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Original Article

Effect of Sevoflurane and Isoflurane on Post-Anaesthesia Cognitive Dysfunction in Normal and Type II Diabetic Rats

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Abstract

Both animal and human studies have documented cognitive and behavioural impairment after exposure to inhalational anaesthetics. Therefore, the current study was designed to demonstrate if the anaesthetics isoflurane and Sevoflurane can result in postoperative cognition dysfunction in normal and diabetic rats. Sixty male Wister rats aged 12 weeks were divided into 6 groups (n=10); group C (standard control), group CD (diabetic control), group S (sevoflurane anaesthesia), group I (isoflurane anaesthesia), group SD (diabetic sevoflurane anaesthesia) group ID (diabetic isoflurane anaesthesia). Animals were anaesthetized with either 2. 5% sevoflurane or 1.5% isoflurane, respectively, for 2h. 1 week later, animals were undergone cognitive tests in (a Morris water maze, T maze and open field arena), the animals were sacrificed, and hippocampus homogenates were studied for caspase 3 activity by western blot assay. Induction of type II diabetes in CD, SD and ID groups was carried out by feeding on a high-fat diet for 8 weeks before the start of the experiment. During the fourth week, Type II diabetes was induced in the experimental group by a single IP injection of 30 mg/kg STZ. Control (normal and diabetic) rats showed no change in long-term/reference memory, non-spatial working memory, exploratory activity or caspase 3 expression in the hippocampus homogenate. Anaesthesia with isoflurane in normoglycemic rats resulted in a significant decline in long-term/reference memory and non-spatial working memory, while exploratory activity and caspase 3 expressions in hippocampus homogenate showed no change to normal control rats. Both isoflurane and Sevoflurane in diabetic rats demonstrated a decline in long-term/reference memory, non-spatial working memory, exploratory activity and caspase 3 expression in hippocampus homogenate compared with normal control rats. Diabetes revealed significant post-anaesthesia cognitive dysfunction after anaesthesia with Sevoflurane or isoflurane in all the studied domains compared to standard control or diabetic control.

Keywords: Sevoflurane, Isoflurane, Cognitive dysfunction, Diabetes mellitus

1. Introduction

Sevoflurane and isoflurane are among the commonly used volatile anaesthetics. Both give dose-dependent amnesia, sedation, and hypnosis sufficient for surgical procedures (1).

They are liquids at room temperature and atmospheric pressure, but they transformfrom liquid to gaseousphase as both have a high vapour pressure. Both have complex mechanisms of action involving numerous membrane proteins and ion channels, and their effect depends on the achievementof the therapeutic tissue concentration in the central nervous system (2).

They reach circulation and do their pharmacologic effects rapidly as they have direct absorption through the respiratory epithelium and mucous membranes of

the respiratory tract avoiding hepatic first-pass metabolism (3).

Cytochrome P450 enzymes metabolize Sevoflurane and isoflurane in the liver, kidney, and lungs. Their biotransformation significantly affects the toxicity of these drugs despite their little effect on their pharmacologic activity (3).

Many studies have revealed histopathological and temporary and long-term cognitive and behavioural effects on average or individuals with pre-existing cognitive dysfunction (4).

Postoperative cognitive dysfunction (POCD) means difficulties with memory, concentration and attention after surgery and anaesthesia that is often mild and only discovered by neuropsychological examinations or presented as memory loss, higher-level cognitive dysfunction, psychomotor disturbances, fine motor incoordination, dementia, delirium, or depression that may be associated with increased needs psychosocial support, and increased mortality (5).

Type II diabetes is a chronic metabolic disorder and is one of the most severe health problems worldwide. Main effects of Type II diabetes including insulin resistance, glucose dysregulation, autophagic pathway changes, and neuronal apoptosis, all increase the risk of neurodegenerative diseases and cognitive dysfunction (6).

The relation between Type II diabetes and neurodegenerative diseases and cognitive dysfunction is not fully explained; however, the inflammatory pathway and insulin resistance plays a central role in the development of this disease (7, 8).

Although the mechanism of postoperative cognitive dysfunction is not well known, one suggested mechanism is that amyloid beta (Aβ) is a peptide naturally present in the central nervous system (9), with higher levels in the ageing brain can interact with general anaesthetics and other perioperative factors increasing the risk for brain changes and postoperative cognitive dysfunction (10). Also, inflammation withan increase incytokines such as IL-6, TNF-α, IL-8, and IL-10 has a role inPOCD (11, 12). Free radicals may contribute to the pathway of POCD (13). So, antioxidant can ameliorate POCD (14). Sevoflurane and isoflurane anaesthetics lead to altered expression of post-synaptic density 95 (PSD-95) and extrasynaptic N-Methyl-D-aspartate (NMDA) receptor, change in synapse structure and function and calcium homeostasis (15). So an L-type calcium channel antagonist can protect against POCD, neuro-inflammation, and apoptosis (4).

The current study was designed to demonstrate if the anaesthetics isoflurane and Sevoflurane can result in postoperative cognition dysfunction in normal and diabetic rats.

2. Materials and Methods

2.1. Animals

Sixty male Wister rats aged 12 weeks weighing (200-250g), bred in the animal house of the pharmacology department of AL-Azhar University. The animals were allowed to acclimatize for 2 weeks before the experiment. The animals were housed in 4 per cage under controlled temperature (23±1°C) in polypropylene cages inside a well-ventilated room, with 40% humidity and a 12-hour light/dark cycle.

Sixty male Wister rats were divided into 6 groups; group C (standard control), group CD (diabetic control), group S (sevoflurane anaesthesia), group I (isoflurane anaesthesia), group SD (diabetic sevoflurane anaesthesia), group ID (diabetic isoflurane anaesthesia). They were fed a standard commercial pellet diet and water ad libitum. The diet comprises 71% carbohydrate, 18% protein, 7% fat, 4% salt mixture and adequate minerals and vitamins; the diabetic animals were fed a high-fat diet.

Animals anaesthetized with either 2.5% sevoflurane or 1.5% isoflurane, respectively, for 2h. 1 week later, animals were undergone cognitive tests in (Morris water maze, T maze and open field arena), after that animal was sacrificed, and hippocampus homogenates were studied for caspase 3 activity by western blot assay. Induction of type II diabetes in CD, SD and ID groups was carried out by feeding on a high-fat diet for

8 weeks. During the fourth week, Type II diabetes was induced in the experimental group by a single IP injection of 30 mg/kg ST in citrate buffer; Streptozotocin (STZ) was obtained from Sigma-Aldrich (St. Louis, MO).

2.2. Drugs and Chemicals

- Streptozotocin (STZ) was supplied by Sigma chemical company.
- Citrate buffer Ph 4.5 (citric acid+sodium citrate) in distilled water 0.1 mole supplied by (Merck KGaA, Darmstadt, Germany).
-TBST (tris-buffered saline (TBS) and Polysorbate 20) supplied by (Merck KGaA, Darmstadt, Germany.
-The bicinchoninic acid (BCA) reagents (Pierce, Rockford 11, USA)
- Isoflurane was supplied by (ABBOT, an American multinational medical devices and health care company USA).
-Sevoflurane was supplied by (Baxter healthcare corporation- USA).

2.3. Experimental Design

- This study was carried out on 60 male Wister rats aged 12 weeks weighing (200-250g).
- They were divided into 6 groups; each group included 10 rats.
- group C (standard control) served as the "Control group" and received a single intraperitoneal injection (IP) injection of citrate buffer in a volume equal to that used as a solvent for STZ to induce diabetes in test groups.
- group CD (diabetic control) included a person with diabetes who was injected with a single IP injection of a freshly prepared solution of streptozotocin in citrate buffer at 30 mg/kg.
- group S (sevoflurane anaesthesia)normoglycemic rats" anaesthetized by 2. 5% sevoflurane for 2h.
- a group I (isoflurane anaesthesia) normoglycemic rats" anaesthetized by 1. 5 % isoflurane respectively for 2h.
- group SD (diabetic sevoflurane anaesthesia)diabeticrats were injected with a single intraperitoneal injection of a freshly prepared solution of streptozotocin in citrate buffer in a dose of 30 mg/kg, then anaesthetized by 2.5% sevoflurane for 2h.
- group ID (diabetic isoflurane anaesthesia) diabeticrats were injected by single intraperitoneal injection of a freshly prepared solution of streptozotocin in citrate buffer in a dose of 30 mg/kg (16) and then anaesthetized by 1. 5 % isoflurane respectively for 2h.

The blood glucose concentration was measured 4 days after the STZ injection. The rats with blood glucose higher than 250 mg⁄dl were considered people with diabetes and were included in the experiment.

One week later, animals underwent cognitive tests (Morris water maze, T maze and open field arena) (Figure 1). Afterwards, animals were sacrificed, and hippocampus homogenates were studied for caspase 3 activity by western blot assay.

Figure 1. Open field arena

2.4. Morris Water Maze (MWM) Test

The MWM test measured the spatial learning and memory function of rats. Theblack water pool was 120 cm in diameter and 60 cm in height, filled withwater (45 cm in depth) of 20–24°C non-toxic water. The pool was in a quiet room with visual cues that rats could see for orientation (Figure 2). A transparent glass platform, 10 cm in diameter and 2 cm below the surface of the water, was placed in the center of one quadrant and remained in the same quadrant during the entire experiment. A computer with a management system was used to record the performance of rats. The training was performed

thrice daily for four consecutive days at 1 h intervals. In this 4-day training test, rats were softly put into the water at one of the four starting positions facing the pool wall and then swam freely to find the platform. The time spent by each rat to reach the submerged platform (escape latency) was recorded. After the rat reached the platform, it was allowed to stay on the platform for 15 s. If the rat could not reach the platform in 90 s, the test was ended, and its escape latency was recorded as 90 s; it was then guided to stay on the platform for 30 s. On the fifth day, the platform was removed, and the rat was allowed to swim freely for 90 s. The time spent in the target quadrant was measured. All the trials were performed between 8:00 a. m. and 5:00 p. m. (17).

Figure 2. Morris Water Maze

2.5. T Maze

T Maze Spontaneous Alternation is a behavioural test measuring exploratory animal behaviour, especially rodent models for CNS disorders (Figure 3). This test is based on the willingness of rodents to explore a new environment, i. e. they prefer to visit a new arm of the maze rather than a familiar arm. Many parts of the brain including the hippocampus, septum, basal forebrain, and prefrontal cortex- are involved in this task.

Figure 3. T Maze

2.6. Open Field Arena

The open-field test is widely used to test mice and rats' exploratory behaviour and general activity (20). The open field consists of a plastic board (1.20 m×1.20 m) surrounded by black plastic walls (50 cm in height). The rats were placed in the arena and allowed to explore it for 10 min. The movements were recorded by a video tracking system and stored on a computer. Considered as the ratio between distance travelled (m) and the time the animals did not move(s) OFRDR, local movements (OFlocal, <10 cm/s) and the average velocity of movement (OFveloc; m/s). The usually used variables of the ratio of the time spent in the central and peripheral part of the arena to assess the motivation to explore unsafe areas voluntarily were not considered because there was minimal variability between animals. Thus they do not provide information about individuality and unnecessarily increase the number of variables in the PCA. In order to provide information about the readiness to enter unsafe areas, the number of entries in open arms of the elevated plus maze test has been considered (21).

2.7. Preparation of Tissue Sample

Overnight fasted rats were deeply anaesthetized. In each group, the rats were decapitated, and the hippocampus was softly isolated from the brain and washed with 0. 9% cold saline three times. The tissues were stored at -80°C until analyzed. The hippocampus was used for Western blot.

2.8. Detection of Caspase-3 Activity

The activity of caspase-3 in cells and tissues can be detected by several methods, such as immunostaining or immunoblotting and colourimetric, and we performed a western blot experiment. Western blot experiment, or Western blotting, is a routine technique for protein analysis; total protein was extracted according to the instructions of the kit and protein concentration was measured by the BicinchoninicAcid(BCA) protein quantification method. (The BicinchoninicAcid(BCA)Pierce, Rockford 11, USA). Protein samples were stored at −70°C before use. Gel electrophoresis was performed

with 10% separation and 5% concentration gel. The positions of the two proteins were determined according to the bands of the marker. After the transmembrane, the membrane was washed with TBST (Tris-Buffered Saline (TBS) and Polysorbate 20) solution for 5 min. After blocking with 5% skim milk at room temperature for 1 h, the membrane was cultured with primary antibody (1:1,000) at room temperature overnight. After that, the membrane was washed 3 times with TBST(5 min each time), followed by incubation with a secondary antibody(1: 1,000) at room temperature for 1 h. The membrane was washed 3 times with TBST (5 min each time). Then, colour development was performed using ElectrochemicalluminescenceECL luminescent liquid in the dark for 2 min. Finally, results were scanned using Multi Gauge Ver. 3. 0 imaging system, ImageJ professional image analysis software was used for image analysis, and OD value was recorded (22).

2.9. Statistical Analysis

Statistical analyses were conducted using a one-way ANOVA test to check the significance of observations obtained from model simulations with various combinations of physics schemes; hereafter termed treatments. Results from ANOVA were reported with 90% confidence intervals and were deemed significant at $P<0.05$. Tukey's post-hoc test is further used to test the significant difference between any two treatment means.

3. Results

Control diabetic rats showed no change in long-term/reference memory, non-spatial working memory, exploratory activity or caspase 3 expression in the hippocampus homogenate. The same previous results were demonstrated after sevoflurane anaesthesia in normoglycemic rats.

Anaesthesia with isoflurane in normoglycemic rats resulted in a significant decline in long-term/reference memory, and non-spatial working memory while exploratory activity and caspase 3 expressions in hippocampus homogenate showed no change as compared to normal control rats. Anaesthesia with either Isoflurane or Sevoflurane in diabetic rats demonstrated a decline in long-term/reference memory, non-spatial working memory, exploratory activity and caspase 3 expression in hippocampus homogenate as compared with normal control rats (Figures 4-8).

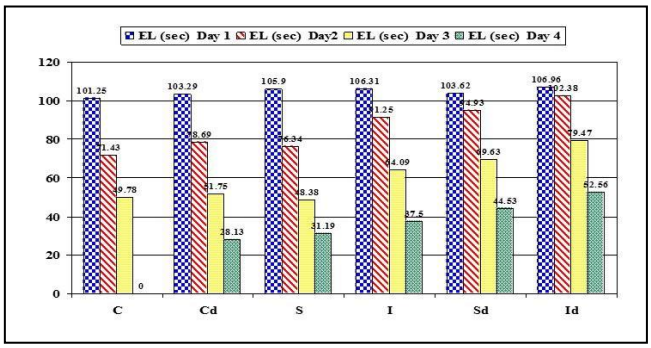

Figure 4. Effect of isoflurane and sevoflurane anaesthesia in normal and type II diabetic mice on mean escape latency (EL) in seconds using Morris water maze
Values are expressed as Mean±SDM. Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test.
**P*<0. 05 as compared to the control
+*P*<0. 05 as compared to the I group

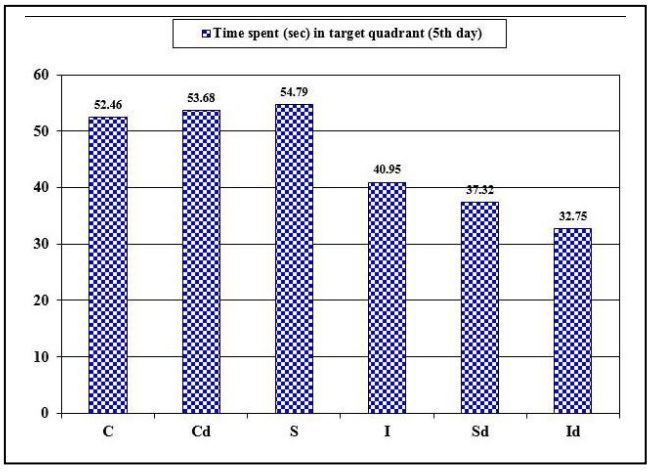

Figure 5. Effect of isoflurane and sevoflurane anaesthesia in normal and type II diabetic mice on time spent in target quadrant using Morris water maze
N=10 Values are expressed as Mean±SDM. Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test.
**P*<0.05 as compared to the control
+*P*<0.05 as compared to the I group

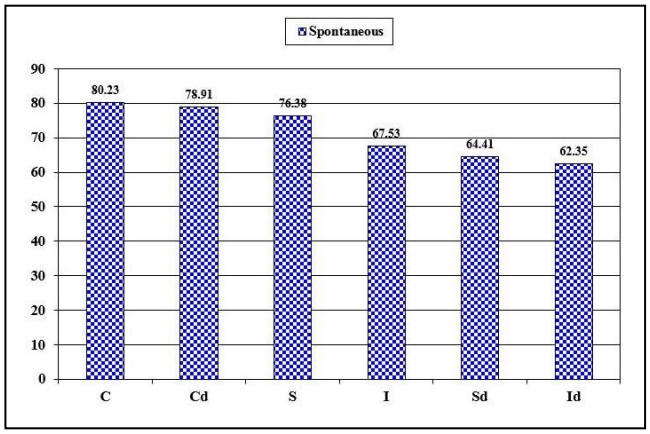

Figure 6. Effect of isoflurane and sevoflurane anaesthesia in normal and type II diabetic mice on non-spatial working memory using T maze in mice
n=10 Values are expressed as Mean±SDM. Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test.
**P*<0.05 as compared to the control
+*P*<0.05 as compared to the I group

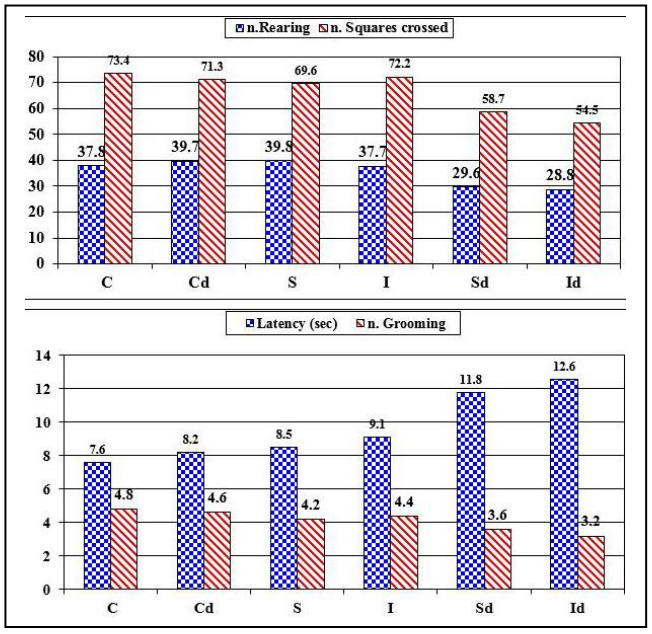

Figure 7. Effect of isoflurane and sevoflurane anaesthesia in normal and type II diabetic mice on non-spatial working memory using T maze in mice
n=10 Values are expressed as Mean±SDM. Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test.
**P*<0.05 as compared to the control
+*P*<0.05 as compared to the I group

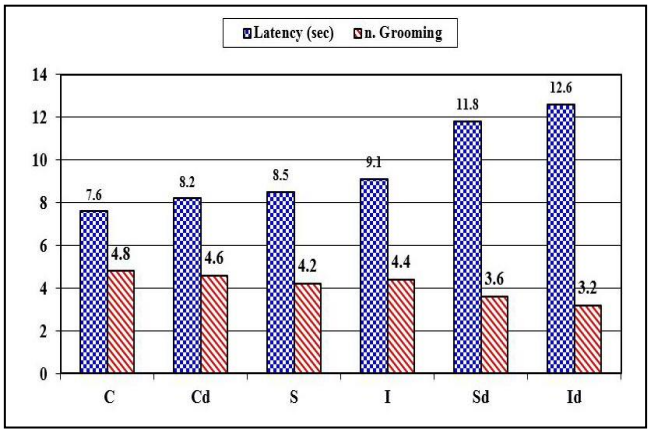

Figure 8. Effect of isoflurane and sevoflurane anaesthesia in average and type II diabetic mice on activated caspase 3 density in mice hippocampus homogenate
n=10 Values are expressed as Mean±SDM. Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test
**P*<0.05 as compared to control

4. Discussion

Many patients experience memory, concentration and attention difficulties after surgery and anaesthesia, referred to as postoperative cognitive dysfunction (POCD). These cognitive changes are usually short-lived, with a standard function returning within a few days (23).

The incidence of POCD after surgery is variable, as high as 26% at one week, 10% at three months, 5% at six months, and 1% at 12 months after non-cardiac surgery but as high as 53%, 36%, 24%, and 42%at discharge, six weeks, six months, and five years, respectively, after cardiac surgery (24).

The difference in POCD incidence might be due to different parameters used in determining POCD because the definition of POCD still (25).

In the present study, we compare the effect of the volatile anaestheticssevoflurane and isoflurane on post-anaesthesia cognitive dysfunction in average and type II diabetic rats.

Our study found that control diabetic rats showed no change in long-term/reference memory, non-spatial

working memory, exploratory activity or caspase 3 expression in the hippocampus homogenate.

Also, sevoflurane anaesthesia in nondiabetic rats showed no change in long-term/reference memory, non-spatial working memory, exploratory activity or caspase 3 expression in the hippocampus homogenate.

That is in contrast with a prospective randomized trial in spinal surgery and clinical cognitive outcomes at 1 year by Tang, Ou (26), who found that Sevoflurane had been associated with an enhanced cognitive impairment.

Our results are also contradicted by the study of Cui, Wang (27), who postulated that sevoflurane anaesthesia alters cognitive function by activating inflammation and cell death in nondiabetic rats.

In our study, anaesthesia with isoflurane in nondiabetic rats resulted in a significant decline in long-term/reference memory and non-spatial working memory, while exploratory activity and caspase 3 expressions in hippocampus homogenate showed no change as compared to normal control rats. This result is supported by Callaway, Wood (28), who found that isoflurane in the presence or absence of surgery increases hippocampal cytokines associated with memory deficits and responses to brain injury in rats.

In the present study, we found that anaesthesia with either Isoflurane or Sevoflurane in diabetic rats demonstrated a decline in long-term/reference memory, non-spatial working memory, exploratory activity and caspase 3 expression in hippocampus homogenate as compared with normal control rats that are supported by Sun, Li (29)who found that, the level of IL-1β as a proinflammatory cytokine is remarkably increased in the hippocampus of Type II diabetes rats. However, Zheng, Meng (30) found no effect of isoflurane or sevoflurane anaesthesia alone on microglial activation and/or proinflammatory cytokine expression.

Li, Liu (31) reported that Sevoflurane induces an exaggerated and persistent cognitive decline in Type II diabetic rats.

Our results are consistent withDong, Zhang (32), who reported that the concentrations of halothane and isoflurane caused aggregation of amyloid peptides in cell cultures, indicating that they brought cytotoxicity to the brain; Sevoflurane also showed the same cytotoxic effect, so both cause cognitive dysfunction.

However,Valentim, Alves (33)showed that Inhalation anaesthetics had a protective effect on postoperative cognitive function, as this study found that 2% isoflurane was associated with better postoperative performance than 1% isoflurane in postoperative cognitive function testing. Also,Schoen, Husemann (34) reported that the depth of anaesthesia played an essential role in postoperative cognitive function.

The effect of depth of anaesthesia on cognitive impairment has also been proposed as a potential risk factor for POCD. A meta-analysis recently compared cognitive outcomes in patients receiving low vshigh-depth anaesthesia as measured by bispectral index(BIS) monitoring. Included studies used either propofol or isoflurane. The authors concluded that the depth of anaesthesiadid not significantly impact the risk of POCD (27).

Royse, Andrews (35) study found that patients receiving propofol-based anaesthesiahad a lower incidence of POCD than those receiving Sevoflurane or desflurane.

Bianchi, Tran (36) postulated that volatile anaesthesia alone has either a minor or no effect on rodent learning and memory in the absence of other risk factors such as age or genetic predisposition.

Authors' Contribution

Study concept and design: E. A.
Acquisition of data: E. M. T.
Analysis and interpretation of data: A. M. T.
Drafting of the manuscript: M. S. A.
Critical revision of the manuscript for important intellectual content: E. A.
Statistical analysis: E. M. T.

Administrative, technical, and material support: A. M. T.

Ethics

The animals were handled according to the guidelines of the local ethical committee, which comply with international laws for the use and care of laboratory animals.

Conflict of Interest

The authors declare that they have no conflict of interest.

Significance of the Study

This study provided evidence that isoflurane leads to post-anaesthesia cognitive dysfunction in average and type II diabetic ratsandSevoflurane leads to post-anaesthesia cognitive dysfunction in type II diabetic rats only.

References

1. Evers AS, Maze M, Kharasch ED. Anesthetic pharmacology: Basic principles and clinical practice: Cambridge University Press; 2011.
2. Butterworth JF, Mackey DC, Wasnick JD. Morgan and Mikhail's clinical anesthesiology: McGraw-Hill Education; 2018.
3. Martin J, Njoku D. Metabolism and toxicity of modern inhaled anesthetics. Miller RD: Philadelphia, Elsevier Churchill Livingstone. 2005:231-72.
4. Zhang Q, Li Y, Bao Y, Yin C, Xin X, Guo Y, et al. Pretreatment with nimodipine reduces incidence of POCD by decreasing calcineurin mediated hippocampal neuroapoptosis in aged rats. BMC Anesthesiol. 2018;18(1):1-7.
5. Ruxanda F, Miclaus V, Rus V, Gal AF, Oana L. Impact of isoflurane and sevoflurane anesthesia on kidney structure and function in rats. Bull Univ Vet Med. 2014;71(2).
6. Candeias E, Sebastião I, Cardoso S, Carvalho C, Santos MS, Oliveira CR, et al. Brain GLP-1/IGF-1 signaling and autophagy mediate exendin-4 protection against apoptosis in type 2 diabetic rats. Mol Neurobiol. 2018;55(5):4030-50.
7. Ribe E, Lovestone S. Insulin signalling in Alzheimer′ s disease and diabetes: from epidemiology to molecular links. J Intern Med. 2016;280(5):430-42.
8. Tang N, Jiang R, Wang X, Wen J, Liu L, Wu J, et al. Insulin resistance plays a potential role in postoperative cognitive dysfunction in patients following cardiac valve surgery. Brain Res. 2017;1657:377-82.
9. Eckenhoff RG, Johansson JS, Wei H, Carnini A, Kang B, Wei W, et al. Inhaled anesthetic enhancement of amyloid-β oligomerization and cytotoxicity. J America Soc Anesthesiol. 2004;101(3):703-9.
10. Wan Y, Xu J, Meng F, Bao Y, Ge Y, Lobo N, et al. Cognitive decline following major surgery is associated with gliosis, β-amyloid accumulation, and τ phosphorylation in old mice. Crit Care Med. 2010;38(11):2190-8.
11. Kline R, Wong E, Haile M, Didehvar S, Farber S, Sacks A, et al. Peri-operative inflammatory cytokines in plasma of the elderly correlate in prospective study with postoperative changes in cognitive test scores. Int J Anesthesiol Res. 2016;4(8):313.
12. Zheng B, Lai R, Li J, Zuo Z. Critical role of P2X7 receptors in the neuroinflammation and cognitive dysfunction after surgery. Brain Behav Immun. 2017;61:365-74.
13. Zhang C, Zhang Y, Shen Y, Zhao G, Xie Z, Dong Y. Anesthesia/surgery induces cognitive impairment in female Alzheimer's disease transgenic mice. J Alzheimers Dis. 2017;57(2):505-18.
14. Wu J, Zhang M, Li H, Sun X, Hao S, Ji M, et al. BDNF pathway is involved in the protective effects of SS-31 on isoflurane-induced cognitive deficits in aging mice. Behav Brain Res. 2016;305:115-21.
15. Ling Y-z, Ma W, Yu L, Zhang Y, Liang Q-s. Decreased PSD95 expression in medial prefrontal cortex (mPFC) was associated with cognitive impairment induced by sevoflurane anesthesia. J Zhejiang Univ Sci B. 2015;16(9):763-71.
16. Arora S, Ojha SK, Vohora D. Characterisation of streptozotocin induced diabetes mellitus in swiss albino mice. Glob J Pharmacol. 2009;3(2):81-4.
17. Morris R. Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods. 1984;11(1):47-60.
18. Bizot J-C, Le Bihan C, Puech AJ, Hamon M, Thiébot M-H. Serotonin and tolerance to delay of reward in rats. Psychopharmacology. 1999;146(4):400-12.

19. Walton M, Kennerley SW, Bannerman D, Phillips P, Rushworth MF. Weighing up the benefits of work: behavioral and neural analyses of effort-related decision making. NN. 2006;19(8):1302-14.
20. Crusio WE. Genetic dissection of mouse exploratory behaviour. Behav Brain Res. 2001;125(1-2):127-32.
21. Carola V, D'Olimpio F, Brunamonti E, Mangia F, Renzi P. Evaluation of the elevated plus-maze and open-field tests for the assessment of anxiety-related behaviour in inbred mice. Behav Brain Res. 2002;134(1-2):49-57.
22. He X, Sun J, Huang X. Expression of caspase-3, Bax and Bcl-2 in hippocampus of rats with diabetes and subarachnoid hemorrhage. Exp Ther Med. 2018;15(1):873-7.
23. Ramaiah R, Lam AM. Postoperative cognitive dysfunction in the elderly. Anesthesiol Clin. 2009;27(3):485-96.
24. Needham MJ W, Bryden DC. Postoperative cognitive dysfunction and dementia: what we need to know and do. Br J Anaesth. 2017;119:i115-i25.
25. Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levitsky S, et al. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. Acta Anaesthesiol Scand. 2010;54(6):663-77.
26. Tang N, Ou C, Liu Y, Zuo Y, Bai Y. Effect of inhalational anaesthetic on postoperative cognitive dysfunction following radical rectal resection in elderly patients with mild cognitive impairment. J Int Med Res. 2014;42(6):1252-61.
27. Cui R-S, Wang K, Wang Z-L. Sevoflurane anesthesia alters cognitive function by activating inflammation and cell death in rats. Exp Ther Med. 2018;15(5):4127-30.
28. Callaway JK, Wood C, Jenkins TA, Royse AG, Royse CF. Isoflurane in the presence or absence of surgery increases hippocampal cytokines associated with memory deficits and responses to brain injury in rats. Behav Brain Res. 2016;303:44-52.
29. Sun X, Li S, Xu L, Wang H, Ma Z, Fu Q, et al. Paeoniflorin ameliorates cognitive dysfunction via regulating SOCS2/IRS-1 pathway in diabetic rats. Physiol Behav. 2017;174:162-9.
30. Zheng J, Meng B, Li X, Lu B, Wu G, Chen J. NF-kappaB/P65 signaling pathway: a potential therapeutic target in postoperative cognitive dysfunction after sevoflurane anesthesia. Eur Rev Med Pharmacol Sci. 2017;21(2):394-407.
31. Li D, Liu L, Li L, Li X, Huang B, Zhou C, et al. Sevoflurane induces exaggerated and persistent cognitive decline in a type II diabetic rat model by aggregating hippocampal inflammation. Front Pharmacol. 2017;8:886.
32. Dong Y, Zhang G, Zhang B, Moir RD, Xia W, Marcantonio ER, et al. The common inhalational anesthetic sevoflurane induces apoptosis and increases β-amyloid protein levels. Arch Neurol. 2009;66(5):620-31.
33. Valentim AM, Alves HC, S Olsson IA, Antunes LM. The effects of depth of isoflurane anesthesia on the performance of mice in a simple spatial learning task. J Am Assoc Lab Anim Sci. 2008;47(3):16-9.
34. Schoen J, Husemann L, Tiemeyer C, Lueloh A, Sedemund-Adib B, Berger K-U, et al. Cognitive function after sevoflurane-vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. Br J Anaesth. 2011;106(6):840-50.
35. Royse C, Andrews D, Newman S, Stygall J, Williams Z, Pang J, et al. The influence of propofol or desflurane on postoperative cognitive dysfunction in patients undergoing coronary artery bypass surgery. Anaesthesia. 2011;66(6):455-64.
36. Bianchi SL, Tran T, Liu C, Lin S, Li Y, Keller JM, et al. Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics. Neurobiol Aging. 2008;29(7):1002-10.