechanisms through which MA induces memory impairments are less studied currently. So, in this study, the effects of repeated MA administration on neurogenesis, synaptic plasticity, mitochondrial biogenesis, and neuroinflammation were investigated.

4.2. Neurogenesis

The findings revealed repeated MA administration reduced the expression of genes involved in neurogenesis (NES and DCX), and THs treatment could reverse these changes in the hippocampus of MA-treated animals. Neurogenesis persists throughout life but various agents such as abuse drugs may impair the production of new

functional neurons (Silva et al., 2010; Mandyam and Koob, 2012). At the present, the little information available points to MA effects on neurogenesis and survival of hippocampal neuronal cells. In this case, some studies have shown that MA administration significantly reduces neurogenesis, proliferation and survival of hippocampal cells in the adult experimental animals (Mandyam et al., 2008; Bento et al., 2011; Singhakumar et al., 2015). Furthermore, an in vitro study has indicated that MA decreases neurogenesis in the mouse dentate gyrus-derived neurosphere cultures without affecting cell proliferation (Baptista et al., 2012). Adult hippocampal neurogenesis impairments, particularly those evoked by psychostimulant drugs, have been consistently linked to deficits in cognitive functions (Canales, 2010). Also, it is established that decreased neurogenesis, especially in the rodent hippocampus, is associated with neurocognitive disorders such as AD (Hollands et al., 2016). Accordingly, MA-induced cognitive deficits in this study can be attributed to the impairments in hippocampal neurogenesis. In vivo and in vitro studies have provided evidence that THs regulate adult hippocampal neurogenesis (Desouza et al., 2005). In this case, Kapoor et al. (2012) have reported that thyroid hormone administration significantly increases DCX- and NeuroD positive hippocampal progenitors in the adult mice. Moreover, it has been shown that moderate degrees of developmental TH insufficiency decrease excitatory synaptic transmission, LTP and hippocampal-dependent memory in adult offspring (Gilbert and Sui, 2006; Gilbert, 2011; Gilbert et al., 2016).

4.3. Synaptic plasticity

Deficiencies in neurogenesis contribute to impairments in behavior and synaptic function (Gilbert, 2011; Gilbert et al., 2016). Reelin, as a modulator of synaptic plasticity, is essential for embryonic and adult brain development (Weeber et al., 2002). Numerous studies have linked decreased levels of Reelin mRNA and protein to the pathophysiology of neuropsychiatric and neurocognitive disorders like AD (Fatemi, 2001; Sáez-Valero et al., 2003; Doehner and Knuesel, 2010). However, little is known about Reelin's role for cognitive dysfunctions induced by MA. Cheng et al. (2015) have demonstrated that long-term MA exposure decreases the expression of synaptic plasticity genes in the frontal cortex and hippocampus of mice. It has been also indicated that hippocampal synaptic transmission and plasticity deficits are accompanied by impairments in hippocampal-dependent memory formation (Gilbert et al., 2016). A study has demonstrated that Reelin supplementation increases dendritic spine density, synaptic plasticity, hippocampal CA1 LTP and cognitive ability in wild-type mice (Rogers et al., 2011). Brosda et al. (2011) have also shown Reelin knockdown during puberty leads to behavioral alterations including object recognition and spatial working memory impairments in young adult rats. In accordance with these findings, our results indicated that MA reduces Reelin expression in the hippocampus of rats that can affect working and passive avoidance memory. While THs treatment partially increased the expression of Reelin in the MA-treated animals. Similarly, other studies have highlighted the protective effects of THs in the regulation of neuroplasticity and memory formation (Bauer et al., 2008; Koromilas et al., 2010). Also, reduced levels of brain-derived neurotrophic factor (BDNF) and Reelin have been reported as potential components in disrupted TH-mediated neuroplasticity in the developing rodent brain (Pathak et al., 2011; Gilbert and Lasley, 2013). These results suggest that an elevation of Reelin through THs treatment can have long-term effects on synaptic function and cognitive ability in MA-treated animals.

4.4. Neurotrophins

Neurotrophins are essential for hippocampal neurogenesis, synaptic plasticity (Sekine et al., 2008), and cognitive processes (Bruel-Jungerman et al., 2007; Vilar and Mira, 2016). In this case, Shimazu et al. (2006) have reported that NT-3 mutant mice indicate impairments in adult neurogenesis, hippocampal plasticity, and memory. Also, it is believed that NT-3 prominently stimulates dopaminergic neurons that involved in cognitive functions (Giordano et al., 1992). In this study, repeated MA administration slightly increased the protein level of NT-3 but it was not significant compared with control group. A study in rats has shown that MA exposure increases mRNA expression of BDNF (a neurotrophic factor) in the multiple brain areas, including prefrontal cortex (PFC) and hippocampus (Braun et al., 2011). Our findings suggest that NT-3 may be upregulated as a compensatory mechanism after repeated MA administration. But in the present study T4 treatment could enhance NT-3 level in the MA-treated rats. A study has demonstrated that TH is capable of inducing significant increases in the RNA levels of NT-3 and NGF in the hippocampus of adult rat brain (Giordano et al., 1992). Another study has also found that T3 administration improves cognitive functions in the rat model of ischemic brain stroke induced by upregulation of BDNF and GDNF in the hippocampus (Mokhtari et al., 2017).

4.5. Mitochondrial biogenesis

In the present study, increasing MA regimen decreased the expression of genes involved in mitochondrial biogenesis in the hippocampus of rats. A recent study has indicated mitochondrial biogenesis disturbance following chronic MA administration in rat hippocampus, which characterized by a reduction in mRNA levels of factors involved in mitochondrial biogenesis (Beirami et al., 2018). Other studies have also reported that MA-mediated degeneration can be dependent on mitochondrial mechanisms in vivo and in vitro (Deng et al., 2002; Gubert et al., 2016). It has been notably indicated that the ability of THs to regulate cellular metabolism is closely linked to their effects on mitochondrial activity and biogenesis (Weitzel and Iwen, 2011; Cheng et al., 2010). Some studies have shown that thyroid-stimulated mitochondrial biogenesis mediates through TH receptors placed in nuclear and mitochondrial compartments, which trigger a series of transcriptional and cell signaling events leading to a greater mitochondrial content (Cheng et al., 2010; Wrutniak-Cabello et al., 2001). Also, it has been shown that THs regulate mitochondrial biogenesis via its effect on many nuclear transcription factors namely PGC-1α, TFAM and NRF-1 (Weitzel and Iwen, 2011). In verification of these evidence, we observed that THs treatment partially enhanced the expression of factors involved in mitochondrial biogenesis, especially PGC-1α in the hippocampus of MA-treated animals. In this case, it has been shown that PGC-1α expression and protein level rapidly and strongly increase, respectively, 13-fold (Weitzel and Iwen, 2011) and 3-fold (Irrcher et al., 2003) 6 h after administration of T3. Besides, other studies reported that PGC-1α knock-out mice and PGC-1α knock-down in cell culture reveal alterations in mitochondrial biogenesis (Ventura-Clapier et al., 2008; Hock and Kralli, 2009) and defects in TH-mediated gene-expression patterns (Wulf et al., 2007), respectively. Also, it has been reported that the PGC-1α expression and/or function decreases in major neurodegenerative diseases such as AD (Qin et al., 2009; Sheng et al., 2012; Golpich et al., 2017). Regarding these finding, in this study, MA-induced cognitive impairments could be due to the decreased levels of mitochondrial biogenesis factors. In addition, induction or improvement of mitochondrial biogenesis by THs treatment provides a new neuroprotective approach.

4.6. Neuroinflammation

Different aspects of neuroinflammation, characterized by the activation of astroglia and microglia (GFAP and Iba-1 as markers, respectively), are believed to be contributory factors in MA toxicity. The enhanced levels of glial cells have been indicated after chronic MA exposure in the brain of rodents (McConnell et al., 2015; Beirami et al., 2017) and human MA abusers (Sekine et al., 2008; Kitamura et al., 2010). In accordance with these reports, we found that repeated increasing regimen of MA-induced glial activation through increased

GFAP and Iba-1 protein levels. Also, the level of COX-2 increased in the hippocampus of MA-treated animals.Activated astrocytes and microglia release pro-inflammatory cytokines that can exacerbate MA neurotoxicity (Thomas and Kuhn, 2005). It has been shown that the inhibition of neuroinflammation induced by psychostimulant drugs can be effective for decreasing the symptoms of these drugs (Snider et al., 2013). In the present study, it was interestingly observed that TH administration partially reduced the levels of glial cell markers and also COX-2 in the MA-treated animals. Indeed, TH alleviated neuroinflammation caused by MA. These findings are in line with a few reports that suggest THs are important factors that affect glial functions in the hippocampus (Mancini et al., 2016; Noda, 2015). In contrast, Schang et al. (2014) have indicated that THs treatment had no therapeutic effect to prevent inflammation-mediated white matter injury in the immature brain. Some studies have shown the involvement of inflammatory responses in neurogenesis impairment and cognitive disorders (Butovsky et al., 2006; Monje et al., 2003). For example, it has been reported that the elevated levels of brain pro-inflammatory cytokines are associated with hippocampal-dependent memory deficits and also AD (Wada-Isoe et al., 2004; Guerreiro et al., 2007). Moreover, Kim et al. (2012) have reported that impairments of spatial memory in vivo and synaptic plasticity in vitro are correlated closely with enhanced cytokine expression in mice. Another study has demonstrated that THs supplementation restores hippocampal markers of neuroinflammation, plasticity-related signaling molecules and cognitive abilities in hypothyroid rats (Chaalal et al., 2018). Further, it has been shown that T3 replacement improves neural functions and alleviates cognitive impairments in AD (Chaalal et al., 2018).

5. Conclusion

Our findings revealed that increasing MA regimen induced hippocampal-dependent cognitive deficits concomitant with impairments in neurogenesis, synaptic plasticity, and mitochondrial biogenesis. MA also induced neuroinflammation in the hippocampus of rats. Then it was interestingly observed that THs administration decreased cognitive deficits mediated by MA, which were associated with partial recovery of the neurogenesis, synaptic plasticity, and mitochondrial biogenesis impairments as well as neuroinflammatory responses. These findings suggest that THs could be considered as potential therapeutic candidates for further studies aimed at the treatment of cognitive deficits and other aversive symptoms correlated with MA abuse.

Conflict of Interest

The authors declare no conflict of interest.

Author contribution

All authors contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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