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Isoflurane anesthesia induces biphasic effect on dopamine release in the rat striatum

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Abstract

The effect of isoflurane anesthesia on changes in the extracellular concentrations of dopamine (DA) and its metabolites (3-methoxytyramine (3-MT), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)) modulated by pargyline, monoamine oxidase inhibitor, was studied using in vivo microdialysis techniques. A microdialysis probe was implanted into the right striatum of male SD rats. Each rat ($n = 5$–6) was given saline or the same volume of 30 or 75 mg kg^{-1} pargyline intraperitoneally with or without 1 h isoflurane anesthesia (1 or 3%). Isoflurane anesthesia increased the extracellular concentration of DA in high dose (3%) and increased the metabolite concentrations in a dose-dependent manner. Pargyline administration increased the extracellular concentration of DA and 3-MT, and decreased that of other metabolites. After 30 mg kg^{-1} pargyline treatment, 1% isoflurane-induced DA release and increasing of 3-MT were preserved, whereas high dose isoflurane (3%) decreased the concentration of metabolites (DOPAC and HVA), despite of the increase by low dose isoflurane (DOPAC). When 75 mg kg^{-1} pargyline was administered, isoflurane anesthesia decreased the concentration of DA and DOPAC. The isoflurane-induced 3-MT increase was preserved in all experiments. Our results suggest that isoflurane anesthesia induced biphasic effect on DA regulation probably by the potentiation of DA release and the inhibition of DA synthesis. Isoflurane might modulate DA homeostasis presynaptically.

Keywords: Microdialysis; Isoflurane anesthesia; Dopamine; Monoamine oxidase inhibitor; Pargyline

1. Introduction

Many investigations demonstrated the neuroprotective effect of volatile anesthetics as a result of antagonizing release of neurotransmitters in central nervous system after cytotoxic insult [3,9,23,26]. In the striatum, exaggerated dopamine (DA) release and subsequent DA metabolism induces neurotoxic effect, including neural death. Previously, we reported that halothane anesthesia itself increased the extracellular concentration of DA and its metabolites using in vivo microdialysis technique in the rat striatum [2]. Opacka-Juffry et al. [16] demonstrated that nomifensine-induced increase in extracellular striatal DA is enhanced by isoflurane anesthesia. In an in vitro model of cerebral ischemia, the antagonizing effect on increasing DA concentration with volatile anesthetics was unclear [24], whereas the ability of the anesthetics to reduce neuronal damage is well known [23,26].

Although the exact mechanism of anesthesia is still unclear, it is possible that volatile anesthetics modulate DA homeostasis including release and metabolism [25]. We hypothesized that the effect of anesthetics on DA release and metabolism might be dependent on the modification of DA regulation before induction of anesthesia. In another study, halothane attenuated haloperidol- and enhanced clozapine-

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induced DA release in the rat striatum [1]. The biphasic effect of halothane might be explained by the non-synaptic neural transmission of striatal interneurons. However, there are scarce investigation for the effect of volatile anesthesia on DA release and metabolism modified by pharmacological treatments in advance to the inhalation of anesthesia. Ischemia-induced DA release has been extensively studied [23] and the certain neuroprotective effect of volatile anesthetics was reported [25].

In the current investigation, we studied the effect of isoflurane anesthesia on pargyline (monoamine oxidase inhibitor)-induced DA increase using in vivo microdialysis techniques in the rat striatum.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats, weighing 280–320 g, were used in the experiments (CLEA Japan, Tokyo, Japan). The animals were housed in an animal room at 20–22 °C and illuminated with a 12-h light:12-h dark cycle (light from 07:00 to 19:00 h). All animals had free access to food and drinking water. The experiments were approved by the Committee for Animal Research at the college.

2.2. Microdialysis

Rats were anesthetized with sevoflurane and ventilated through an oro-tracheal tube. A unilateral guide cannula was implanted just above the striatum (AP +0.6 mm, ML +3.0 mm, DV −3.8 mm) following the atlas of Paxinos and Watson [18]. The rats were allowed to recover for at least 2 days before the experiment. After each experiment, the brain of rat was removed and the placement of the microdialysis probe was identified histologically.

Microdialysis probes were obtained from EICOM (Kyoto Japan) (o.d. 0.22 mm, membrane length 3 mm, polycarbonate tubing, cutoff molecular weight 50,000). The probe was inserted carefully into the striatum through a guide cannula and fixed to the cannula with a screw at about 7:00 a.m. on the day of experimentation. The rat was placed in a clear open Plexiglas box (15 L capacity, 27 cm diameter × 26 cm high), and the probe was continuously perfused with modified Ringer solution (145.4 mEq L^{-1} Na^+, 2.8 mEq L^{-1} K^+, 2.3 mEq L^{-1} Ca^{2+}, 150.5 mEq L^{-1} Cl^-) at a flow rate of 2 μL min^{-1} using a micro-infusion pump (ESP-64, EICOM, Kyoto, Japan) to determine the baseline concentrations of DA and its metabolites. Samples were collected every 20 min and directly injected into an online analytical system with an auto-injector (EAS-20, EICOM), as described elsewhere [1,2]. The concentrations of DA, 3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxytyramine (3-MT) and homovanillic acid (HVA) in each dialysate (40 μL/20 min) were determined by HPLC with an electrochemical detector (ECD-300, EICOM). These compounds were separated by reverse-phase ion-pair chromatography with a 5 μm C-18 column (MA5-ODS, 150 mm × 2.1 mm, EICOM) using an isocratic mobile phase (0.1 M sodium acetate, 0.1 M citric acid, 1.4 mM sodium 1-octanesulfonate, 5 μM EDTA-Na_2 and 13–14% methanol, pH 3.9), delivered at a flow rate of 230 μL min^{-1} by a high-pressure pump (EP-300, EICOM). The compounds were quantified by electrochemical detection using a glassy carbon working electrode set at 650 mV against a Ag/AgCl reference electrode. The detection limit for each of the compounds was roughly 0.1 pg per sample.

DA and its metabolites reached stable baseline concentrations within about 4.5 h after implantation of the microdialysis probe. Therefore, at least six dialysate samples were collected before starting the pharmacological experiment. The mean value obtained from the last three samples was used as the baseline concentration. The time at which the pharmacological manipulation started is hereafter called ‘fraction number 1’ (Fr. 1).

2.3. Experiments

Each rat (n = 5–6) was intraperitoneally given saline or the same volume of 30 or 75 mg kg^{-1} pargyline preceding 3 h before inhalation. The rat was anesthetized in a semi-closed Plexiglas box, into which 5% isoflurane was initially introduced at a rate of 3 L min^{-1} for about 5 min until a steady state was achieved. Subsequently, 1 or 3% isoflurane was applied at a rate of 2 L min^{-1}, using air (23% oxygen) as the carrier. The rectal temperature of the rat was monitored and maintained at 37 °C with an electrical heating pad. The concentrations of isoflurane and oxygen in the box were monitored using an infrared anesthetic gas analyzer (Capnomac Ultima, Datex, Helsinki, Finland) during each anesthesia. Immediately after the 1 h anesthesia, the gas in the box was exchanged with room air by forced ventilation.

2.4. Drugs

Isoflurane was obtained from Abboot Japan Co. Ltd. (Tokyo, Japan). Pargyline were purchased from Sigma (Sigma Chemical Co., St. Louis, MO, USA).

2.5. Statistical analysis

Data were analyzed by one-way analysis of variance with drugs as the between subjects variable for each fraction. For significant ($p < 0.05$) drug interactions, a subsequent Newman–Keuls post hoc multiple comparison test was performed (NCSS 2000, Number Cruncher Statistical Systems, Kaysville, UT, USA).

3. Results

Isoflurane anesthesia increased the extracellular concentration of DA in high dose (3%) and increased the metabolite