J Anesth (2000) 14:82–90

Journal of
Anesthesia

Halothane anesthesia decreases the extracellular level of dopamine in rat striatum: a microdialysis study in vivo

Yushi Adachi, Yoshitaka Uchihashi, Kazuhiko Watanabe, and Tetsuo Satoh

Department of Anesthesiology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan

Abstract

Purpose. In our previous microdialysis study, sevoflurane or isoflurane anesthesia significantly decreased the extracellular level of dopamine in rat striatum in vivo. On the other hand, other investigators demonstrated that halothane anesthesia either increased or did not affect the extracellular dopamine level. To explore the differences among these volatile anesthetics, the effects of halothane and nitrous oxide on the striatal dopamine level were reinvestigated.

Methods. Halothane alone, nitrous oxide with or without halothane, or drugs known to affect the dopaminergic pathway were administered to rats. Microdialysates were collected every 20 min and directly applied to an on-line high-performance liquid chromatograph without any pretreatment. The effects of halothane on respiratory and cardiovascular variables were monitored.

Results. General anesthesia with halothane alone decreased the dialysate (extracellular) concentration of dopamine but increased that of dopamine metabolites. Nitrous oxide alone slightly increased dopamine metabolites in dialysates but did not affect the halothane-induced decrease in extracellular dopamine. Apomorphine and haloperidol reproduced reported results, confirming the adequacy of our methodology. Nomifensine- or methamphetamine-induced increase in extracellular dopamine was augmented by halothane.

Conclusion. These results suggest that halothane potently enhances striatal dopamine release and activates the reuptake or metabolic process, which is consistent with our previous results for sevoflurane or isoflurane. Volatile anesthetics interfere with dopamine regulation, at least in the rat striatum.

Address correspondence to: Y. Adachi
Received for publication on July 12, 1999; accepted on December 14, 1999

Key words: Halothane, Dopamine release, Dopamine uptake, Microdialysis, Rat

Introduction

The volatile anesthetic isoflurane potentiates the inhibitory effect of nomifensine on dopamine uptake to increase the brain level of interstitial dopamine, probably by releasing dopamine from axon terminals [1]. Halothane has been reported to increase [2–4] or not to affect [5] the interstitial level of brain dopamine during anesthesia. In our previous microdialysis studies in vivo in freely moving and anesthetized rats [6], sevoflurane, a newly developed general anesthetic, and isoflurane significantly decreased the dialysate concentration of dopamine and significantly increased that of dopamine metabolites. In addition, nomifensine, a selective inhibitor of dopamine uptake, enhanced the isoflurane-induced increase of dopamine metabolites, as reported by Opacka-Juffry et al. [1], suggesting that sevoflurane or isoflurane may affect the reuptake of dopamine.

We therefore hypothesized that not only sevoflurane or isoflurane, but also other volatile anesthetics, might reduce the level of extracellular dopamine by accelerating reuptake. To examine this hypothesis, the effect of the more conventional and well-documented volatile anesthetic halothane on the extracellular level of striatal dopamine was reinvestigated in the present study. The effect of nitrous oxide was also investigated, because this anesthetic had been used together with halothane in some previous studies. In addition, we tested apomorphine and haloperidol to confirm the adequacy of our methodols. Furthermore, to explore the mechanism of the decrease in dopamine, nomifensine and methamphetamine were administered, with or without halothane. In other operated rats, respiratory and cardiovascular parameters were monitored to evaluate the

influence of the disturbing factor, halothane-induced hypoxia.

Materials and methods

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

The rats were anesthetized with sevoflurane and ventilated through an orotracheal tube. Surgical operations were performed with the additional topical application of 1% lidocaine. With the use of a stereotaxic apparatus, a unilateral guide cannula was implanted just above the striatum (AP +0.6 mm, ML +3.0 mm, DV −3.8 mm) according to the atlas of Paxinos and Watson [7]. The rats were allowed to recover for at least 2 days before experiments were started. After the experiment, the rats were sacrificed by inhalation of excess isoflurane and intravenous injection of thiopental. The placement of a microdialysis probe was venfied by histological examination.

Microdialysis probes were obtained from EICOM (Kyoto, Japan) (o.d. 0.22 mm, membrane length 3 mm, polycarbonate tubing, cutoff molecular weight 50000). On the day of the experiment, at about 7:00 a.m., the rat was briefly anesthetized with sevoflurane. The probe was inserted carefully into the striatum through a guide cannula and fixed to the cannula with a screw. This procedure was performed within 5 min, and the rat was immediately placed in a clear, open Plexiglas box (15 l in capacity, 27 cm in diameter, and 26 cm in height) for recovery. After recovery, the probe was constantly perfused with Ringer's solution (in $mEq \cdot l^{-1}$: 147.0 Na^+, 4.0 K^+, 2.4 Ca^{2+}, 155.8 Cl^-) at a flow rate of $2\,\mu l \cdot min^{-1}$ using the microinfusion pump (ESP-64, EICOM, Kyoto, Japan) to determine the baseline levels of dopamine and its metabolites. Samples were collected every 20 min and directly injected into an on-line analytical system with the auto-injector (EAS-20, EICOM). The contents of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxytyramine (3-MT), and homovanillic acid (HVA) in each dialysate ($40\,\mu l \cdot 20\,min^{-1}$) were determined by HPLC with the electrochemical detector (ECD-300, EICOM). These compounds were separated by reverse-phase ion-pair chromatography with the 5-μm C-18 column (MA5-ODS, 150 × 2.1 mm, EICOM) using the isocratic mobile phase (0.1 M sodium acetate, 0.1 M citric acid, 1.4 mM sodium 1-octanesulfonate, 5μM EDTA-Na_2, and methanol 16%–17%, pH 3.9), which was delivered at a flow rate of $230\,ml \cdot min^{-1}$ by a high-pressure pump (EP-300, EICOM). The guard column (MA, 5 × 4 mm, EICOM) prevented the deterioration and plugging of the analytical column. The compounds were quantified by electrochemical detection using a glassy carbon working electrode set at 650 mV against an Ag/AgCl reference electrode. The detection limit for each of the compounds was about 1.0 pg per sample.

The levels of dopamine and its metabolites reached stable baseline levels about 4.5 h after the implantation of a microdialysis probe. Thus, at least six dialysate samples (each 40 μl collection taking 20 min) were obtained before starting a pharmacological experiment. The mean value obtained from the last three samples was used as the baseline level. The time when a pharmacological manipulation started was termed fraction number 1 (Fr. 1).

The following four pharmacological experiments were carried out:

Experiment 1. Each rat was anesthetized in the semiclosed Plexiglas box into which 3% halothane was initially introduced at a rate of $3\,l \cdot min^{-1}$ for about 5 min until a steady state was achieved, then 1.5% halothane was applied at rate of $2\,l \cdot min^{-1}$, both using oxygen as a carrier. After achieving a steady state, 1.5% halothane alone, 50% nitrous oxide, or 1.5% halothane with 50% nitrous oxide was introduced for 1 h from Fr. 1 collecting striatal dialysates. The anesthetic gas was introduced into the center of the box and escaped through several small holes connecting the rat to analytical apparatuses. The collection of dialysates was continued for 4 h after the completion of the 1-h anesthesia. The rectal temperature of the rat was monitored and maintained at 37°C by an electrical heating pad. The concentration of inhalation gas in the box was monitored by the 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 for room air by forced ventilation.

Experiment 2. Apomorphine or haloperidol, classical drugs known to affect dopaminergic activity, was systemically administered at Fr. 1. Apomorphine and haloperidol are the agonist and antagonist of the dopamine autoreceptor, respectively. Apomorphine was dissolved in physiological saline and administered intraperitoneally at a dose of $50\,\mu g \cdot kg^{-1}$ ($2.0\,ml \cdot kg^{-1}$). Haloperidol was dissolved in a few drops of glacial acetic acid and diluted with saline (final pH adjusted to 5.0 with 0.1 M NaOH) and administered intraperitoneally at a dose of $200\,\mu g \cdot kg^{-1}$ ($2.0\,ml \cdot kg^{-1}$). The control group received 0.6 ml of physiological saline intraperitoneally.

Experiment 3. Nomifensine maleate and methamphetamine, typical drugs affecting dopaminergic activity, were tested in this experiment. Nomifensine is a dopamine re-uptake inhibitor, and methamphetamine is a dopamine releaser at nerve endings. Nomifensine

and methamphetamine were dissolved in physiological saline (with warming for nomifensine) at 5 mg·ml^{-1} and 1 mg·ml^{-1}, respectively. At Fr. 1, nomifensine at a dose of 10 mg·kg^{-1} (2.0 ml·kg^{-1}) or methamphetamine 2 mg·kg^{-1} (2.0 ml·kg^{-1}) was injected intraperitoneally, followed or not followed by inhalation of 1.5% halothane for 1 h.

Experiment 4. The effects of halothane on respiratory and cardiovascular variables were tested. A microdialysis probe was perfused as in other experiments, and 1.5% halothane was administered as in experiment 1. Instead of analyzing dialysates, however, we cannulated the right femoral artery of each rat under infiltration local anesthesia, and the arterial blood pressure and heart rate were measured during halothane anesthesia. At 30 and 60 min after the induction of anesthesia, 300 µl of blood was withdrawn for blood gas analysis, and the same volume of physiological saline was infused. The samples were immediately analyzed with the blood gas analyzer (GEM Premier, Sensor Systems, Mallinckrodt, Ann Arbor, MI, USA).

The data were analyzed by two-way analysis of variance, with drugs as a between-subjects variable and time as a within-subject variable. Significant ($P < 0.05$) drug–time interactions were followed for each drug by one-way analysis of variance and by subsequent Newman-Keuls post-hoc comparison (NCSS 2000, Kaysville, UT, USA).

Results

In the untreated control group, the dialysate dopamine level gradually and significantly decreased throughout the experiment, while the dialysate levels of dopamine metabolites decreased then increased following a U-shaped curve. These trends were consistent with our other microdialysis study [6] and appear to be common to microdialysis experiments on dopamine dynamics. The results of in vivo microdialysis experiments are known to be affected by many factors, including the period after probe implantation [8,9], the type of perfusion medium [10,11], and stress on animals [12,13]. In the present study, the changes in dialysate dopamine and its metabolites were taken as the baseline, and drug-induced changes were statistically compared with this baseline.

Effects of halothane, nitrous oxide, or both

As shown in Fig. 1, the induction of halothane anesthesia significantly decreased the level of dopamine in the dialysates (Fr. 2–4) and increased the levels of DOPAC (Fr. 2–13), 3-MT (Fr. 3–10), and HVA (Fr. 3–13), as compared with the control group. During a 4-h recovery period from anesthesia, the level of dopamine increased rapidly, but the levels of dopamine metabolites recovered with a delay. Nitrous oxide alone did not affect the dialysate level of dopamine and weakly but significantly increased that of the dopamine metabolites, DOPAC and HVA, during anesthesia (Fr. 3–6), as compared with the control group or the halothane group. The results of anesthesia with halothane plus nitrous oxide were not different from those of anesthesia with halothane alone (Fig. 1).

Effects of other drugs

Apomorphine (50 µg·kg^{-1}) decreased the level of dopamine in striatal dialysate (Fr. 2–5) and did not change the level of any metabolite of dopamine except for 3-MT (Fr. 2–4). Haloperidol (200 µg·kg^{-1}) markedly increased the levels of dopamine (Fr. 2–15) and its metabolites in dialysate (Fr. 2–15) (Fig. 2).

Effects of nomifensine and methamphetamine on halothane-induced changes in the levels of dopamine and its metabolites

Nomifensine (10 mg·kg^{-1}) and methamphetamine (2 mg·kg^{-1}) markedly increased the level of dopamine in striatal dialysates as compared with the control group (Fr. 2–9, Fr. 2–15, respectively), and 1.5% halothane enhanced the increases of dopamine induced by both drugs (Figs. 3 and 4). Nomifensine diminished the increase in DOPAC induced by halothane anesthesia (Fig. 3) and induced by itself a small increase of DOPAC (Fr. 2–4) as compared with the control group. Unlike the methamphetamine-induced dopamine increase described above, the nomifensine-induced increase in 3-MT was not affected by halothane (Fr. 2–9). HVA was significantly increased by nomifensine, with or without halothane. Methamphetamine completely depressed the halothane-induced increases in DOPAC and HVA levels, but it augmented the halothane-induced increase in 3-MT (Fr. 2–4) (Fig. 4).

Cardiovascular and respiratory effects of halothane anesthesia

Heart rate and blood pressure did not change during the period from 30 to 60 min after the induction of halothane anesthesia. At 30 and 60 min after induction, the mean heart rates were 304 ± 15 per minute and 313 ± 13 per minute (mean ± SEM, $n = 5$), respectively, and the mean arterial pressures were 103 ± 4 and 105 ± 3 mmHg, respectively. Blood gas analysis revealed mild hypercapnia. $PaCO_2$ was 46 ± 2 mmHg and PaO_2 was 524 ± 53 mmHg at 30 min after induction. $PaCO_2$ was 52

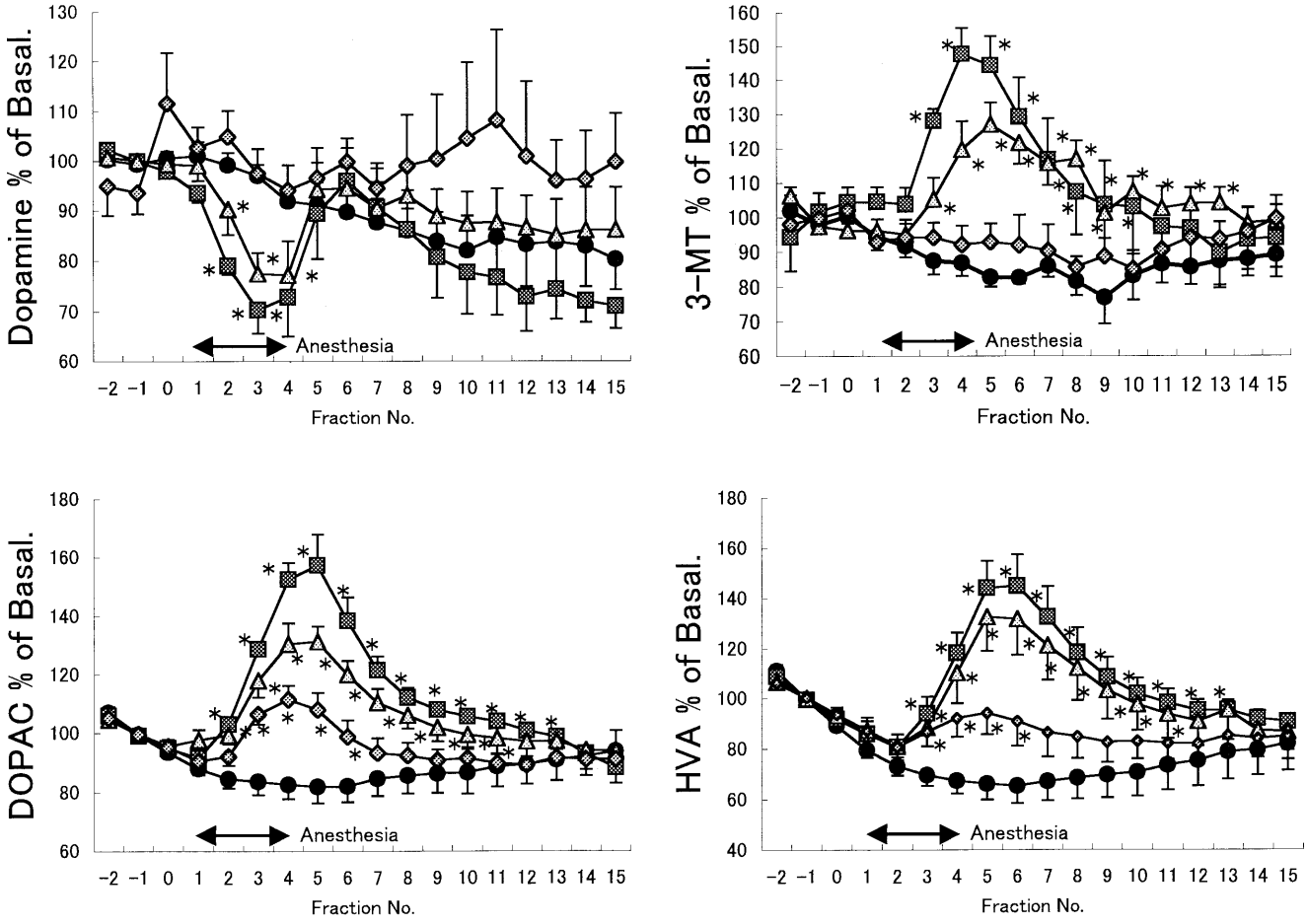

Fig. 1. Effect of halothane and halothane-nitrous oxide anesthesia on the levels of extracellular dopamine and its metabolites (3-MT, DOPAC, and HVA). In this and the following figures, the ordinate of each graph shows the level of dopamine or its metabolites expressed as the percentage of the baseline level, which is the mean of three consecutive values observed immediately before the start of halothane anesthesia; each point is the mean ± SEM ($n = 5$); dialysate fractions were obtained every 20 min, and *asterisks* indicate significant changes (* $P < 0.05$, Newman-Keuls post-hoc comparison test) compared with the control value at the corresponding time point. *Circles*, control; *squares*, halothane; *triangles*, halothane plus nitrous oxide; *diamonds*, nitrous oxide

± 1 mmHg and PaO_2 was 501 ± 55 mmHg at 60 min after induction.

Discussion

The extracellular levels of dopamine decreased when the animals were anesthetized with halothane and rapidly returned to the original levels after discontinuation of halothane inhalation. This finding is completely consistent with our previous finding for sevoflurane or isoflurane [6]. The halothane-induced changes in extracellular dopamine metabolites were greater and longer-lasting than the changes in extracellular dopamine. Inconsistent or opposite results have been reported as to the effect of halothane on the extracellular dopamine level. Osborne et al., Stahle et al., and Miyano et al. reported increases in the extracellular level of dopamine in rat striatum during halothane anesthesia [2–4], whereas Fink-Jensen et al. found no change in dopamine [5]. The type of microdialysis probe used and the surgical operation performed in the present study were similar to those in the above investigations. Moreover, we placed the microdialysis probe following the methods of these previous investigators exactly, since O'Connor et al. have pointed out that a difference in probe placement is the major factor affecting microdialysis results [14]. Thus, it is hard to specify the cause of the discrepancy between the present and previous findings. One reason might be a difference in the length of time from sampling to analysis. In the present study, sequential perfusate samples were directly injected into our on-line HPLC analytical system every 20 min without any manipulation, and consequently each sample

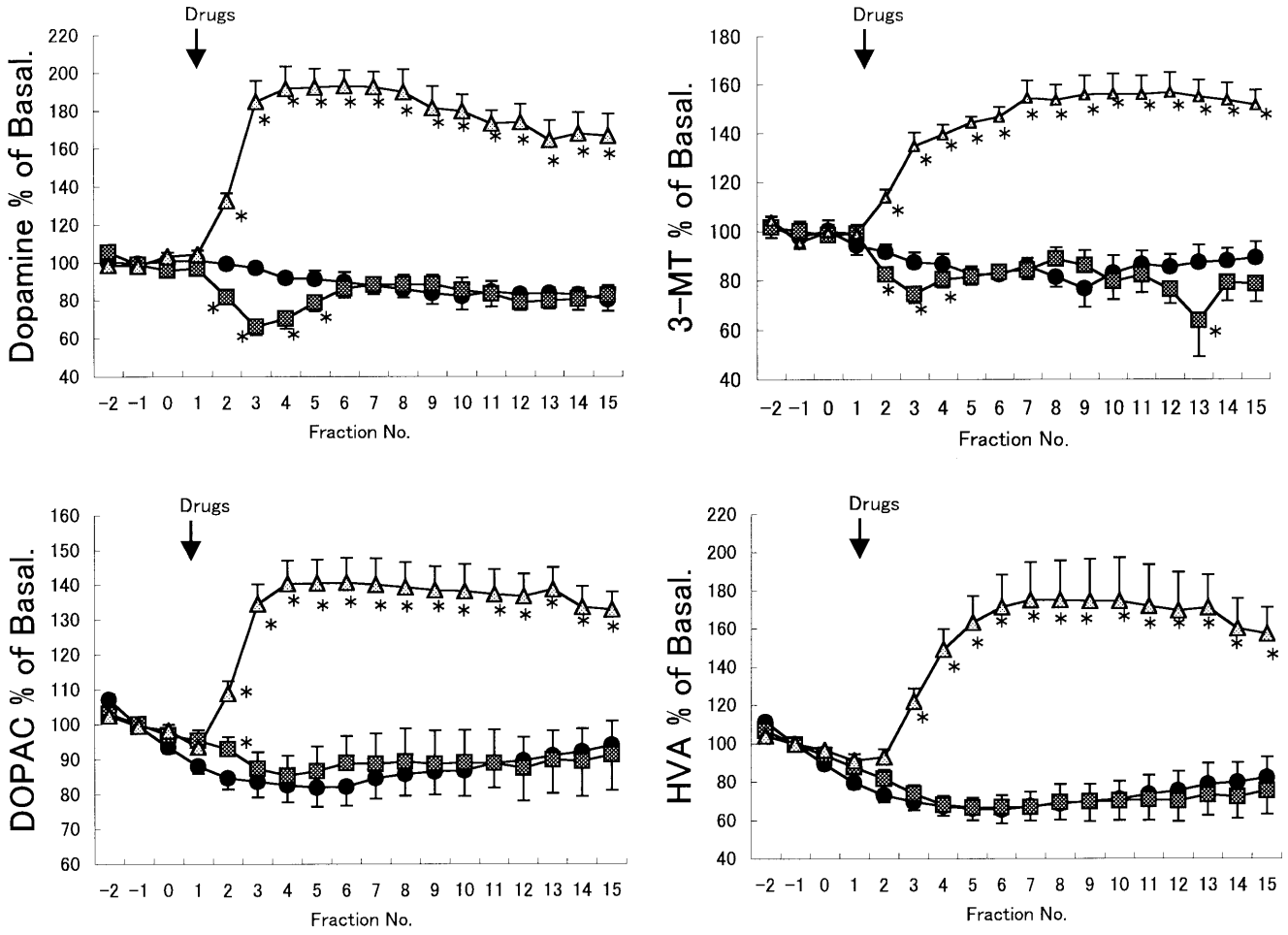

Fig. 2. Effects of apomorphine (*squares*) and haloperidol (*triangles*) on the levels of extracellular dopamine and its metabolites. *Circles*, control. See the legend of Fig. 1 for explanation

quickly reached an HPLC detector after exactly the same time delay. This integrated efficient system is thought to have realized the detection of a decrease in the extracellular level of striatal dopamine during halothane anesthesia.

The metabolites of dopamine, DOPAC, 3-MT, and HVA, showed significant increases during halothane anesthesia, as reported by Stahle et al. [3] and Fink-Jensen et al. [5], although Ford and Marsden [15] and Miyano et al. [4] found no such increases.

Nitrous oxide, which is commonly used together with general anesthetics in clinical practice and sometimes in laboratory experiments, was confirmed to have no influence on the effect of halothane on the extracellular level of dopamine.

The classical drugs apomorphine and haloperidol decreased and increased the level of dopamine in perfusates, respectively. Apomorphine is a dopamine autoreceptor agonist that has been reported to dose-dependently reduce the dialysate levels of dopamine, DOPAC, and HVA [16, 17], whereas haloperidol is a dopamine d_2 autoreceptor antagonist that has been shown to increase the levels of dopamine and its metabolites in a dose-dependent manner [18–20]. The results of experiment 2 in the present study are essentially consistent with those of previous microdialysis experiments. This agreement demonstrates that our methodol of measuring the levels of dopamine and its metabolites in dialysate was adequate, and also suggests that a difference in the animals or experimental procedures used may not be a critical factor affecting the results of microdialysis experiments.

In experiment 3, we investigated the effect of halothane on the changes in extracellular dopamine levels induced by nomifensine or methamphetamine. Nomifensine is a dopamine reuptake inhibitor that has been reported to increase the extracellular dopamine level and not to change the levels of DOPAC and HVA [19,21, 22]. In the present study, halothane anesthesia augmented the increase in extracellular dopamine in-

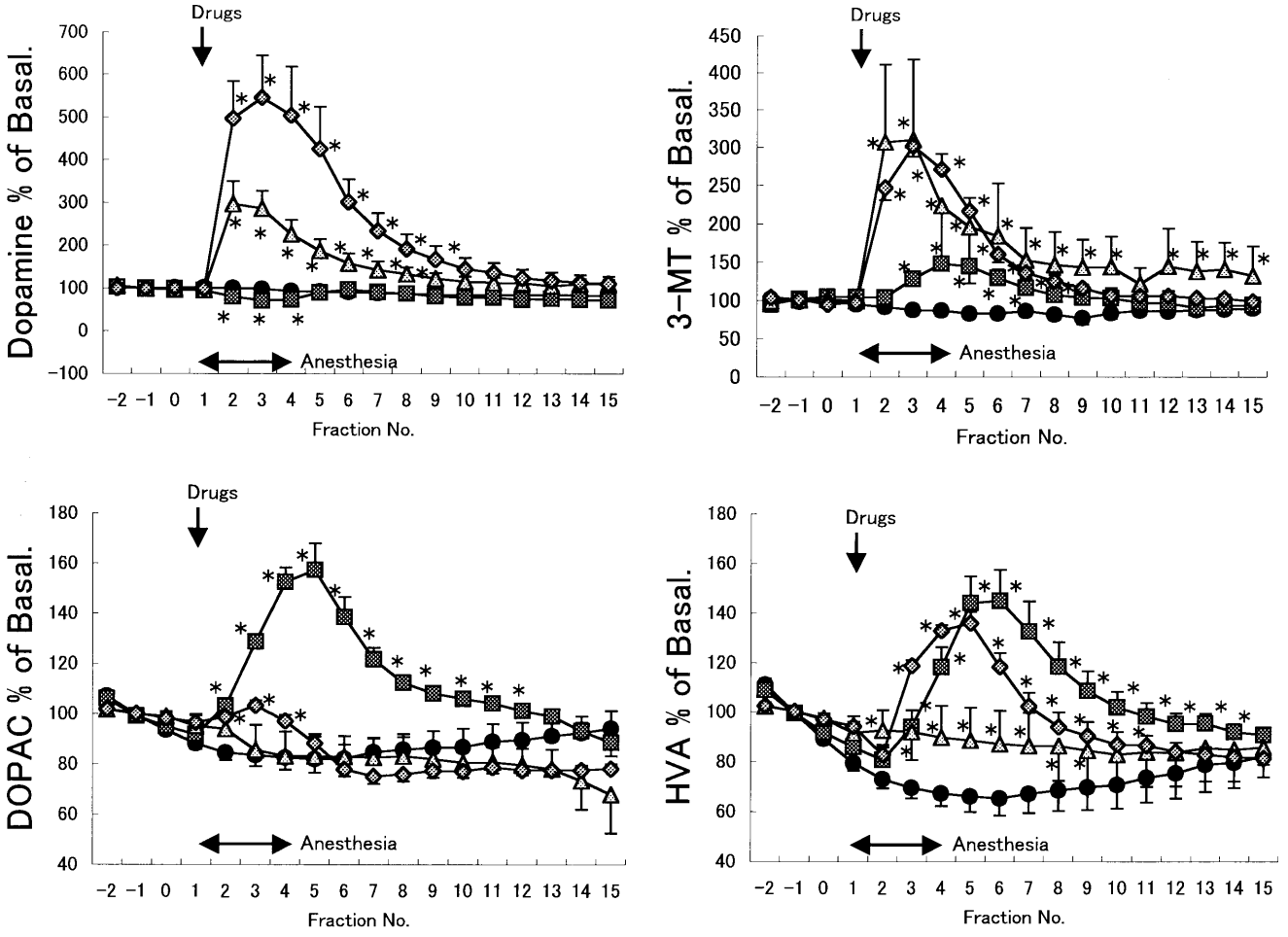

Fig. 3. Effects of nomifensine on the levels of extracellular dopamine and its metabolites, with or without halothane anesthesia. *Circles*, control; *squares*, halothane; *triangles*, *nomifensine*; *diamonds*, nomifensine plus halothane. See the legend of Fig. 1 for explanation

duced by nomifensine, whereas halothane itself decreased dopamine in experiment 1. Augmentation of anesthesia-induced dopamine release by dopamine reuptake inhibitors has previously been reported by Opacka-Juffry et al. for isoflurane and nomifensine [1] and by Fink-Jensen et al. [5] for halothane and vanoxerine. They have suggested that volatile anesthetics might increase the rate of release of dopamine, and the level of dopamine was equally compensated by an increase in dopamine reuptake activity. Methamphetamine is a dopamine releaser like amphetamine, and amphetamine has been reported to increase the levels of extracellular dopamine and 3-MT but to decrease the levels of DOPAC and HVA [19, 23]. We demonstrated that methamphetamine enhanced the halothane-induced increase of dopamine, as nomifensine did, whereas the increase in 3-MT induced by methamphetamine but not by nomifensine was enhanced by halothane. Nomifensine itself does not increase dopamine release from axon terminals. These differences between nomifensine and methamphetamine in dopamine release and metabolism support the hypothesis that halothane enhances the release and reuptake of dopamine.

In experiment 4, we evaluated the degree of cerebral ischemia during halothane anesthesia. Halothane has been reported to decrease blood pressure dose-dependently and to cause respiratory depression [4,24]. Miyano et al. [4] and Fink-Jensen et al. [5] have suggested that halothane may cause respiratory depression and brain hypoxia, thereby increasing extracellular dopamine. Severe brain hypoxia produces an increase in extracellular dopamine through its leakage from damaged axons [25,26]. Our monitoring, however, suggested that no marked hypoxia occurred during halothane anesthesia, although respiration was mildly depressed. The blood pressure and heart rate of rats under halothane anesthesia were within their normal ranges, except for the presence of mild hypercapnia,

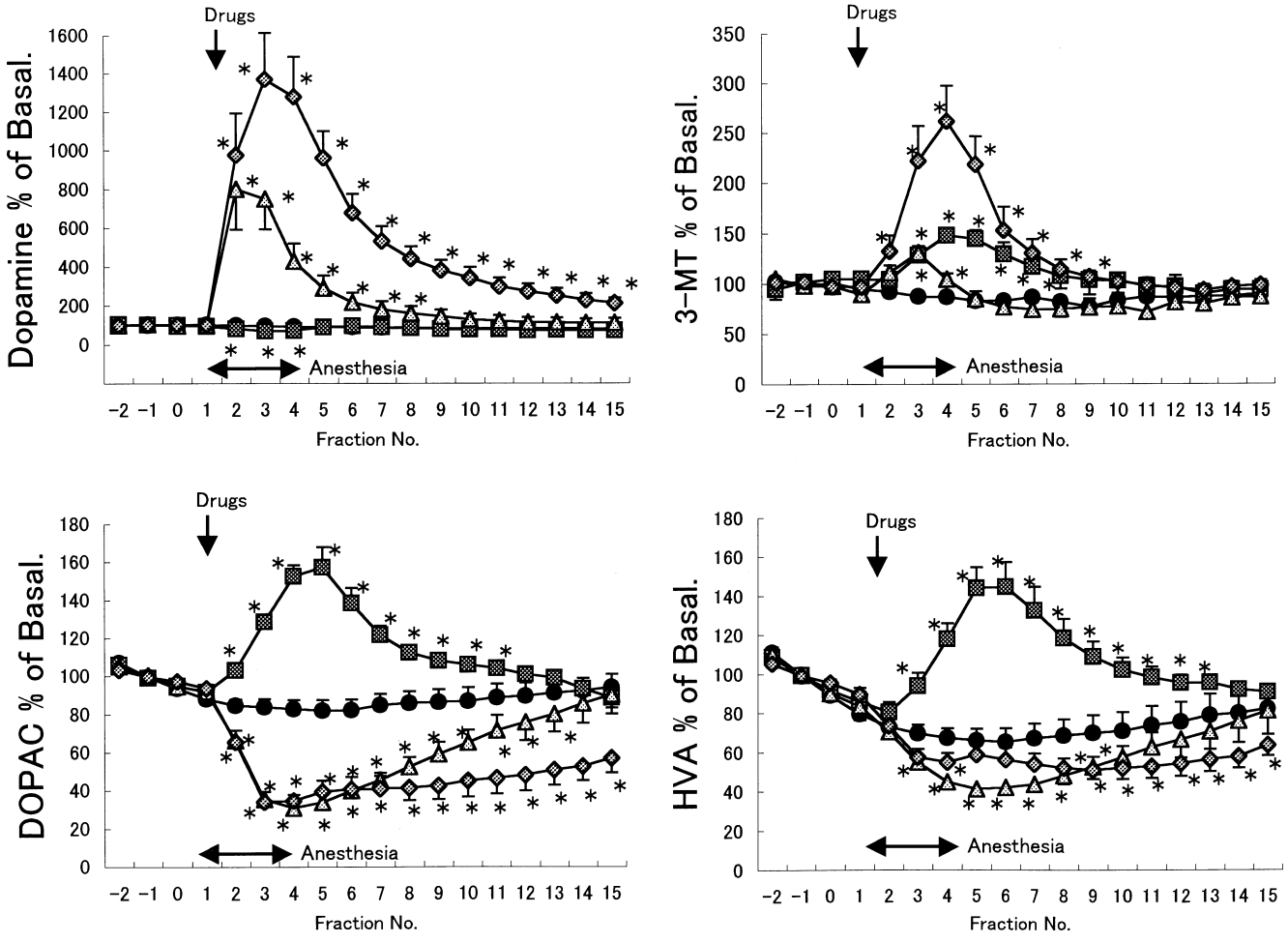

Fig. 4. Effects of methamphetamine on the levels of extracellular dopamine and its metabolites, with or without halothane anesthesia. *Circles*, control; *squares*, halothane; *triangles*, methamphetamine; *diamonds*, methamphetamine plus halothane. See the legend of Fig. 1 for explanation

and the arterial oxygen tension showed that the animals were not in a state of brain hypoxia. On this basis, it may be said that the pharmacological actions of halothane are reflected in an observed decrease in extracellular dopamine and increases in dopamine metabolites.

Our observation that halothane anesthesia increased extracellular DOPAC and HVA is in agreement with the results of Stahle et al. [3] and Fink-Jensen et al. [5]. We measured 3-MT as an indicator of the dopamine released from nerve endings. Although Westerink [27] and Waldmeier et al. [28] have suggested that 3-MT is not a appropriate indicator of dopamine release, we assessed the level of 3-MT as an indicator of actually released dopamine, because 3-MT is a catabolic product of the postsynaptic enzyme, catechol-*o*-methyltransferase [29–32]. During halothane anesthesia, dopamine metabolites, including 3-MT, were markedly increased, whereas dopamine was reduced. These increases in dopamine metabolites suggest that the release and metabolism of dopamine are definitely elevated by halothane anesthesia. Augmentation of the increase in 3-MT during halothane anesthesia by methamphetamine, but not by nomifensine, may support this hypothesis. Furthermore, the decrease in extracellular dopamine suggests that the reuptake of dopamine from the synaptic cleft or the extraneuronal metabolism of dopamine might be enhanced by halothane. Fink-Jensen et al. [5] have explained their observation that extracellular dopamine was unchanged during halothane anesthesia by speculating that a maintained balance between the release and uptake of dopamine, i.e., the halothane-induced increase of dopamine release, may be accounted for by halothane-induced increase in the activity of dopamine uptake carriers. However, the decrease in extracellular dopamine observed in the present study cannot be explained solely by their hypothetical mechanism, compensation for dopamine overflow. The present results suggest that

halothane potently enhances striatal dopamine release and moreover activates its reuptake or metabolism. Halothane anesthesia thus interferes with a mechanism controlling dopamine regulation, at least in the rat striatum. However, the quantitative relationship between the reuptake process and the metabolism of dopamine is still unknown in our investigation. Further study is needed to clarify the dopamine control mechanism.

In previous in vitro studies with rat brain synaptosomes, halothane inhibited dopamine uptake into synaptosomes [33,34], and either increased [33] or did not affect [34] the release of dopamine from synaptosomes. Whether the release of dopamine is increased or not, if halothane were a dopamine reuptake inhibitor in vivo as it is in vitro [33,34], the level of extracellular dopamine would be increased and never would be decreased or unchanged [5]. Recently, Bonhomme et al. [35] and Deurwaerdere et al. [36] have demonstrated by in vivo microdialysis studies that the release of striatal dopamine is modulated by serotonin. Thus, we infer that the increases in the release and re-uptake of dopamine observed during halothane anesthesia may not be primary events at nerve endings and may be due to such a secondary factor as serotonin modulation. More studies are required to elucidate the factors modulating the release and uptake of striatal dopamine, not only under halothane anesthesia but also under physiological conditions.

In conclusion, the present study clearly shows that halothane anesthesia decreases the level of extracellular dopamine in rat striatum, which is consistent with our previous study of the other volatile anesthetics sevoflurane and isoflurane. Augmentation by halothane of nomifensine- or methamphetamine-induced increases in extracellular dopamine suggests acceleration of dopamine release by anesthesia. Increases in dopamine metabolites under halothane anesthesia in spite of a decreased extracellular dopamine level support the hypothesis that net dopamine release might be facilitated. These findings suggest that halothane potentially interacts with dopamine during anesthesia, at least in the rat striatum, as far as the synaptic release, reuptake, and metabolism of dopamine are concerned.

Acknowledgment. We express our sincere thanks to Dr. K. Okamoto and Prof. J. Okamoto for reviewing and commenting on the manuscript of this paper.

References

1. Opacka-Juffry J, Ahier RG, Cremer JE (1991) Nomifensine-induced increase in extracellular striatal dopamine is enhanced by isoflurane anaesthesia. Synapse 7:169–71
2. Osborne PG, O'Connor WT, Drew KL, Ungerstedt U (1990) An in vivo microdialysis characterization of extracellular dopamine and GABA in dorsolateral striatum of awake freely moving and halothane anaesthetised rats. J Neurosci Methods 34:99–105
3. Stahle L, Collin AK, Ungerstedt U (1990) Effects of halothane anaesthesia on extracellular levels of dopamine, dihydroxyphenylacetic acid, homovanillic acid and 5-hydroxyindolacetic acid in rat striatum: a microdialysis study. Naunyn-Schmiedeberg's Arch Pharmacol 342:136–140
4. Miyano K, Tanifuji Y, Eger EI II (1993) The effect of halothane dose on striatal dopamine: an in vivo microdialysis study. Brain Res 605:342–344
5. Fink-Jensen A, Ingwersen SH, Nielsen PG (1994) Halothane anesthesia enhances the effect of dopamine uptake inhibition on interstitial levels of striatal dopamine. Naunyn-Schmiedeberg's Arch Pharmacol 350:239–244
6. Adachi Y, Uchihashi Y, Watanabe K, Satoh T (1999) The effect of sevoflurane and isoflurane on striatal dopamine of awake freely moving rats using in vivo microdialysis study. Masui (Jpn J Anesth) 48:960–965
7. Paxions G, Watson C (1998) The rat brain in stereotaxic coordinates. 4th ed. Academic Press, San Diego
8. Drew KL, O'Connor WT, Kehr J, Ungerstedt U (1989) Characterisation of gamma aminobutyric acid and dopamine overflow following acute implantation of a microdialysis probe. Life Sci 45:1307–1317
9. Osborne PG, O'Connor WT, Kehr J, Ungerstedt U (1991) In vivo characterisation of extracellular dopamine, GABA and acetylcholine from the dorsolateral striatum of awake freely moving rats by chronic microdialysis. J Neurosci Methods 37:93–102
10. Abercrombie ED, Keefe KA, DiFrischia DS, Zigmond MJ (1989) Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. J Neurochem 52:1655–1658
11. Feenstra MGP, Botterblom MHA (1996) Rapid sampling of extracellular dopamine in the rat prefrontal cortex during food consumption, handling and exposure to novelty. Brain Res 742:17–24
12. Osborne PG, O'Connor WT, Ungerstedt U (1991) Effect of varying the ionic concentration of a microdialysis perfusate on basal striatal dopamine levels in awake rats. J Neurochem 56:452–456
13. Chen NNH, Lai Y, Pan WHT (1997) Effects of different perfusion medium on the extracellular basal concentration of dopamine in striatum and medial prefrontal cortex: a zero-net flux microdialysis study. Neurosci Lett 225:197–200
14. O'Connor WT, Drew KL, Ungerstedt U (1995) Differential cholinergic regulation of dopamine release in the dorsal and ventral neostriatum of the rat: an in vivo microdialysis study. J Neurosci 15:8353–8361
15. Ford APDW, Marsden CA (1986) Influence of anaesthetics on rat striatal dopamine metabolism in vivo. Brain Res 379:162–166
16. Ozaki N, Nakahara D, Miura H, Kasahara Y, Nagatsu T (1989) Effects of apomorphine on in vivo release of dopamine and its metabolites in the prefrontal cortex and the striatum, studied by a microdialysis method. J Neurochem 53:1861–1864
17. Tanganelli S, von Euler G, Fuxe K, Agnati LF, Ungerstedt U (1989) Neurotensin counteracts apomorphine-induced inhibition of dopamine release as studied by microdialysis in rat neostriatum. Brain Res 502:319–324
18. Zetterstrom T, Sharp T, Ungerstedt U (1985) Effect of neuroleptic drugs on striatal dopamine release and metabolism in the awake rat studied by intracerebral dialysis. Eur J Pharmacol 106:27–37
19. Zetterstrom T, Sharp T, Collin AK, Ungerstedt U (1988) In vivo measurement of extracellular dopamine and DOPAC in rat striatum after various dopamine-releasing drugs; implications for the origin of extracellular DOPAC. Eur J Pharmacol 148:327–334
20. Gainetdinov RR, Grekhova TV, Sotnikova TD, Rayevsky KS (1994) Dopamine D2 and D3 receptor preferring antagonists differentially affect striatal dopamine release and metabolism in conscious rats. Eur J Pharmacol 261:327–331

21. Hurd YL, Ungerstedt U (1989) In vivo neurochemical profile of dopamine uptake inhibitors and releasers in rat caudate-putamen. Eur J Pharmacol 166:251–260
22. Hurd YL, Ungerstedt U (1989) Ca^{2+} dependence of the amphetamine, nomifensine, and Lu 19-005 effect on in vivo dopamine transmission. Eur J Pharmacol 166:261–269
23. Butcher SP, Fairbrother IS, Kelly JS, Arbuthnott GW (1988) Amphetamine-induced dopamine release in the rat striatum: an in vivo microdialysis study. J Neurochem 50:346–355
24. Walfson B, Hetrick WD, Lake CL, Siker ES (1978) Anesthetic indices — further data. Anesthesiology 48:187–190
25. Koorn R, Kahn RA, Brannan TS, Martinez-Tica J, Weinberger J, Reich DL (1993) Effect of isoflurane and halothane on in vivo ischemia-induced dopamine release in the corpus striatum of the rat. Anesthesiology 79:827–835
26. Warner DS, McFarlane C, Todd MM, Ludwig P, McAllister AM (1993) Sevoflurane and halothane reduce focal ischemic brain damage in the rat. Anesthesiology 79:985–992
27. Westerink BHC (1979) Further studies on the sequence of dopamine metabolism in the rat brain. Eur J Pharmacol 56:313–322
28. Waldmeier PC, Lauber J, Blum W, Richter WJ (1981) 3-Methoxytyramine: its suitability as an indicator of synaptic dopamine release. Naunyn-Schmiedeberg's Arch Pharmacol 315: 219–225
29. Kaplan GP, Hartman BK, Creveling CR (1979) Immunohistochemical demonstration of catechol-*o*-methyltransferase in mammalian brain. Brain Res 167:241–250
30. Westerink BHC, Spaan SJ (1982) On the significance of endogenous 3-methoxytyramine for the effects of centrally acting drugs on dopamine release in the rat brain. J Neurochem 38:680–686
31. Saller CF, Salama AI (1986) 3-Methoxytyramine accumulation: effects of typical neuroleptics and various atypical compounds. Naunyn-Schmiedeberg's Arch Pharmacol 334:125–132
32. Kaakkola S, Wurtman RJ (1992) Effects of COMT inhibitors on striatal dopamine metabolism: a microdialysis study. Brain Res 587:241–249
33. El-Maghrabi EA, Eckenhoff RG (1993) Inhibition of dopamine transport in rat brain synaptosomes by volatile anesthetics. Anesthesiology 78:750–756
34. Mantz J, Varlet C, Lecharny J, Henzel D, Lenot P, Desmonts J (1994) Effects of volatile anesthetics, thiopental, and ketamine on spontaneous and depolarization-evoked dopamine release from striatal synaptosomes in the rat. Anesthesiology 80:352–363
35. Bonhomme N, Deurwaerdere PD, Moal ML, Spampinato U (1995) Evidence for 5-HT4 receptor subtype involvement in the enhancement of striatal dopamine release induced by serotonin: a microdialysis study in the halothane-anesthetized rat. Neuropharmacology 34:269–279
36. Deurwaerdere PD, Bonhomme N, Lucas G, Moal ML, Spampinato U (1996) Serotonin enhances striatal dopamine outflow in vivo through dopamine uptake sites. J Neurochem 66:210–215