Original Article

# Changes in Rat Brain MicroRNA Expression Profiles Following Sevoflurane and Propofol Anesthesia

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## Abstract

**Background:** Sevoflurane and propofol are widely used anesthetics for surgery. Studies on the mechanisms of general anesthesia have focused on changes in protein expression properties and membrane lipid. MicroRNAs (miRNAs) regulate neural function by altering protein expression. We hypothesize that sevoflurane and propofol affect miRNA expression profiles in the brain, expect to understand the mechanism of anesthetic agents.

**Methods:** Rats were randomly assigned to a 2% sevoflurane group, 600 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol group, and a control group without anesthesia ($n$ = 4, respectively). Treatment group was under anesthesia for 6 h, and all rats breathed spontaneously with continuous monitoring of respiration and blood gases. Changes in rat cortex miRNA expression profiles were analyzed by miRNA microarrays and validated by quantitative real-time polymerase chain reaction (qRT-PCR). Differential expression of miRNA using qRT-PCR among the control, sevoflurane, and propofol groups were compared using one-way analysis of variance (ANOVA).

**Results:** Of 677 preloaded rat miRNAs, the microarray detected the expression of 277 miRNAs in rat cortex (40.9%), of which 9 were regulated by propofol and (or) sevoflurane. Expression levels of three miRNAs (rno-miR-339-3p, rno-miR-448, rno-miR-466b-1*) were significantly increased following sevoflurane and six (rno-miR-339-3p, rno-miR-347, rno-miR-378*, rno-miR-412*, rno-miR-702-3p, and rno-miR-7a-2*) following propofol. Three miRNAs (rno-miR-466b-1*, rno-miR-3584-5p and rno-miR-702-3p) were differentially expressed by the two anesthetic treatment groups.

**Conclusions:** Sevoflurane and propofol anesthesia induced distinct changes in brain miRNA expression patterns, suggesting differential regulation of protein expression. Determining the targets of these differentially expressed miRNAs may help reveal both the common and agent-specific actions of anesthetics on neurological and physiological function.

**Key words:** Brain; MicroRNA; Propofol; Sevoflurane

## Introduction

A large number of structurally diverse molecules are used as general anesthetics, such as the volatile gas sevoflurane and the intravenously administered agent propofol. Individual anesthetic agents are known to have unique effects on brain function. Compared to other halogenated anesthetics, sevoflurane demonstrated an intrinsic cerebral vasodilatory effect, inducing a dose-dependent increase in cerebral blood flow (CBF) and decrease in cerebrovascular resistance.[1] Propofol can reduce both cerebral metabolism and regional CBF, and has been recommended as an ideal hypnotic for neurosurgical procedures.[2] General anesthetics may alter consciousness by changing membrane lipid interactions and protein properties (such as ion channel gating and second messenger signaling).[3] In addition, several studies have shown that anesthetic agents can affect the expression of genes in the brain.[4]

MicroRNAs (miRNAs) are approximately 22nt-long, single-stranded noncoding RNA molecules that regulate gene expression by binding to the 3'-untranslated regions of target mRNAs. This initiates formation of silencing complexes that regulate posttranscriptional gene expression by translational repression, mRNA cleavage, and mRNA decay initiated by miRNA-guided rapid deadenylation.[5] Through translational repression, miRNAs are critical regulators of cell proliferation, inflammation, and metabolism; indeed, miRNAs negatively regulate more than 30% of the transcriptome.[6] miRNAs

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are also essential for neurogenesis and brain development, synaptic plasticity,[7] and responses to pathological insults like stroke.[8] Sevoflurane and propofol anesthesia also altered miRNA expression patterns in healthy rat liver.[9]

We speculated that sevoflurane and propofol anesthesia affected miRNA expression in the brain as well. To confirm this, we conducted miRNA microarray chip analysis and quantitative real-time polymerase chain reaction (qRT-PCR) on rat brain tissues following general anesthesia induced by clinical doses of sevoflurane or propofol.

## Methods

Animal care and sacrifice were conducted according to methods approved by the Animal Research Committee, Beijing Tiantan Hospital, Capital Medical University. RNA labeling and hybridization on miRNA microarray chips were performed by Capital-Bio (Beijing, China). Other experiments were preceded in the central lab of Beijing Tiantan Hospital, Capital Medical University.

### Sample preparation

Seven-week-old male Sprague-Dawley rats (Vital River Laboratory Animal Technology Co. Ltd., Beijing, China) weighing 250 ± 10 g were housed in plastic cages in an animal room under a controlled 12 h light-dark cycle with *ad libitum* access to food and water for 1-week before experiments. Rats were then randomly divided into three groups, each group consisting four rats. Rats in the sevoflurane group were administered 2% sevoflurane (AbbVie Inc., North Chicago, IL, USA) and those in the propofol group were infused with 1% propofol at 600 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (AstraZeneca Plc, London, UK) from 9:00 AM to 3:00 PM. Control group was kept in the same anesthesia box for 6 h breathing regular air.

A catheter was inserted into the tail vein of all rats without anesthesia to deliver normal saline at 1 mL/h during treatment. Each rat was allowed to breathe spontaneously in the anesthesia box supplied with an air-oxygen mixture (fraction of inspired oxygen = 0.6) at 3 L/min, body temperature was maintained at approximately 37°C during ventilation/anesthesia using a heat lamp. Rats were decapitated at 3:00 PM. The left cortex of the brain was obtained from each rat within 1 min after death. Brain samples were washed twice with 4°C phosphate buffered saline (pH 7.4) and immediately stored at − 80°C. Total RNA was extracted using the mirVana miRNA Isolation kit (Ambion, Austin, TX, USA). RNA quantity and quality were assessed by a NanoDrop ND-2000 spectrophotometer (Thermo Fisher Scientific Inc., Waltham, MA, USA). An $A_{260/280}$ of 1.8 or more was required for subsequent quantitative analysis of miRNAs using miRNA microarray.

### Physiological parameters

Physiological variables were measured in three parallel groups of rats (6/group) during sevoflurane, propofol, or control treatment. To monitor heart rate as well as arterial blood pressure, $PO_2$, $PCO_2$, and pH, catheters were inserted into the tail artery and vein after intraperitoneal injection of chloral hydrate (0.6 mg/kg). After full recovery from chloral hydrate anesthesia, rats in the anesthesia groups were administered the same doses of sevoflurane or propofol used for miRNA expression studies. Blood samples were taken 3 and 6 h after the induction of sevoflurane or propofol anesthesia. In the control group, blood samples were taken 3 and 6 h after full recovery from chloral hydrate anesthesia.

### MicroRNA microarray analysis

RNA labeling and hybridization on miRNA microarray chips were performed by Capital-Bio (Beijing, China). Briefly, 200 ng total RNA was labeled with Cy3 using the miRNA Complete Labeling and Hyb Kit (Agilent Technologies, Inc., CA, USA) and hybridized to arrays in a hybridization oven (Agilent Technologies, CA, USA) at 55°C and 20 r/min for 20 h. The miRNA microarray chip contained 677 preloaded rat miRNA probes, all cataloged in the Sanger miRBase V16.0 (Agilent Technologies, CA, USA). After hybridization, the microarrays were washed in staining dishes (Thermo Shandon, Waltham, MA, USA) with the Gene Expression Wash Buffer Kit (Agilent Technologies, CA, USA). Hybridization data were extracted by Agilent Feature Extraction (v10.7, Agilent Technologies, CA, USA) software and analyzed using Agilent GeneSpring. Data are expressed as threshold cycle (Ct) values, the fractional cycle number at which the sample fluorescence signal surpasses a fixed threshold above baseline.

### Quantitative real-time polymerase chain reaction for individual microRNA quantification

To verify the accuracy of microarray data, we performed individual qRT-PCR measurements on seven miRNAs differentially expressed by anesthetic-treated brain relative to control brain on the samples which we did the microarray analysis: Rno-miR-466b-1*, rno-miR-339-3p, rno-miR-347, rno-miR-378*, rno-miR-412*, rno-miR-448, and rno-miR-7a-2*.We could not find the primers for miR-702-3p and miR-3584-5p from the database, so we did not perform qRT-PCR for these two miRNAs. Total RNA was isolated with TRIzol reagent (Invitrogen, USA) and RT performed using the Takara RT Reagent Kit (Takara Bio, Japan). Each reaction mixture for RT contained 200 ng RNA template, 1.2 μl miRNA RT primer, 4 μl RT buffer 5X, 1 μl RT enzyme mix, and RNase-free water in a total volume of 20 μl. Reaction mixtures were then incubated for 30 min at 37°C and for 5 s at 85°C.

The PCR reactions were performed using the Takara SYBR Premix Ex Taq Kit (Takara Bio, Japan) and Thermal Cycler Dice Real-time System (Takara Bio, Japan). The 20 μl qPCR reaction mixture contained 10 μl SYBR Green Mix, 1 μl miRNA RT Product, 0.8 μl miRNA Forward Primer (10 μmol/L), 0.8 μl miRNA Reverse Primer (10 μmol/L) (Ibsbio Co., Ltd., China), and RNase-free water. Reaction mixtures were incubated at 95°C for 30 s, followed by 40 cycles of 95°C for 5 s, 62°C for 20 s, and 72°C for 30 s, and finally 95°C for 15 s, 60°C for 30 s, and 95°C for 15 s.

The expression of each miRNA was normalized using U6 as the internal control and group differences calculated as the inverse

log of the ΔΔCt to yield the relative fold-change in miRNA levels. The PCR reaction for each miRNA was repeated 3 times using separate reaction mixtures.

### Data presentation

Changes in miRNA expression are presented using heat maps. These heat maps are commonly used for visualization of high-dimensional data by two-dimensional images, with colors representing the intensity values. After individually clustering columns (samples) and rows (miRNAs), the heat map simultaneously displays the separate sample and miRNA clusters in one graphic. The magnitude of miRNA expression changes is denoted by color, and the corresponding numbers are the ΔCt values.

### Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., USA). All data were expressed as the mean ± standard deviation (SD). Physiological data among the control, sevoflurane, and propofol groups were compared by repeated measure analysis of variance (ANOVA). Differential expression of miRNA using qRT-PCR among the control, sevoflurane, and propofol groups were compared by one-way ANOVA. Anesthesia-regulated miRNAs were defined as those with a mean fold-change (increase or decrease) greater than 2 and values of $P < 0.05$ were considered statistically significant when compared to the control group.

## Results

All rats survived until sacrifice and data from all animals were included in the analysis. There were no significant differences in the measured physiological parameters between anesthesia groups and the control group, and no incidences of hypoxia, hypercapnia, hypocapnia, hypotension, hypothermia, or hyperthermia [Table 1].

Microarray analysis detected 277 of 677 preloaded miRNAs (40.9%). Of these, 9 were upregulated by anesthetic agents relative to control, 3 by sevoflurane and 6 by propofol [Table 2]. Three miRNAs were differentially expressed by the two anesthetic groups [Table 3]. No significantly downregulated miRNAs were detected. A clustergram of the samples and the anesthetic-regulated miRNAs is shown in Figure 1 as a heat map generated using ΔCt values. The figure indicates the relatedness of the samples based on overall miRNA expression values, and separates into three main branches, the control group, the sevoflurane anesthesia group, and the propofol anesthesia group.

To validate the altered expression of these 9 miRNAs, the expression of 7 was re-examined by qRT-PCR. Results were consistent with microarray analysis [Figure 2]. Expression levels of rno-miR-339-3p, rno-miR-448, and rno-miR-466b-1* were significantly increased after sevoflurane anesthesia compared to controls ($P < 0.05$), whereas rno-miR-339-3p, rno-miR-347, rno-miR-378*, rno-miR-412*, and rno-miR-7a-2* were increased by propofol ($P < 0.05$). The expression of rno-miR-466b-1* was significantly increased after sevoflurane anesthesia compared to propofol ($P < 0.05$).

## Discussion

A variety of structurally distinct molecules acting on transmitter receptors, ion channels, and other protein targets induce general anesthesia.[10] Neuroimaging has revealed that different anesthetics induce both global and region-specific reductions in cerebral metabolic rate and blood flow.[11] Anesthetics also alter functional connectivity.[12] However, the ultimate question of how general anesthetics reversibly alter human consciousness remains obscure. These agents also alter gene expression, but the specific changes in expression pattern induced by individual general anesthetics and how these changes affect brain function in both the intraoperative and postoperative periods remain largely unexplored. Here we demonstrate that two widely used general anesthetics, propofol and sevoflurane, alter miRNA expression patterns. This may

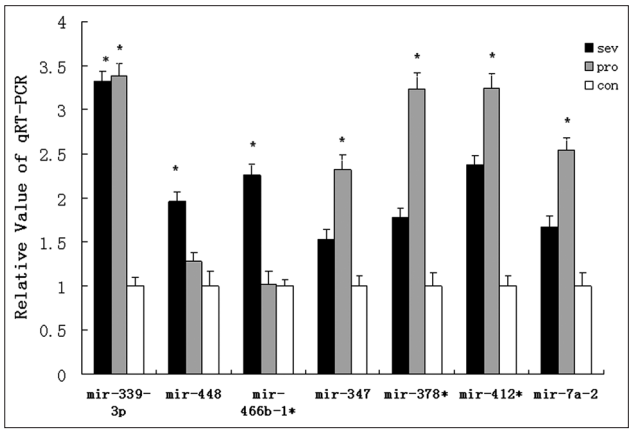


**Figure 1:** The heat map of differentially expressed miRNAs. Rows represent individual genes, and columns represent individual samples. The samples separate the three groups: The control group (c), the sevoflurane anesthesia group (s), and the propofol anesthesia group (p).

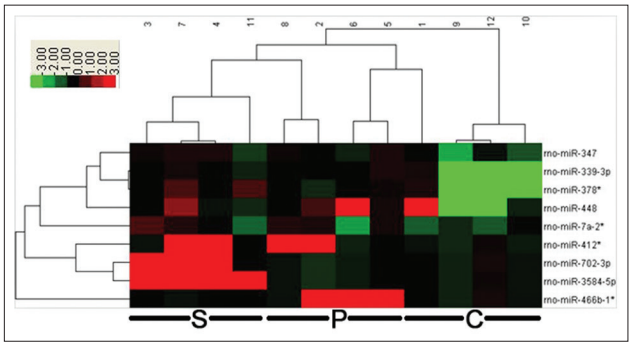


**Figure 2:** The quantitative real-time polymerase chain reaction (PCR) validation for some expression-altered miRNAs. *The 7 differentially expressed miRNAs (rno-miR-466b-1*, rno-miR-339-3p, rno-miR-347, rno-miR-378*, rno-miR-412*, rno-miR-448 and rno-miR-7a-2*) as detected by the miRNA microarray were confirmed using qPCR (data are presented as the mean ± standard deviation, *compared with control group, *$P < 0.05$; $n = 4$), sev: Sevoflurane; pro: Propofol; con: Control.

**Table 1: Physiological data among the control, sevoflurane, and propofol groups ($n$ = 6)**

| Indicators | Control group | Sevoflurane group | | Propofol group | | $F$ | $P$ |
|---|---|---|---|---|---|---|---|
| | | 3 h | 6 h | 3 h | 6 h | | |
| pH | 7.35 ± 0.02 | 7.35 ± 0.02 | 7.31 ± 0.03 | 7.34 ± 0.01 | 7.28 ± 0.08 | 3.60 | 0.053 |
| $PaO_2$ (mmHg) | 102 ± 22 | 104 ± 15 | 103 ± 22 | 112 ± 10 | 100 ± 14 | 0.07 | 0.935 |
| $PaCO_2$ (mmHg) | 42 ± 6 | 39 ± 5 | 47 ± 5 | 46 ± 5 | 42 ± 4 | 0.17 | 0.845 |
| HR (beats/min) | 245 ± 20 | 251 ± 19 | 248 ± 16 | 264 ± 21 | 236 ± 6 | 0.17 | 0.846 |
| MAP (mmHg) | 82 ± 4 | 80 ± 2 | 83 ± 6 | 82 ± 12 | 79 ± 7 | 0.07 | 0.936 |

HR: Heart rate; MAP: Mean arterial pressure.

**Table 2: Differential expression of miRNA using miRNA microarrays ($n$ = 4)**

| Sevoflurane group | | | Propofol group | | |
|---|---|---|---|---|---|
| Assay | FC | $P$ | Assay | FC | $P$ |
| rno-miR-339-3p | 18.33 | 0.016 | rno-miR-339-3p | 17.75 | 0.016 |
| rno-miR-448 | 45.34 | 0.033 | rno-miR-347 | 2.25 | 0.024 |
| rno-miR-466b-1* | 11.83 | 0.024 | rno-miR-378* | 24.05 | 0.042 |
| | | | rno-miR-412* | 29.16 | 0.025 |
| | | | rno-miR-702-3p | 32.63 | 0.026 |
| | | | rno-miR-7a-2* | 2.17 | 0.012 |

miRNAs were significantly increased by the sevoflurane and propofol groups compared with the control group by miRNA microarrays, respectively. FC: Foldchange; miRNA: MicroRNA; rno: Rattusnorvegicus.

**Table 3: Differential expression of miRNA between the sevoflurane group and the propofol group compared with the control group using miRNA microarrays**

| Assay | FC | $P$ | Regulation |
|---|---|---|---|
| rno-miR-466b-1* | 11.78 | 0.024 | Up |
| rno-miR-3584-5p | 24.49 | 0.023 | Down |
| rno-miR-702-3p | 35.45 | 0.024 | Down |

FC: Fold change; miRNA: MicroRNA; rno: Rattusnorvegicus.

provide a new angel to understand the mechanism of anesthetic agents of the brain. Three of these miRNAs were specifically upregulated by only one of these agents, suggesting that different anesthetics induce unique changes in neural protein expression patterns that may in turn explain their specific neurological effects.

Individual miRNAs are conserved across species and expressed in both spatially and temporally specific patterns during development and under varying physiological conditions.[13] Each miRNA can bind 100 different target mRNAs on average, and the same target gene may be regulated by a given miRNA only under specific conditions, allowing for enormous regulatory complexity and flexibility. Indeed, region-specific miRNAs in the brain can establish and maintain the protein expression profiles underlying regional cellular phenotypes.[14] Expression of several miRNAs also changes under pathological conditions.[15] In the current study, we identified 9 miRNAs (miR-466b-1*, miR-3584-5p, miR-702-3p, miR-339-3p, miR-347, miR-448, miR-378*, miR-412*, and miR-7a-2*) that may be involved in the mechanism of general anesthetic action in the mammalian CNS.

The anesthesia-regulated miRNA-339-3p binds to the μ-opioid receptor (MOR) mRNA 3'-UTR and suppresses receptor activity, thereby acting as a negative feedback modulator of MOR signaling. Thus, these anesthetic may alter MOR signaling, consistent with the time- and dose-dependent regulation of MOR expression by propofol in human neuroblastoma cells.[16] MiRNAs may also impact higher cognitive function such as learning and memory. MiR-132 and miR-212 differentially alter long-term potentiation, a neurocellular model of associative learning, in the hippocampus and neocortex.[17] MiR-132 expression decreases both in Alzheimer's disease patients' prefrontal cortex and hippocampus area and in their serum, also it is provided that miR-132 may contribute to disease progression.[18] The microarray results of our research showed that miR-132 expression in rat cortex as well as decreased about 40% by propofol and 30% by sevoflurane (data is not shown), which strongly suggests anesthetics possess neurotoxicity and anesthetics play important function to general anesthesia caused postoperative cognitive dysfunction. MiR-466b, a miRNA upregulated by sevoflurane but not propofol, is strongly expressed in the marginal division (MrD) compared to the hippocampus, since previous study has shown that MrD - basal nucleus of Meynert-hippocampus circuit may play an important role in modulating learning and memory, mir-466b may play a possible role in this process.[19] Cerebral 5-HT receptors and subunits regulate aggressive behavior, and the 5-HT (2C) gene harbors the sevoflurane-regulated miR-448 in the 4$^{th}$ intron. In contrast to 5-HT (2C), miR-448 reduced adipocyte differentiation, again indicating a negative feedback relationship.[20] Reduced adipocyte differentiation may result from miR-448-mediated suppression of the transcription factor Krueppel-like factor 5.[21] MiRNAs also regulate responses to brain ischemia and ischemic tolerance induced by ischemic preconditioning.[22] Transient focal ischemia in adult rat regulated the expression of miRNAs predicted to target proteins involved in signal transduction and ionic homeostasis.[23] A recent study reported (propofol-regulated) miR-347 downregulation following ischemic stroke, intracerebral hemorrhage, and kainite-induced seizures, implicating this analgesic-related miRNA in the response to acute brain injury.[24] Melamed proposed that RNA splicing negatively regulates the

processing of pre-miRNAs that overlap exon-intron junctions, and demonstrated that tissue-specific alternative splicing regulates maturation of miR-412, resulting in effects on its targets, a protein network involved in neuronal cell death.[25] Upregulation of miR-412 by propofol anesthesia may account, at least in part, for the neuroprotective effects of this anesthetic.[26,27] Kim showed that sevoflurane-induced miR-702 promoted proliferation of Dgcr8-deficient embryonic stem cells.[28] Deng used chemically synthesized miR-Pirate to specifically silence mature miR-378, providing an experimental approach to study the function of this and other anesthetic-induced miRNAs.[29] In contrast, little is known about miR-7a-2* and miR-3584-5p functions in the brain. As far as we know, this is the first study focusing on the miRNA expression after general anesthesia.

Our study has several limitations. Although changes in miRNA expression are likely to affect subsequent protein levels, many additional dynamically regulated processes can alter protein expression while having no effect on gene expression. Indeed, the final functional entities in cells are not mRNAs and miRNAs, but proteins that undergo posttranslational modifications controlling activity, localization, and interactions with other proteins and molecules. This is just a preliminary study; further studies are needed to understand the functional consequences of these changes. Second, we used extracts of whole cortex as samples, but many miRNAs are expressed in more restricted regions. Therefore, it is possible that our results reflect a diluted response or summation of both suppression and activation in different regions. Third, we used 1% propofol with intralipid as solvent, not pure propofol, and we did no control for the effects of Intralipid on miRNA expression. Finally, we investigated only two anesthetics at fixed doses and did not evaluate the functional effects of these changes. Further research using miRNA antagonist or knockout animal models is needed to explore the functional implications of these anesthetic-dependent changes in miRNA expression.

In conclusions, we demonstrate that clinical doses of the anesthetics sevoflurane and propofol differentially regulate multiple miRNAs in the mammalian CNS. It may be very important to understand the mechanism of different anesthetic agents on brain. Further studies in protein expression are needed to determine the unique neurological effects of these agents.

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