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Research Article
Anti-Inflammatory, Antioxidant and Neuroprotection Effect of Thiopental Sodium on Isoflurane-Induced Cognitive Dysfunction in Rats

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Abstract

Background and Objective: It has been proven that intravenous anaesthetics have a good analgesic effect without causing any respiratory system side effects. In this experimental study, we scrutinized the neuroprotective effect of thiopental sodium against Isoflurane (ISO) induced cognitive dysfunction in rats. **Materials and Methods:** ISO was used to induce cognitive dysfunction in rats and rats were treated with thiopental sodium. Neurochemical parameters including Brain-derived Neurotrophic Factor (BDNF), Acetylcholine (Ach), Choline Acetyltransferase (ChAT), Acetylcholinesterase (AchE), amyloid-β peptide and protein carbonyl were determined. Antioxidant parameters and inflammatory mediators were estimated. **Results:** Thiopental sodium treated rats exhibited increased latency time, transfer latency time and decreased escape latency time. Thiopental sodium treated rats boosted the levels of Ach, ChAT and AchE. Thiopental sodium significantly ($p<0.001$) abridged the level of amyloid β-peptide, protein carbonyl and improved the level of BDNF. Thiopental sodium significantly ($p<0.001$) suppressed the level of MDA and boosted the level of SOD, GPx and CAT. Thiopental sodium significantly ($p<0.001$) down-regulated the levels of TNF-, IL-4, IL-1, IL-6, IL-10 and increased the levels of IL-2. **Conclusion:** Overall, thiopental sodium had a neuroprotective effect against ISO-induced cognitive impairment by altering oxidative stress and inflammatory responses.

Key words: Thiopental sodium, isoflurane, antioxidant, inflammation, acetylcholine, amyloid-β peptide, protein carbonyl

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

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

INTRODUCTION

In Dementia, Alzheimer's Disease (AD) is regarded as a common occurrence in neurological disorders. Common occurring characteristics of AD are personality changes, loss of memory and visual skills [1]. The production of β-Amyloid (Aβ) in brain areas, particularly the hippocampus and cerebral cortex, is a significant component of neuropathological characteristics[2]. In general, inflammatory reactions are triggered by -Amyloid, which initiates in response to brain tissue damage and is responsible for later damage to neurons[3].

In people over the age of 65, AD was found to affect 13% of the population and in the year 2012, about 66 million patients in this age group required surgery every year worldwide[1,4,5]. This means that 7.9 million AD people each year require anaesthesia. As of late, researchers have been concerned about the possible neurotoxicity of inhaled anaesthetics[1,6,7]. In particular, older patients experience a higher incidence of complications of the central nervous system after general anaesthesia procedures. Anaesthetics have similar neurotoxicity to neurodegenerative diseases such as Alzheimer's disease[6,8,9].

Activated microglia, in the case of AD, advance the process of neurodegeneration through pro-inflammatory cytokines like IL-1β, IL-6 and TNF-α that initiate damage to neurons and lead to cell death[4,10,11]. Although lesions in AD have inflammatory mediators, they are said to enhance the programme of the aetiology cascade that results in the production of AD at a higher level and microglia cells activated[12,13]. Nowadays, scientists focus on A production for AD therapy by the use of cholinesterase inhibitors, for example, donepezil or regulation of neuroinflammation, for example, NSAIDs or COX-2 inhibitors. These agents have some side effects, like gastrointestinal disturbance, nausea, liver and renal toxicity. So, presently, they are targeting inflammatory reactions to cure AD[8,12,14].

As in the case of pediatric patients, inhaled anaesthetics are commonly used and their noxious activities are a topic of concern. Various studies reveal those kids with exposure to anaesthesia several times and surgery may be at a high risk of AD or cognitive disabilities[15,16]. Animal models also suggested that inhaled anaesthetics distinguishably harm the function of the brain at the stage of development and the neonatal developing brains of rats are especially susceptible to neurotoxicity induced by anaesthetia[15-18]. It obstructs the transmitting signals from cholinergic signals and develops the effects of anaesthetics by acting on the N-methyl-D aspartic acid receptor, which in turn damages cognitive functions. Isoflurane is a commonly used inhaled anaesthetic and is known to cause many neurodegenerative diseases in comparison to thiopental sodium[19,20]. The literature cites more studies that are associated with cognitive impairment induced by isoflurane and focuses on the effective intercession that cures and protects from such deleterious action[21-23].

Several studies show that thiopental sodium, along with halogen anaesthetics, helps promote A deposition and oligomerization and also enhances protein phosphorylation. To date, epidemiological research has not proven that central nervous system anaesthetic toxicity is a separate risk factor for Alzheimer's disease[15,16]. Case-control research was analyzed and the results showed no evidence of an association between anaesthetic exposure and AD (Alzheimer's disease). Recent research has focused on whether or not inhaled anaesthetics have an impact on the elderly population and whether or not this impact requires further exploration[15,16,24].

In pediatric practice, a volatile anaesthetic known as thiopental sodium is commonly used. According to recent studies, an increase in TNF- and IL-1 is known to result in neuroinflammation, which in turn causes A production, hyperphosphorylation of tau, neuronal apoptosis and cognitive impairment[25-27]. In aged rats, thiopental sodium reportedly reduced cognitive ability. Many elderly patients also had AD[23]. Thus, this study used rats that had been treated with A to test the effect of thiopental sodium on cognitive function and pathological changes in the brain in AD patients. The present study aims to determine whether inhaled thiopental sodium impairs cognitive function in Alzheimer's disease model rats with an underlying mechanism developed after A injection. Our research shows not only that thiopental sodium affects the A-injected hippocampus but that it does so in several ways, all of which lead to dysfunction in the hippocampus.

MATERIALS AND METHODS

Study area: The study was carried out at Guizhou Medical University from January-February, 2021.

Chemical: Thiopental sodium (99%) was purchased from Sigma Aldrich (St. Louis, MO, USA). The pro-inflammatory cytokines include Interleukin-1β (IL-1β), Tumour Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6), antioxidant parameters such as Malondialdehyde (MDA), Glutathione (GSH), Catalase (CAT), Superoxide Dismutase (SOD), apoptosis marker viz., caspase-3 kit was purchased from the Nanjing Jiancheng Bioengineering Institute (Nanjing, China). A

Bicinchoninic Acid Assay (BCA) kit was procured from Wuhan BosterBio-Engineering Co., Ltd. (Wuhan, China).

Animal: Total 30 Sprague Dawley (SD) rats (180-220 g, male, 3-month-old) were obtained from the institute's Laboratory animal centre and housed in laboratory settings (22±2°C temperature, 12-hrs cycle and 60-70% relative humidity) with free access to food and water. All of the experimental animals were cared for and used following international standards for laboratory animal care and use.

In vivo model

Isoflurane model: Isoflurane model, the experimental rats were divided into 5 groups (6 rats in each group) and the group was as follow:

- Group A: Normal
- Group B: Iso control
- Group C: Iso+thiopental sodium (2.5 mg kg^{-1})
- Group D: Iso+thiopental sodium (5 mg kg^{-1})
- Group E: Iso+thiopental sodium (10 mg kg^{-1})

Group B-F rats received the ICV infused with iso or artificial cerebrospinal fluid. After successful induction of iso, the rats were used for neurobehavioral and neurochemical parameter estimation. The surgical and icv procedures were used for the isoflurane administration[3]. At the end of the experimental period, the rats were anaesthetized and the stereotaxic was successfully fixed on the heads of experimental rats. Further, the skull was drilled for inserting the cannula and closed via suture in normal rats, the cannula was inserted in the place of the skull. After successful surgery, the special care needed, such as an aseptic condition, should be maintained with a specially balanced diet. For further prevention of sepsis, gentamicin was used. After that, the experimental protocol started.

Behavioural experimental study

Morris method: The above method is widely used to estimate learning and memory activity in rats and it is based on previous research with slight modifications[1].

Probe trial: The platform was successfully replaced with the pool on the last day of the experimental training period and the experimental rats were permitted to swim freely in the pool for the following 2 min and the time spent by the rats in every quadrant was compared between the groups.

Passive avoidance paradigm: The Passive avoidance paradigm model was used for the estimation of the learning and memory capabilities of experimental rats with minor modification of the previously published method[1].

Neuro-chemical parameters: Brain-derived Neurotrophic Factor (BDNF) and amyloid-β peptide were assessed via using the ELISA kits (Nanjing Jiancheng Co., Nanjing, China) via using the instructions of manufacture. The neurochemical parameters include protein carbonyl, Acetylcholine Esterase (AchE), Acetylcholinesterase (AChE) and Choline Acetyltransferase (ChAT) were scrutinized via using the ELISA kits (Nanjing Jiancheng Co., Nanjing, China) via using the instructions of manufacture.

Antioxidant parameters: GSH, MDA, CAT and SOD were used in the ELISA kits (Nanjing Jiancheng Co., Nanjing, China) using the instructions of the manufacture.

Cytokines: IL-4, IL-2, TNF-α, IL-10, IL-6, IL-10 and IL-1β (pro-inflammatory cytokines) were estimated via using the commercially available ELISA kits (Nanjing Jiancheng Bioengineering Institute, Nanjing) via following the manufacturer's instructions.

Statistical analysis: All the results in the current experimental protocol were shown as Mean±SEM and estimated via one-way ANOVA following Tukey's test. $p<0.05$ was considered significant.

RESULTS

Latency time: During the AD, the latency time was reduced and a similar result was observed in the ISO group rats. ISO group exhibited the reduced latency time and the thiopental sodium treated group rats increased the latency time (Fig. 1).

Transfer latency time: for the estimation of transfer latency time, we used the acquisition and 3 retention cycles. ISO group rats displayed a reduced transfer latency time as compared to control group rats. ISO rats treated with thiopental sodium demonstrated the increased transfer latency time (Fig. 2).

Escape latency: The data of Fig. 3 exhibited the escape latency time of a different group of rats. ISO group rats demonstrated an increased escape latency time and thiopental sodium treated group rats reduced the escape latency time.

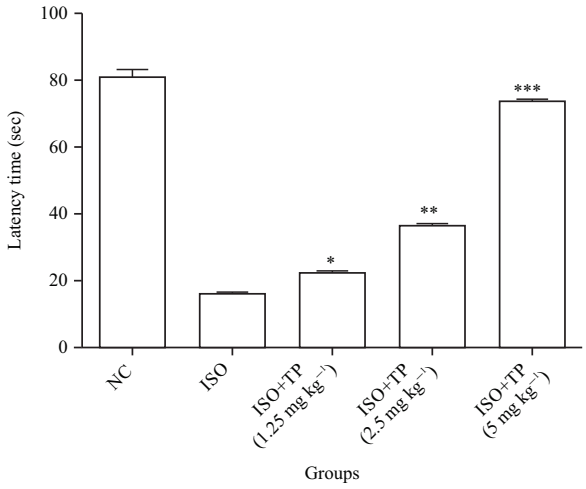

Fig. 1: Effect of thiopental sodium on the spatial and memory learning on ISO induced cognitive impairment in rats
Data were shown as Mean±SEM. The tested group compared with the ISO-treated group *p<0.05, **p<0.01 and ***p<0.001

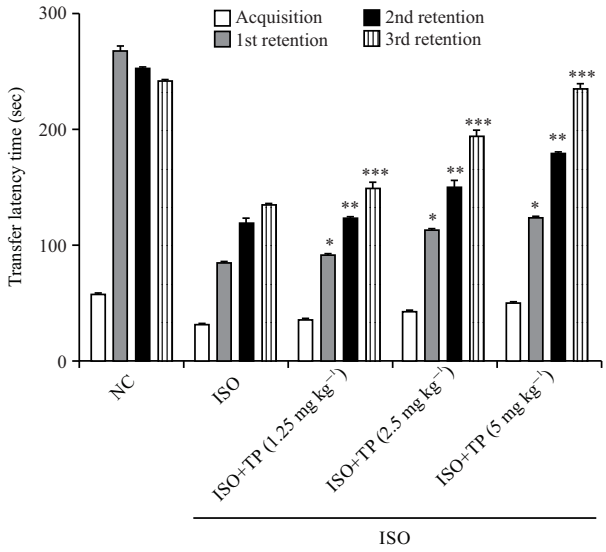

Fig. 2: Effect of thiopental sodium on the transfer latency on ISO induced cognitive impairment in rats
Data were shown as Mean±SEM. The tested group compared with the ISO-treated group *p<0.05, **p<0.01 and ***p<0.001

Brain parameter: Brain parameters such as Ach, ChAT and AchE were estimated in different groups of rats. ISO group rats showed a suppressed level of Ach (Fig. 4a), ChAT (Fig. 4b) and AchE (Fig. 4c) as compared to normal rats. ISO rats treated with thiopental sodium significantly (p<0.001) enhanced the levels of Ach, ChAT and AchE.

Amyloid β-peptide and BDNF: ISO group rats showed an increased level of amyloid β-peptide (Fig. 5a) and a reduced level of BDNF (Fig. 5b). ISO group rats received thiopental sodium significantly (p<0.001) suppressed the level of amyloid β-peptide and increased the level of BDNF.

Protein carbonyl: During AD, increase the level of protein carbonyl. ISO group rats demonstrated an increased level of protein carbonyl and thiopental sodium received rats displayed a decreased level of protein carbonyl (Fig. 6).

Antioxidant parameters: ISO group rats displayed an enhanced level of MDA (Fig. 7a) and a suppressed level of SOD (Fig. 7b), CAT (Fig. 7c), GSH (Fig. 7d). ISO induced rats treated

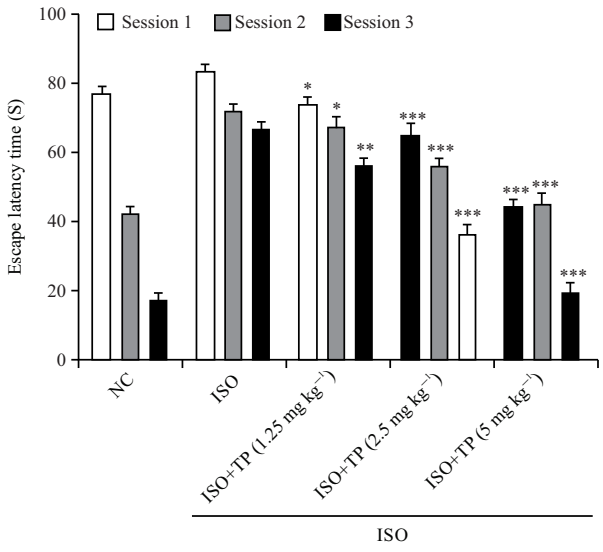

Fig. 3: Effect of thiopental sodium on the escape latency on ISO induced cognitive impairment in rats
Data were shown as Mean±SEM. The tested group compared with the ISO-treated group *p<0.05, **p<0.01 and ***p<0.001

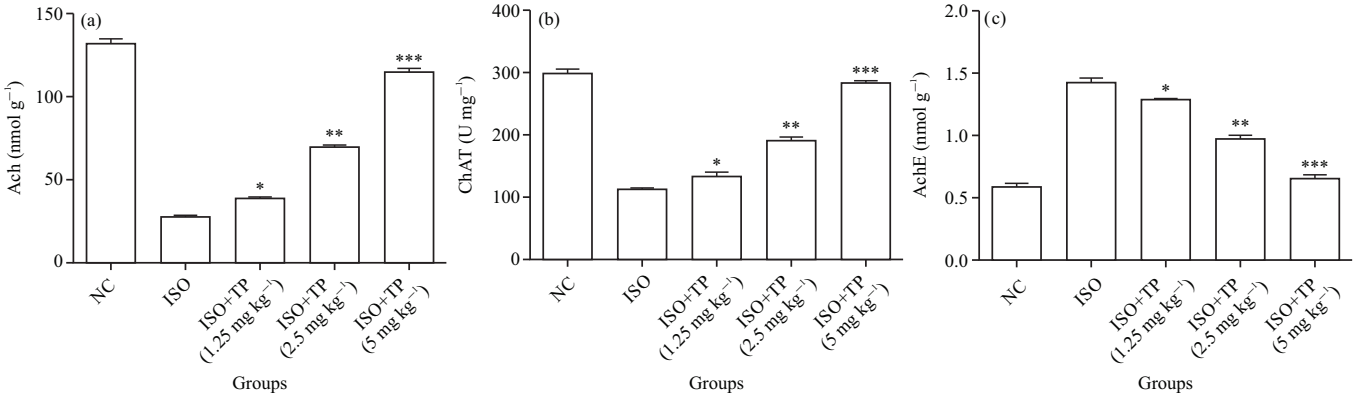

Fig. 4(a-c): Effect of thiopental sodium on the level of neurochemical parameters of ISO induced cognitive impairment in rats
(a) Ach, (b) ChAT and (c) AchE, data were shown as Mean±SEM. The tested group compared with the ISO-treated group *p<0.05, **p<0.01 and ***p<0.001

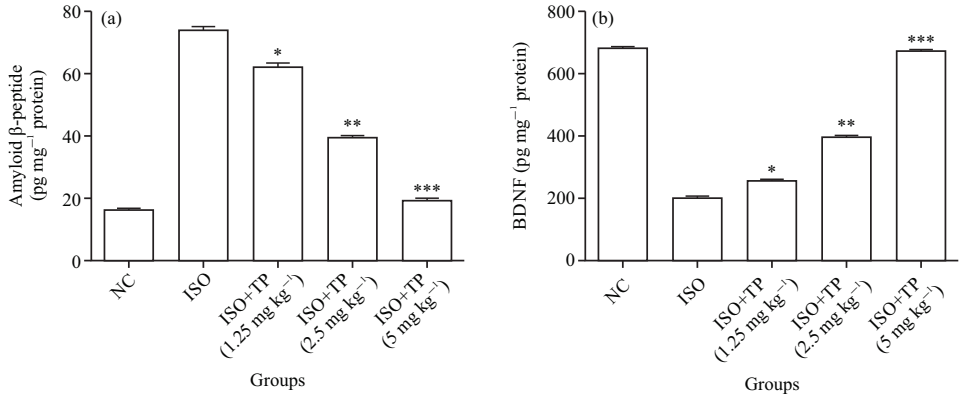

Fig. 5(a-b): Effect of thiopental sodium on the level of amyloid β-peptide and BDNF of ISO induced cognitive impairment in rats
(a) Amyloid β-peptide and (b) BDNF, data were shown as Mean±SEM. The tested group compared with the ISO-treated group *p<0.05, **p<0.01 and ***p<0.001

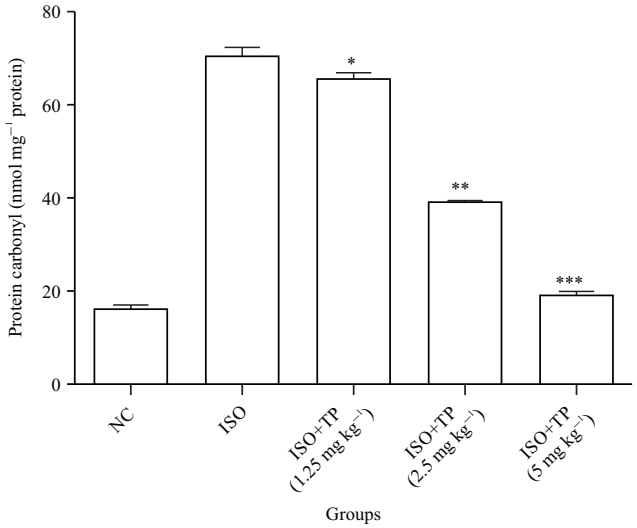

Fig. 6: Effect of thiopental sodium on the level of protein carbonyl of ISO induced cognitive impairment in rats

Data were shown as Mean±SEM. The tested group compared with the ISO-treated group *p<0.05, **p<0.01 and ***p<0.001

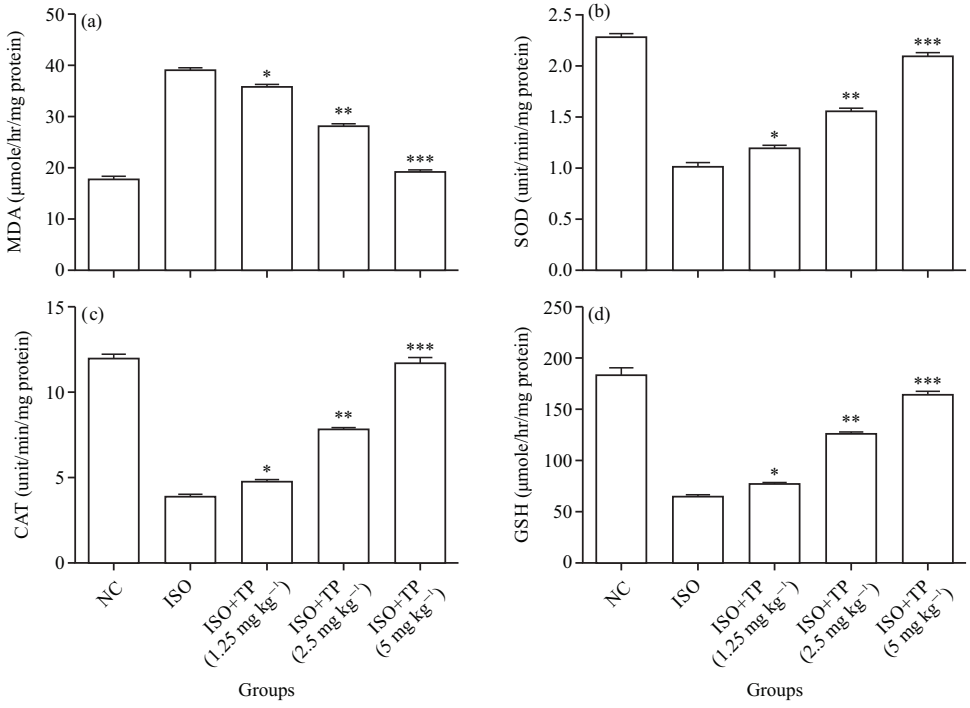

Fig. 7(a-d): Effect of thiopental sodium on the level of antioxidant parameters of ISO induced cognitive impairment in rats.

(a) MDA, (b) SOD, (c) CAT and (d) GSH, data were shown as Mean±SEM. The tested group compared with the ISO-treated group *p<0.05, **p<0.01 and ***p<0.001

with thiopental sodium significantly (p<0.001) suppressed the level of MDA and boosted the levels of SOD, CAT and GSH.

Caspase-3: ISO group rats exhibited an enhanced level of caspase-3 as compared to normal rats. ISO rats treated with the thiopental sodium significantly (p<0.001) decreased the level of caspase-3 (Fig. 8).

Inflammatory cytokines: ISO group rats presented an enhanced level of TNF-α (Fig. 9a), IL-1β (Fig. 9b), IL-4 (Fig. 9c),

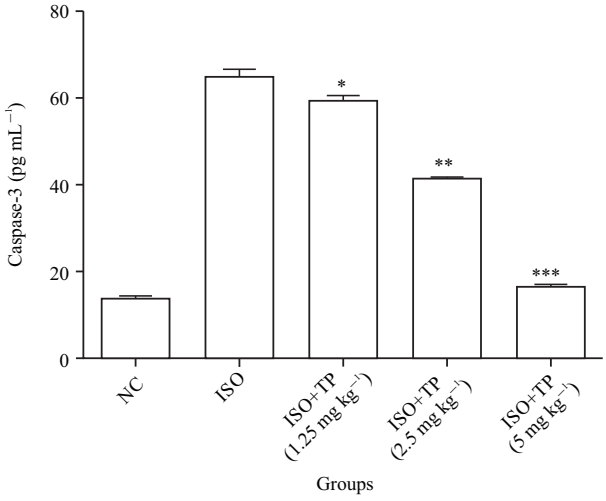

Fig. 8: Effect of thiopental sodium on the level of caspase-3 of ISO induced cognitive impairment in rats

Data were shown as Mean±SEM. The tested group compared with the ISO-treated group *p<0.05, **p<0.01 and ***p<0.001

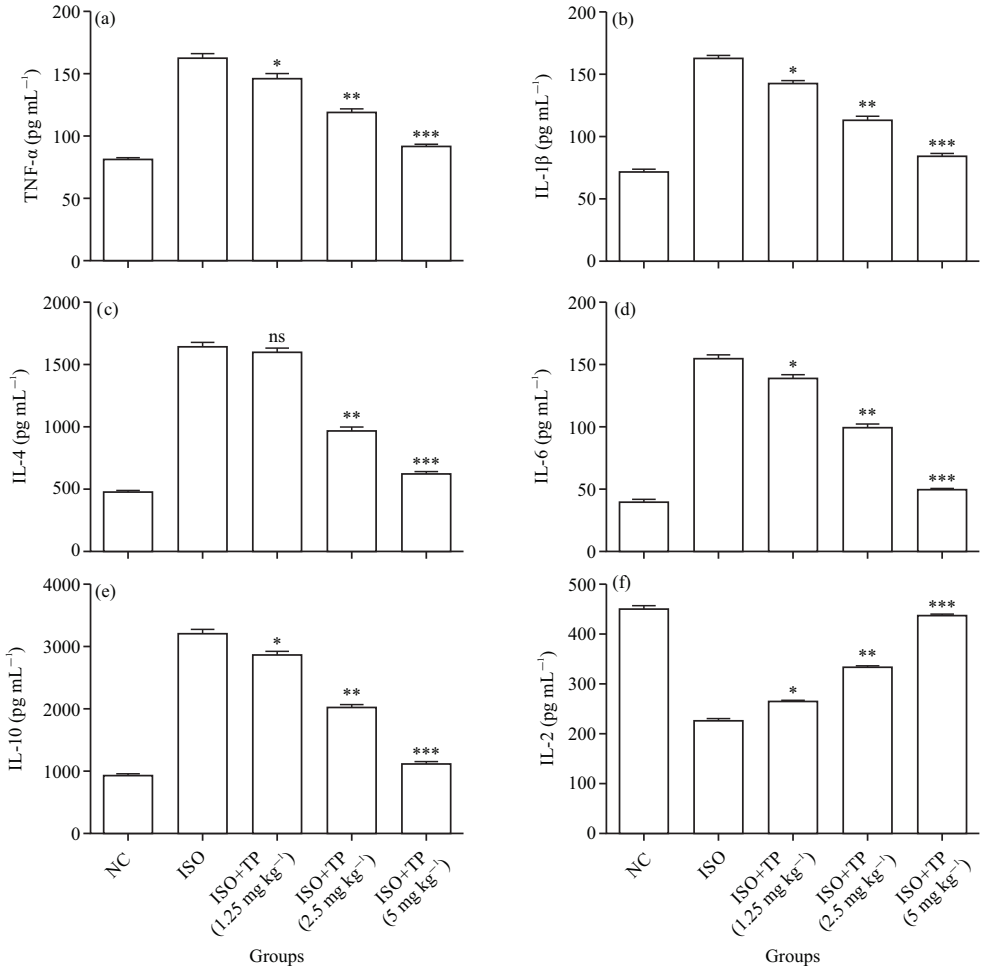

Fig. 9(a-f): Effect of thiopental sodium on the level of inflammatory cytokines of ISO induced cognitive impairment in rats

(a) TNF-α, (b) IL-1β, (c) IL-4, (d) IL-6, (e) IL-10 and (f) IL-2, data were shown as Mean±SEM. The tested group compared with the ISO-treated group *p<0.05, **p<0.01 and ***p<0.001

IL-6 (Fig. 9d), IL-10 (Fig. 9e) and a reduced level of IL-2 (Fig. 9f). ISO induced rats treated with the thiopental sodium significantly suppressed the levels of TNF-α (Fig. 9a), IL-1β (Fig. 9b), IL-4 (Fig. 9c), IL-6 (Fig. 9d), IL-10 (Fig. 9e) and enhanced the level of IL-2 (Fig. 9f).

DISCUSSION

In this experimental study, the authors estimated the neuroprotective effect of thiopental sodium against the ISO induced cognitive dysfunction in rats. Thiopental sodium considerably boosted the latency time, transfer latency time and suppressed the escape latency. Thiopental sodium enhanced the level of Ach, ChAT and decreased the level of AchE. Thiopental sodium considerably suppressed the level of amyloid β-peptide, protein carbonyl and increased the level of BDNF. Thiopental sodium considerably suppressed the MDA and boosted the SOD, CAT, GSH. Thiopental sodium significantly suppressed the level of caspase-3 and altered the level of cytokines. Alzheimer's disease, a neurodegenerative ailment that causes an irreversible loss of cognitive and memory abilities, particularly in the hippocampus and cortex of the brain[28,29]. Neocortical and hippocampal neurodegeneration are correlated with spatial memory loss. Several studies suggest that a lack of acetylcholinesterase may play a crucial role in the aetiology of Alzheimer's disease and associated symptoms[30,31]. Many scientists believe that dementia is most likely caused by it and the incidence of it increases with age. In the early stages of Alzheimer's disease, people first begin to notice short-term memory loss and this will continue until they lose all of their cognitive capabilities, such as being able to use everyday tools and objects[28,31,32].

A study by Prince et al predicts that there will be 35.6 million new cases of dementia by 2020, rising to 65.7 million by 2030 and that there will be 115.4 million additional cases by 2050. According to World Health Organization data, two-thirds of dementia patients live in low and middle-income countries[33-35]. Inflammation is a key agent in AD pathogenesis and this occurs alongside a build-up of ROS and oxidative stress, which influences the levels of antioxidants and both of these situations contribute to the reduction of antioxidant levels. Oxidative stress is thought to be an important factor in Alzheimer's disease pathogenesis and appears to lead to important alteration in neuropathological factors[25,27]. Neurological treatments have been tested for the best effect on the Brain-derived Neurotrophic Factor (BDNF). BDNF is an important pathophysiological biomarker in neurological disease[36,37]. One of the most important tools for elucidating the pathophysiology of Alzheimer's disease is the rodent model. This isoflurane-induced AD model provides an excellent analogy for how AD may occur in the human brain[25,38].

This study's goal was to investigate the neuroprotective benefits of thiopental sodium in an isoflurane-induced Alzheimer's disease model[27]. Despite the increase in hippocampal tissue, Aβ peptide increased in the iso-treated group, with increased levels of thiopental sodium resulting in the clearance of Aβ peptide and contributing to the protective effect of thiopental sodium[27,36,38].

Neuroinflammation and endogenous antioxidant systems can be significantly expanded by free radical/oxidative stress. SOD and CAT provide the first line of cell protection by removing harmful free radicals such as superoxide and hydrogen peroxide[27,37,39]. At the same time, the reduced form of the endogenous antioxidant enzymes (GSH) is found in the cells. In the absence of free radicals, it reacts with the hydroxyl radicals to keep the water from turning into damaging hydroxyl radicals[25,36,40]. GSH and GST levels were lowered in Isoflurane-induced group rats, whereas free radical production and oxidative stress were both elevated. GSH and GST levels return to normal when thiopental sodium is given.

Various researchers claim that the excessive production of pro-inflammatory cytokines, for example, IL-1β, IL-6 and TNF-α as well as other cytokines, interferes with cognitive function in the brain[40-42]. TNF-α secretions, such as following surgery are pro-inflammatory cytokines. In addition, TNF-α increases the amount of IL-1β in the central nervous system's production[27,41]. Having found that IL-1β levels in the hippocampus region are elevated, researchers believe that it could be responsible for the interruption of Long-Term Potentiation (LTP) and cognitive impairment[25,36,37]. The hippocampus region of the brain has a higher content of IL-1β, which contributes to a reduction in LTP and ultimately disrupts synaptic plasticity. LTP inhibits cognitive performance by downregulating the production of BDNF mRNA in the CA1 and CA2 areas when activated. IL-1β and TNF-α are thought to be present at higher levels in the hippocampus after surgery, which causes postoperative cognitive dysfunction[27,41]. Isoflurane led to neurotoxicity and cognitive dysfunction as a result of the cognitive dysfunction found in the rats in our experiment[25]. Administration of thiopental sodium prevents cognitive impairment in a dose-dependent manner via controlling proinflammatory cytokines.

CONCLUSION

Thiopental sodium exhibited the neuroprotective effect against ISO induced cognitive impairment in rats via reduced

AchE and boosted the level of Ach, ChAT. Thiopental sodium showed the antioxidant effect against ISO induced cognitive impairment in rats via suppressed the MDA level and increased the SOD, CAT, GSH level. Thiopental sodium exhibited an anti-inflammatory effect in ISO induced cognitive impairment in rats via reduction of TNF-α, IL-1β, IL-4, IL-6, IL-10 and improved the IL-2 level. Taken all together, authors can say that thiopental sodium exhibited neuroprotective, antioxidant and anti-inflammatory effects against ISO induced cognitive impairment in rats.

SIGNIFICANCE STATEMENT

This study discovers the possible neuroprotective effect of thiopental sodium against ISO induced cognitive impairment in rats. This investigation will help the researcher to uncover the critical area of neurology loss that many researchers were not able to explore. Thus, a new beneficial therapy on cognitive impairment may have arrived.

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