Potentiating Effect of Tyramine on Acetaldehyde-Induced Vasoconstriction in Isolated Dog Mesenteric Arteries

Shigetoshi CHIBA and Miyoko TSUKADA
Department of Pharmacology, Shinshu University School of Medicine,
Matsumoto 390, Japan
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Abstract—The stainless steel cannula inserting method was used to investigate the effects of acetaldehyde on isolated and perfused dog mesenteric arteries. Acetaldehyde when intraluminally administered induced a marked vasoconstriction, but repetitive injections of acetaldehyde caused tachyphylaxis. Acetaldehyde-induced vasoconstrictions were blocked by bunazosin, an alpha-1 adrenoceptor antagonist. After tyramine treatment, the acetaldehyde-induced constriction was consistently restored temporarily. It is suggested that tyramine may induce a release of norepinephrine mostly from the vesicle to the neuronal cytosol, and acetaldehyde may cause a release of norepinephrine from the cytosol to the extracellular space in the isolated canine mesenteric artery.

It has been widely accepted that the norepinephrine stored in the adrenergic varicosity is mostly released by three mechanisms, i.e., 1) leakage represented by organic solvents, 2) pharmacological displacement represented by indirect sympathomimetic amines, and 3) exocytotic release represented by membrane depolarization (1). It has been considered that acetaldehyde is one of the compounds that can activate the leakage of stored transmitter from adrenergic storage vesicles (1, 2). In 1975, Lai and Hudgins (2) reported that tetrodotoxin did not abolish contractile responses in rat vas deferens induced by tyramine or acetaldehyde. They also demonstrated that, unlike acetaldehyde, tyramine-induced release of [14C]norepinephrine from rabbit aorta was prevented by cocaine. In 1979, Kobayashi et al. (3) reported that acetaldehyde induced positive chronotropic and inotropic responses by releasing catecholamines from the adrenergic nerve storage in isolated canine atrial preparations. They also reported that the acetaldehyde-induced responses were inhibited by beta-adrenoceptor blockade, but not by tetrodotoxin. Moreover, imipramine, an uptake blocker, frequently caused an enhancement of acetaldehyde-induced cardiac actions. In the present study, we made an attempt to investigate the effects of acetaldehyde on isolated dog arterial vessels, using the cannula inserting method developed by Hongo and Chiba (4), which was modified by Tsuji and Chiba (5).

Nine mongrel dogs weighing 6 to 16 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). After treatment with sodium heparin (200 units/kg, i.v.), dogs were sacrificed by rapid exsanguination from the right common carotid artery. Median branches of the cranial mesenteric artery which supply the large middle portion of the small intestine were carefully isolated. Isolated arteries selected for study were 10–15 mm in length and 0.8–1.2 mm in outer diameter; they were cannulated as described previously (4, 5). Briefly, the cannulated artery was placed in a bath maintained at 37°C and perfused with Krebs’ solution by means of a peristaltic pump. The perfusion solution was bubbled with 95% O₂ and 5% CO₂ which maintained the pH of the solution between 7.2–7.4. The flow rate was initially adjusted so that the perfusion pressure was between 50–100 mmHg; subsequently, the flow rate was kept constant at 0.5–2.0 ml/min throughout the experiments. The constrictor response
was, therefore, observed as an increase in perfusion pressure. Drugs used in this study were acetaldehyde (Wako), tyramine hydrochloride (Tokyo Kasei), norepinephrine hydrochloride (Sankyo) and bunazosin hydrochloride (Eisai). Acetaldehyde was freshly distilled from the purchased acetaldehyde solution on the day of the experiments. The drug solution was administered in the rubber tubing close to the cannula in a volume of 0.01-0.03 ml.

When acetaldehyde was administered into the cannulated mesenteric artery in an adequate dose (10–50 μmol), immediate increases in perfusion pressure were obtained. The acetaldehyde-induced vasoconstriction became smaller and smaller during repetitive injections as shown in Fig. 1, showing the establishment of tachyphylaxis. Tyramine restored the acetaldehyde-induced vasoconstriction as shown in Fig. 1. Summarized data are shown in Fig. 2. Throughout the experiments by use of acetaldehyde, vasoconstrictor responses to norepinephrine were consistently induced in almost the same degree. Before and after establishment of acetaldehyde tachyphylaxis, maximum increases in perfusion pressure of 0.3 μg of norepinephrine were 61±25 mmHg (mean±S.E., n=6) and 72±13 mmHg, respectively, indicating no significant differences. When tyramine was administered, only small increases less than 20 mmHg were induced in doses of 10–100 μg. At 100 μg, tyramine frequently induced no significant vasoconstriction as shown in Fig. 1. Vasoconstrictor responses to 0.1 and 0.3 μg of norepinephrine and 50 μmol of acetaldehyde were completely inhibited by 10 μg of bunazosin in two experiments. Thus, postsynaptic mechanisms might not participate in the phenomenon of acetaldehyde-induced tachyphylaxis.

As reported before (3), a release of catecholamine induced by acetaldehyde might not be due to tyramine-like action, because acetaldehyde-induced cardiac responses were not modified by imipramine in doses which significantly inhibited tyramine-induced effects. Moreover, it had been demonstrated that acetaldehyde-induced actions were not influenced by the use of tetrodotoxin, which blocks electrical stimulation of the autonomic nervous system (6), indicating that acetaldehyde may induce catecholamine release without accompanying nerve excitation. In the present study by use of isolated vessel preparations, acetaldehyde produced tachyphylactic actions different from isolated heart preparations. The differences may be due to different tissues, i.e., heart and vessel, different perfusion system, i.e., blood-perfused or Krebs’ solution-perfused preparations, or other unknown mechanisms.

It has been considered that tyramine is taken up in succession by the neuronal uptake carrier and by the vesicular membrane carrier, and it displaces norepinephrine toward the neuronal cytosol and the extracellular space (1, 7). However, in isolated

Fig. 1. Tachyphylactic vasoconstrictor responses to repetitive injections of 50 μmol of acetaldehyde (AA) and its recovery after treatment with 100 μg of tyramine in an isolated, perfused canine mesenteric artery (M).
mesenteric arteries, tyramine has no clear vasoconstrictor responses as reported previously (8). It is considered that the isolated dog mesenteric arterial preparation contains sufficient amounts of norepinephrine in its adrenergic nerve terminals, because periarterial electric stimulation readily caused a marked vasoconstriction which was suppressed by alpha-adrenoceptor blockade or tetrodotoxin treatment as reported previously (9). Thus, it is suggested that tyramine may displace norepinephrine dominantly toward the cytoplasm but not toward the extracellular space in relatively large canine mesenteric arteries. The norepinephrine in the cytosol may be readily released by acetaldehyde. It seems that decreases in the norepinephrine in the cytosol cause decremental vasoconstrictor responses to acetaldehyde. After tyramine treatment, increased norepinephrine in the cytosol from the vesicle may be temporarily restored, causing a release of norepinephrine by acetaldehyde.

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Fig. 2. Summarized data of tachyphylactic responses to repetitive injections of 50 μmol of acetaldehyde (AA) and its recovery after treatment with 100 μg of tyramine. Initial injection of 50 μmol of AA induced an increase of 181 ± 27 mmHg (mean ± S.E.) in perfusion pressure in 6 preparations. P.P.: perfusion pressure. Vertical bars shows the S.E. of the means.

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