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Local Anesthetic- and Halothane-induced Alterations of the Stimulation-induced Release of ^{3}H-Dopamine from Rat Striatal Slices

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The purpose of this study was to evaluate and compare the effects of halothane with those of several local anesthetics in altering the release of ^{3}H-dopamine from the rat striatum by nicotinic activation and depolarization with potassium chloride. Slices from rat striatum were dissected and incubated with ^{3}H-dopamine (8 μM) for 30 min prior to being placed in isolated superfusion chambers. Following a washout period, release of ^{3}H-dopamine was induced by 300 μM dimethyl-4-phenylpiperazine (DMPP), a known nicotinic agonist, or potassium chloride (KCl), 50 mM. Drugs were added to the superfusion buffer for various periods prior to DMPP or KCl. Halothane produced a significant and dose-dependent decrease in the DMPP-induced release of dopamine. Dopamine release was decreased 20, 35, and 38 per cent with halothane 0.95, 1.5, and 2.5 per cent, respectively. Halothane had no effect on the release induced by KCl. All the local anesthetics produced marked decreases in the DMPP-induced release of ^{3}H-dopamine in concentrations commonly used in patients receiving the drugs for regional block. There were 56, 77, and 70 per cent decreases in the DMPP-induced release with procaine (3×10^{-5}M), cocaine (2.9×10^{-5}M), and lidocaine (2.1×10^{-5}M), respectively. Lidocaine and procaine had no effect on KCl-induced release, while cocaine and bupivacaine facilitated KCl-induced release. It is concluded that both halothane and local anesthetics can modify the release of dopamine from the striatum induced by activation of cholinergic–nicotinic receptors. (Key words: Anesthetics, volatile, halothane; Anesthetics, local, lidocaine; Anesthetics, local, cocaine; Anesthetics, local, bupivacaine; Anesthetics, local, procaine; Sympathetic nervous system, dopamine; Nicotinic agonist, DMPP.)

NUMEROUS INVESTIGATORS have demonstrated that local anesthetics inhibit the release of norepinephrine following electrical stimulation of adrenergic nerves.[1–3] In addition, local anesthetics can block the release of norepinephrine induced by activation of nicotinic receptors, although they are without effect in preventing the release of norepinephrine following depolarization with high potassium concentrations.[4,5] Although the final steps in secretion coupling are similar following all three stimulation methods, and all require extracellular calcium,[6–8] the initial steps leading to release differ. In contrast to the effects of local anesthetics, those of general anesthetics such as halothane on the release of norepinephrine are controversial. Muldoon *et al.*[9] and Roizen *et al.*[10] observed that halothane decreased the electrically induced release of norepinephrine from dog saphenous vein and guinea pig vas deferens, respectively. On the other hand, Göthert reported that halothane had no effect on the release of norepinephrine from the rabbit heart following electrical or potassium chloride stimulation, while it antagonized the response to nicotinic agonists.[4] Göthert *et al.* observed similar phenomena with other general anesthetic agents.[11] Göthert proposed that halothane produces a selective inhibition of nicotine-induced release of norepinephrine from the rabbit heart by inducing a conformational change of receptor proteins, which may prevent the interaction of agonists with the nicotinic receptor.[4]

The purpose of the present study was to compare the effects of halothane and local anesthetics on the release of dopamine from the central nervous system. Since it had been shown that nicotinic agonists can release ^{3}H-dopamine from superfused rat striatal slices,[12] this model was used to evaluate these effects of anesthetics on catecholamine release.

Methods

Preparation of Slices

Male Sprague-Dawley rats weighing 150–200 g were killed by decapitation. The brains were immediately removed and the striata rapidly dissected out with glass manipulators at 4 C. The isolated striata were then sliced at a thickness of 0.7 mm by a McIlwain tissue chopper. Individual slices were selected (10 mg) and preincubated in minivials for 10 min at 37 C in 1.9 ml Krebs–Ringer bicarbonate buffer containing, in mM: NaCl, 118.6; $NaHCO_3$, 25.0; KCl, 4.8; KH_2PO_4, 1.2; $CaCl_2$, 2.5; $MgSO_4$, 7.0; H_2O, 1.2; glucose, 11.1. Following preincubation for 10 min, the slices were incubated with 10 μCi ^{3}H-dopamine (100 μl; SA 6.1 Ci/mmol, final concentration 0.8 μM) for 30 min in an atmosphere of oxygen,

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95 per cent–carbon dioxide, 5 per cent. Individual slices were transferred to perfusion chambers jacketed with warm water at 37 C. The slices were held in place between two platinum mesh grids and superfused with buffer at a flow rate of 0.5 ml/min with a Harvard pump.

Application of Drugs

For studies of local anesthetics, slices were superfused for 15 min with normal buffer and then switched to buffer containing a local anesthetic. Following an additional 30 min, the slices were stimulated for 5 min with a buffer containing potassium chloride, 50 mM, or 300 μM dimethyl-4-phenylpiperazine (DMPP), a drug with known nicotinic agonist activity, plus a local anesthetic. Control slices were superfused with normal buffer prior to switching to the buffer containing KCl or DMPP. Superfusate fractions were collected at 5-min intervals into iced tubes containing 100 μl of a protector solution (EDTA, 5 ml, 2 per cent, *p*H 7; dopamine [100 μg/ml], 5 ml, and thioglycollic acid, 400 μl). A portion was taken for determination of total ^{3}H and the remaining sample processed for separation of ^{3}H-dopamine and ^{3}H-metabolites according to the procedure described by Westfall *et al.*[13] The following local anesthetics were studied: lidocaine (2.1×10^{-5} M),§ procaine (3×10^{-5} M),§ bupivacaine (3×10^{-6} M),§ and cocaine (2.9×10^{-5} M).§ These concentrations were chosen because they compare favorably with those seen in the plasma of patients receiving the drugs for regional block.

For the halothane studies, Krebs–Ringer bicarbonate buffer was saturated with various concentrations of halothane by use of a Fluotec vaporizer using oxygen, 95 per cent–carbon dioxide, 5 per cent, as the inflow gas. The concentration of halothane being delivered to the perfusion buffer was continuously monitored by a halothane meter (Model 73 Cavitron). Halothane concentration was also determined in samples obtained directly from the outflow of the vaporizer, as well as from the perfusion buffer, and assayed daily by gas chromatography by direct injection or using the tonometry method described by Sawyer, *et al.*[14]

Following saturation of the perfusion buffer for 45 min, the buffer was taken in closed 50-ml syringes, placed in a Harvard infusion pump, and delivered to glass perfusion chambers. The concentration of halothane in the perfusion buffer entering the superfusion chambers was assayed for each experiment by gas chromatography. Three concentrations of halothane, 1.0, 1.5, and 2.5 per cent, were studied. The slides were superfused for 30 min with a buffer containing halothane and then switched to a buffer containing 50 mM KCl (ED_{70}) or 300 μM DMPP (ED_{70}) plus halothane. Control slices were superfused with normal buffer in place of buffer with halothane. Superfusate samples were collected in 5-ml fractions as described above.

Identification and Assay of ^{3}H-Dopamine

The superfusate samples were collected into 100 μl of the protector solution as described above. Two milliliters of absolute alcohol were added to each sample and the samples placed in a freezer at −30 C for one to two days. The superfusate samples were adjusted to *p*H 6.6–6.9 with a NaH_2PO_4 buffer (0.01 M, *p*H 7.2) and then passed over an Amberlite column (Amberlite CG50 Type II, 200–400 mesh, purified and buffered with a NaH_2PO_4–$K_2H\,PO_4$ solution, 0.2 M, *p*H 6.1; 2.5 cm high, 0.5 cm diameter) to separate ^{3}H-dopamine and ^{3}H-3 methoxytyramine from ^{3}H acid metabolites that passed through the column in the effluent. One milliliter of the effluent was taken for analysis by liquid scintillation spectrometry. The Amberlite column was washed with 5 ml of 3:5 ethanol–H_2O and with 5 ml of water containing Triton X-100 (1 per cent). ^{3}H-dopamine and ^{3}H-methoxytyramine (3-MT) were eluted with 5 ml of 0.2 N acetic acid in tubes containing 400 μl of a protective solution (EDTA, 2 per cent–thioglycollic acid, 0.6 per cent).

Finally, ^{3}H-dopamine was separated from the ^{3}H-O-methylated amine by adsorption on alumina columns. Each Amberlite eluate was adjusted to *p*H 8.4 with Tris buffer (0.5 ml) and passed over an alumina column (100 mg, 0.5 cm diameter). The alumina columns were washed with 5 ml sodium acetate (0.2 M, *p*H 8.4) and then with 5 ml water containing 1 per cent Triton X-100. ^{3}H-dopamine was eluted and collected directly into scintillation vials with 1 ml HCl (0.2 N). For liquid scintillation counting, samples were placed in 10 ml of a Triton-based solution containing 5.5 g 2.5 diphenyloxazole, 150 mg 1.2 bis[2-15-phenyloxazolyl]-benzene, and a 2:1 mixture of toluene and Triton X-100. The samples were counted in a Packard Tri-Carb liquid scintillation spectrometer. The mean recovery of dopamine added to superfusate samples and carried through the procedure was 73 per cent. All samples have been corrected for this recovery.

§ Lidocaine, 2.1×10^{-5} M = 5 μg/ml; procaine, 3×10^{-5} M = 7 μg/ml; bupivacaine, 3×10^{-6} M = 1 μg/ml; cocaine, 2.9×10^{-5} M = 9 μg/ml.

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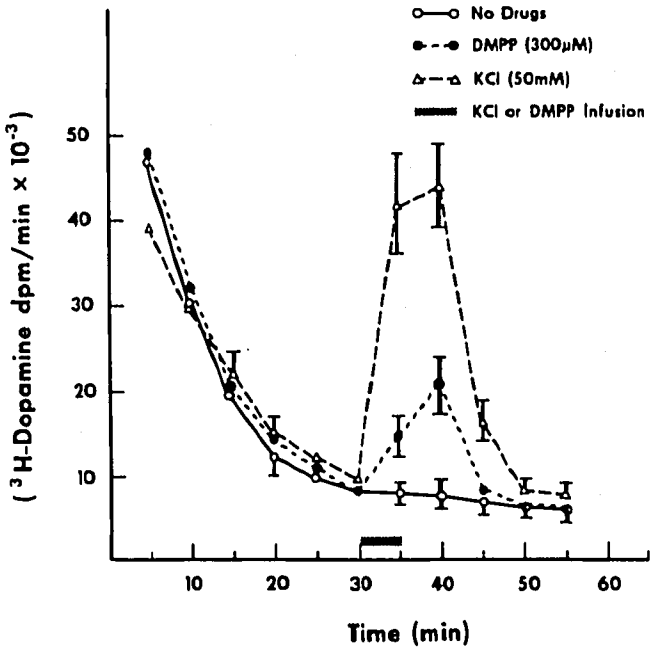

FIG. 1. The effect of a 5-min pulse of DMPP (300 μM) or KCl (50 mM) on the efflux of ^{3}H-dopamine from superfused striatal slices. Slices were prepared and superfused according to details described in Methods. Data are plotted as dpm/min of ^{3}H-dopamine × 10^{-3} versus time in min. Each point represents mean data ± SEM in at least ten separate slices.

Tissues were obtained at the end of the superfusion and homogenized with 2 ml of 3:1 methanol–water containing EDTA, 100 μl, 2 per cent, and sodium metabisulfite, 100 μl, 20 per cent, and placed in the freezer. The next day the tissues were mixed on a vortex mixer and centrifuged in a Sorvall refrigerated centrifuger tube at 10,000 rpm for 10 min. A 50-μl volume of the superfusate was taken for assay of total ^{3}H and the remaining sample processed as described above for the superfusate samples.

Uptake of ^{3}H-Dopamine

The effect of bupivacaine on the uptake of ^{3}H-dopamine was compared with effects of cocaine, lidocaine, and benztropine according to the method described by Tassin *et al.*[15] Cocaine, lidocaine and benztropine were used as control substances. Synaptosomes were prepared from rat striatum by homogenization of 50 mg tissue in 0.32 M sucrose (dilution 1/20) and centrifugation at 1,000 × *g* for 10 min. An amount (100 μl) of the supernatant representing 5 mg tissue was added to separate incubation vessels containing a total volume of 4 ml of physiologic medium (described above) containing pargyline (1.25×10^{-4} M) and ascorbic acid (2×10^{-3} M) and preincubated at 37 C for 5 min in the presence or absence of benztropine (10^{-6} M), bupivacaine (3×10^{-6} M), cocaine (2.9×10^{-5} M), or lidocaine (2.1×10^{-5} M). ^{3}H-dopamine was added in a concentration of 7.4×10^{-8} M and 0.5-ml aliquots (0.6 mg tissue) were taken at 45, 90, and 135 seconds for determination of ^{3}H-dopamine uptake. The synaptosomes were collected by passage through millipore filters (Millipore 0.8 μM, 25 mm at 25 C) following a wash at room temperature with NaCl, 0.5 ml, 0.9 per cent. The filters were added directly to scintillation vials containing ethanol/methanol, 4 ml (3/1, v/v) and toluene, 10 ml, containing 2,5-diphenyloxazole (PPO), 0.4 per cent, and 1,4-bis[2-(5 phenyloxazolyl)]-benzene (POPOP), 0.01 per cent, and assayed by liquid scintillation spectrometry.

Calculation of Data

The release of ^{3}H-dopamine was calculated from the formula:

$$\frac{A - B}{A + B + C} \times 100$$

and expressed as the stimulation-induced overflow of ^{3}H-dopamine or as the stimulation-induced overflow of ^{3}H-dopamine as a percentage of the total ^{3}H-dopamine in the tissue at the onset of the stimulation.

A = the total overflow of ^{3}H-dopamine during the stimulation.

B = the estimated spontaneous overflow during the stimulation period.

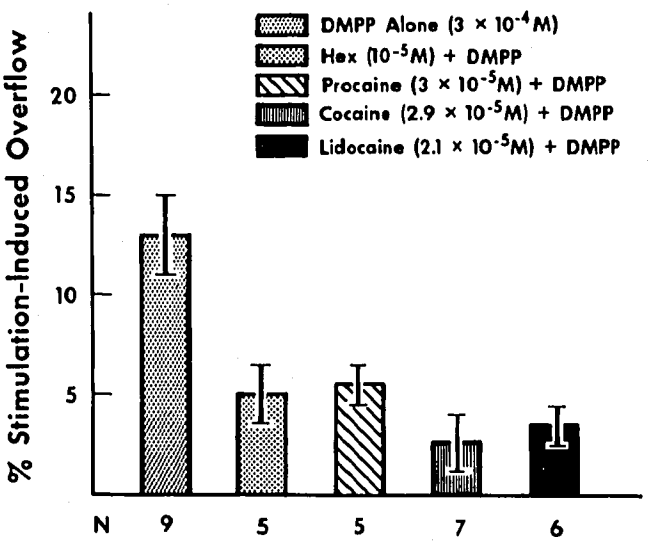

FIG. 2. Effects of DMPP alone and in the presence of various drugs on the efflux of ^{3}H-dopamine from superfused striatal slices. Data are plotted as described in the legend of figure 3. For details see Methods.

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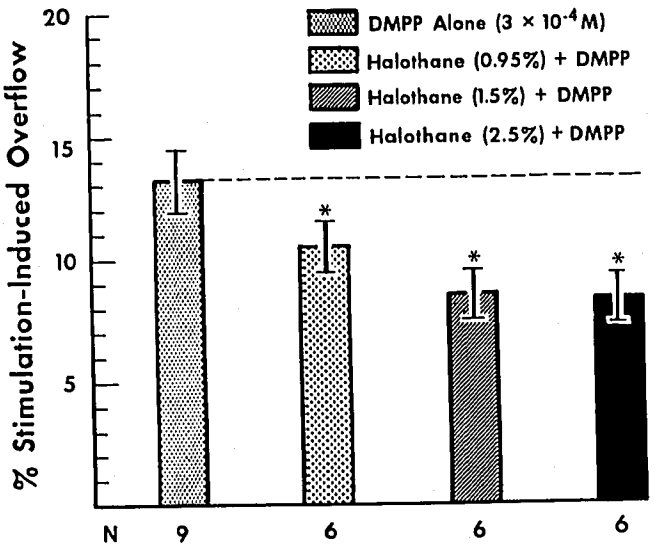

FIG. 3. Effects of DMPP and DMPP + halothane on the efflux of ^{3}H-dopamine from superfused striatal slices. Slices were prepared and superfused as described in Methods. Data are plotted as percentage stimulated induced overflow of ^{3}H-dopamine (fractional release) in response to a 5-min pulse of DMPP in the absence or presence of halothane. Each bar is the mean ± SEM obtained from the number (N) of experiments listed at the bottom of the bar. (*$P < .05$.)

A − B = the stimulation-induced release.
A + B + C = total ^{3}H-dopamine content in the tissue at the onset of stimulation calculated by adding the ^{3}H-dopamine overflow and the ^{3}H-dopamine content in the tissue at the end of the superfusion.

Student's t test was used for statistical analysis of the data.

Results

We previously reported that following 30-min superfusion, 9.8 per cent of the total radioactivity in the superfusate is represented by various metabolites.[16] Similar results were obtained in the present study. Following application of either a medium containing a high potassium concentration or a medium containing DMPP, there was a highly significant increase in the overflow of ^{3}H-dopamine (fig. 1), as well as a similar but smaller increase in ^{3}H-metabolites (data not shown). This is quite similar to the increase seen following electrical stimulation.[16] With the concentration used, potassium chloride produced a greater increase in ^{3}H-dopamine overflow than DMPP. The effect of DMPP was blocked by the stimultaneous administration of hexamethonium (10^{-5} M) (fig. 2), while the ganglion

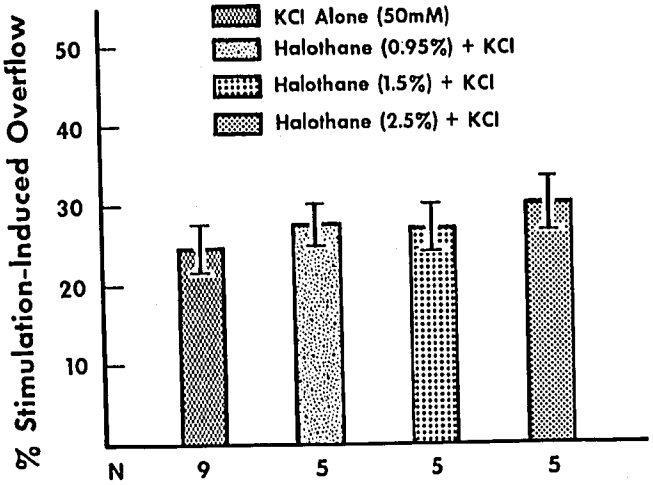

FIG. 4. Effects of KCl and KCl + halothane on the efflux of ^{3}H-dopamine from superfused striatal slices. Data are plotted as described in the legend of figure 3. For details see Methods.

blocker had no effect on the release of ^{3}H-dopamine induced by potassium chloride.

Halothane produced a small but significant concentration-dependent decrease in the release of ^{3}H-dopamine, with a maximum effect at 1.5 per cent (fig. 3). In contrast, halothane had no effect on the release of ^{3}H-dopamine induced by potassium

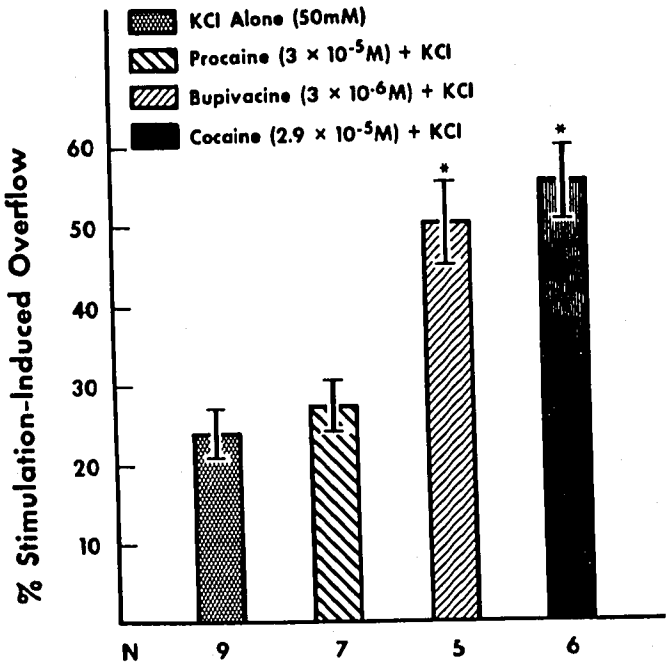

FIG. 5. Effects of KCl alone and in the presence of local anesthetics on the efflux of ^{3}H-dopamine from superfused striatal slices. Data are plotted as described in the legend of figure 3. For details see Methods. (*$P < .001$.)

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TABLE 1. Effects of Benztropine and Local Anesthetics on the Uptake of ^{3}H-Dopamine into Crude Synaptosomes of Rat Striatum

Addition	Concentration M	Time after ^{3}H-DA Addition (Sec) 45	90	135
None	—	2.9 ± 0.2*	4.6 ± 0.3	5.8 ± 0.4
Benztropine	10^{-6}	0.65 ± 0.03†	0.9 ± 0.02†	1.0 ± 0.05†
Bupivacaine	3×10^{-6}	2.7 ± 0.3	4.4 ± 0.4	4.7 ± 0.4
Bupivacaine	3×10^{-5}	2.65 ± 0.2	3.9 ± 0.5	5.3 ± 0.4
Lidocaine	2.1×10^{-5}	2.7 ± 0.5	4.4 ± 0.4	5.5 ± 0.4
Cocaine	2.9×10^{-5}	1.2 ± 0.1†	1.8 ± 0.2†	2.2 ± 0.2†

* Data reported as dpm × 10^{-3}/assay (0.5 mg protein) ± SEM.
† $P < .001$, compared with control.

chloride even at a very high concentration, 2.5 per cent (fig. 4).

Procaine, cocaine, and lidocaine all produced marked inhibition ($P < .001$) of the DMPP-induced release of ^{3}H-dopamine (fig. 2). In marked contrast to the effect on DMPP-induced release, bupivacaine and cocaine produced potentiation of the release of ^{3}H-dopamine following potassium chloride administration (fig. 5), while procaine and lidocaine (data not shown) had no effect. Since cocaine is well known to inhibit the neuronal uptake of catecholamines, resulting in increased overflow to stimulated release, the effect of bupivacaine on dopamine uptake was sought as a possible explanation for a similar (to cocaine) increase in the KCl-induced overflow. Bupivacaine produced no alteration in the uptake of ^{3}H-dopamine into striatal synaptosomes, while both cocaine and benztropine produced marked inhibition of dopamine uptake (table 1).

Discussion

Halothane is well known to depress several variables of cardiovascular function, including cardiac output, stroke volume, mean arterial pressure, and myocardial contractility, as well as to dilate peripheral veins. The mechanism of these effects is controversial. Roizen *et al.*[10] have observed that halothane causes a decrease in spontaneous and electrically stimulated release of norepinephrine from the isolated guinea pig hypogastric nerve–vas deferens preparation. These investigators suggest that depression of adrenergic discharge is due to a direct action of halothane on sympathetic nerve endings, which may account, in part, for the cardiovascular depression. A similar conclusion was reached by Muldoon *et al.*,[9] who observed that halothane caused inhibition of electrically induced vasoconstriction in cutaneous veins by interfering with the release of norepinephrine from sympathetic nerve terminals. In sharp contrast, Göthert observed that halothane was without effect in altering electrically induced or potassium chloride-induced release of norepinephrine from the rabbit heart, while it was very effective in blocking the release of norepinephrine by activation of nicotinic receptors.[4] He found good agreement between the concentration of anesthetic that would produce 50 per cent inhibition of norepinephrine release and the minimum alveolar concentration (MAC) needed for general anesthesia. Using the oil/gas partition coefficient, similar results have been found for a wide range of anesthetics and alcohols.[11] Göthert postulated that the inhibition of nicotine-induced norepinephrine release may be due to conformational changes of receptor protein, which prevents the interaction of agonists with the nicotinic receptor.

Since this may have great relevance to its mechanism of action as a general anesthetic, this study of the effect of halothane on the release of monoamines from central nervous system tissue was undertaken. Activation of nicotinic receptors causes release of dopamine from striatal slices,[12] and this appeared to be a good model in which to study the effects of halothane. DMPP was chosen as a nicotinic agonist and was shown to increase the release of ^{3}H-dopamine from striatal slices. The effect of DMPP was blocked by the administration of hexamethonium, suggesting that the release was caused by activation of nicotinic receptors and not by its well-known tyramine-like effect. The demonstration that local anesthetics produced marked inhibition of the release induced by DMPP is consistent with DMPP acting at nicotinic receptors, since local anesthetics do not alter the release of dopamine produced by tyramine.[12] A similar release of ^{3}H-dopamine was previously seen following application of high concentrations of acetylcholine.[17] This was likewise blocked by nicotinic antagonists. The inhibition of the DMPP-induced release of ^{3}H-dopamine from striatal slices by local anesthetics observed in this study is analogous to the effect of these drugs in antagonizing the release of norepinephrine by nicotinic activation in peripheral adrenergic neurons.[4,5]

The mechanism by which drugs act to produce central nervous system depression and general anesthesia remains unknown. Adrenergic mechanisms have been shown to be modulators of anesthetic requirements. Depletion of central nervous system catecholamines produced by reserpine or methyldopa causes anesthetic requirements to decrease by 30–40 per cent.[18,19] Similar decreases in anesthetic requirement can be achieved by producing lesions in the large

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central norepinephrine-containing cell bodies of the locus ceruleus.¶ Local anesthetics acting at the central nervous system level can produce either sedation or stimulation, depending on the local anesthetic and dose chosen. Lidocaine, which is known to produce sedation, was shown to decrease anesthetic requirement in a manner similar to that produced by catecholamine depletion, showing a ceiling effect at a 30–40 per cent decrease.[20] In sharp contrast, cocaine, which blocks catecholamine reuptake and increases catecholamine concentration at nerve terminals, increases central nervous system activity and anesthetic requirement.[21]

This study demonstrates that halothane and local anesthetics decrease the nicotine-induced release of ^{3}H-dopamine from the rat striatum. This is consistent with the effect of these agents in altering the nicotine-induced release of norepinephrine from the rabbit heart.[4] All local anesthetics tested produced much greater inhibition of the release of dopamine after nicotinic stimulation than was seen following maximal concentrations of halothane. Potassium-induced catecholamine release, however, was not altered by procaine and lidocaine (CNS sedatives), but was increased by cocaine (CNS stimulant) and bupivacaine (non-sedative but stimulant at high concentrations). The mechanism of release induced by a medium containing a high potassium concentration is apparently due to a decrease in the membrane potential of the neuron, and it is this, rather than the action potential, that is responsible for the liberation of transmitters such as norepinephrine and dopamine.[22] Although the initial events leading to transmitter release by neural stimulation (invasion of the nerve terminal in some unknown way by the action potential) and potassium (diminution of the electrogenic transmembrane potential gradient) differ, the subsequent steps in secretion coupling are similar, *i.e.*, entrance of extracellular calcium and release by exocytosis.[22–24] Therefore, this technique is very useful, and has been frequently employed for studying the release of transmitters in situations where the nerve terminals themselves cannot be effectively activated by electrical stimulation. It will be interesting to see whether halothane and the local anesthetics influence the electrically-induced release of dopamine and the release induced by potassium similarly. This study also demonstrated that bupivacaine and cocaine did not block dopamine uptake in similar ways (table 1). This suggests that inhibition of dopamine uptake is not the explanation for the potentiation of the potassium-induced release following cocaine and bupivacaine.

Similarities between the effects of halothane and those of local anesthetics that have central nervous system sedative properties on dopamine release suggest that nicotinic receptors on catecholamine neurons may play a modulating role in determining anesthetic requirements. Further studies are needed to document the effects of these anesthetics on norepinephrine release, since it could be argued that there may be differences in the effects of drugs on the release of dopamine, compared with norepinephrine.

In summary, this study shows that both local anesthetics and halothane depress the nicotinic-induced release of dopamine, although the inhibitory effect of local anesthetics is much greater. In contrast, halothane, lidocaine, and procaine had no effect on the release induced by potassium chloride. It will be of great interest to determine whether similar effects are seen in central noradrenergic neurons.

¶ Roizen, MF, et al, Abstracts, American Society of Anesthesiologists, 1976, pp 501–502.

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