Mechanism of cognitive dysfunction induced by isoflurane mediated by activated TGFβ/Smad signaling pathway

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ABSTRACT

Objective: To explore the mechanism of cognitive dysfunction induced by isoflurane mediated by activated TGFβ/Smad signaling pathway. Methods: A total of 120 patients in our hospital received anesthesia by isoflurane were analyzed. The cognitive function in each patient was assayed by MMSE before anesthesia and after anesthesia induction at different time points. The expression of TGFβ/Smad signaling pathway related proteins were detected by Western Blotting. 60 cases of healthy subjects in our hospital at the same period were taken as control. Results: The results showed that the cognitive dysfunction exits in patients received isoflurane anesthesia when compared with control patients. The results also showed that the expression of TGFβ, Smad3 and Smad 7 was enhanced dramatically with a statistical difference when compared with control. Conclusion: Activated TGFβ/Smad signaling pathway participates in isoflurane anesthesia induced cognitive dysfunction.

1. Introduction

In clinic work, isoflurane is commonly used for inhalation anesthetics because it can induce sympathetic nervous system excitement without causing major liver toxicity[1-3]. Cognitive dysfunction refers to central nervous system abnormalities after undergoing anesthetics or surgery which may affect patients' life seriously[4,5]. Till now, the mechanism, epidemiology, etiology characters remains unclear. Previous study showed that cognitive dysfunction occurred among patients underwent isoflurane anesthesia. It’s believed that TGF beta/Smad pathway, a widely existed signal pathway, involved with a variety of pathological process[6-8]. This study aims to analyze the role of TGF beta/Smad pathway in the occurrence of short-term postoperative cognitive dysfunction.

2. Materials and methods

2.1. General data

A total of 120 patients underwent isoflurane anesthesia from October 2011 to October 2014 in our hospital were enrolled as study group including 62 males and 58 females with an average age of (59.5±11.4) years. 60 healthy volunteers were also enrolled as control group. In the control group there were 31 males and 29 females with an average age of (59.9±12.7) years. Before undergoing the surgery, patients with MMSE score less than 24 or have auditory or visual impairment were excluded. There was no significant difference in ratio of male and female, average age, height, weight (P>0.01).

2.2. Observed indexes

MMSE scale was used to evaluate patients’ cognitive function at different time points. Expression levels of TGF beta 1, Smad3 and Smad7 TGF which are involved in the beta/Smad signaling pathways were detected by Western Blotting analysis.
2.3 Expression of molecular targets by Western Blotting analysis

Total protein contents were determined by kjeldahl nitrogen kjeldahl nitrogen instrument, then equal quantity of proteins were collected from each group for vertical polyacrylamide gel electrophoresis separation in order to get proteins with different molecular weights, which were then transferred to nitrocellulose membrane by gelatin with half dry gel film method. The nitrocellulose membrane was sealed with 3.0% fetal bovine serum for 4 h, then washed by PBS for 3 times for quantitative analysis of protein expression levels.

2.4. Statistical analysis

All the data were analyzed with SPSS 19.0 software. Data were expressed as (Mean±SD). Comparisons were analyzed with variance method and P<0.05 was considered as statistically significant.

3. Results

3.1. EES score of cognitive dysfunction in patients underwent isoflurane anesthesia

There was no significant difference in cognitive function between the two groups (P>0.05). But for the observation group, significant changes in MMSE score was found after undergoing isoflurane anesthesia comparing with the score before undergoing the anesthesia (P<0.05 or P<0.01) (Figure 1).

3.2. Changes in TGF beta 1 expression level in patients underwent isoflurane anesthesia

It was found that protein expression of TGF beta 1 was significantly increased comparing with that before undergoing the isoflurane anesthesia (P<0.05 or P<0.01). But no significant difference in the expression level was found between the observation group and the control group before undergoing isoflurane anesthesia (P>0.05) (Figure 2).

3.3. Changes in expression level of protein Smad3 in the observation group after undergoing isoflurane anesthesia

Expression of protein Smad3 was significantly increased comparing with the expression level before undergoing the anesthesia (P<0.05 or P<0.01). But no significant difference in the expression level of protein Smad3 was found between the observation group and the control group before undergoing isoflurane anesthesia (P>0.05) (Figure 3).

It was found that protein expression of Smad3 was significantly increased comparing with that before undergoing the isoflurane anesthesia (P<0.05 or P<0.01). But no significant difference in the expression level was found between the observation group and the control group before undergoing isoflurane anesthesia (P>0.05) (Figure 4).
such as undergoing surgery or anesthetics, and its mechanism is still not complete clear till now[9,10]. Previous studies have proved that isoflurane anesthesia can induce cognitive dysfunction[11]. In this study, we found short-term cognitive dysfunction existed in patients undergoing isoflurane inhalation anesthesia. In these patients, the expression of protein TGF β 1, Smad3 and Smad7 were significantly increased which was consistent with the MMES scores of these patients. Since those proteins were involved with TGF beta/Smad, we may conclude that activation of TGF beta/Smad pathway may contribute to the occurrence of cognitive dysfunction after undergoing isoflurane inhalation anesthesia.

TGF beta/Smad signaling pathway is the common signaling pathways of a variety of pathological process in cells, and excessive activation of this pathway involved in the occurrence of cerebral diseases. Study on the molecular mechanism of epithelial mesenchymal cell transformation induced by Tanshenping and lipopolysaccharide showed that Tanshenping combing with lipopolysaccharide can regulate expression of TGF beta 1 and mRNA, meanwhile, the expression of protein Smad2/3 was also increased. However, Tanshenping actually can inhibit abnormal expression of these proteins and α-SMA indicating that Tanshenping can inhibit the differentiation of foot cells by suppressing the activation of TGF β -Smad2/3 pathway[12].

Researchers on Dan phenolic acid B also showed that abnormally increased phosphorylation expression of Smad2 and Smad3 in TGF beta 1 cells can be resorted indicating that Dan phenolic acid B play its role by inhibiting TGF beta/Smad signaling pathways[13]. Study on correlation between malignant astrocytoma and TGF beta 1 and Smad7 showed that expression level of TGF β 1 and Smad7 were significantly increased in high malignant astrocytoma comparing with that in high malignant astrocytoma. And the increase degree was consistent with malignancy of the astrocytoma[14]. Relevant study also showed that activated TGF beta/Smad signaling pathway involved with hydrocephalus rat models[15,16]. In this study, expression level of proteins TGF β 1, Smad3 and Smad7 were significantly increased and the occurrence of cognitive dysfunction was consistent with MMSE scores indicating TGF beta/Smad signaling pathway also involved with the occurrence of cognitive dysfunction in patients underwent isoflurane inhalation anesthesia. We can conclude that, isoflurane inhalation anesthesia can affect patients’ cognitive function by activation of TGF β /Smad pathway.

4. Discussion

Postoperative cognitive dysfunction is induced by several reasons

References


