Modifications by Lidocaine and Its N-Dealkylated Metabolites of the Response of the Isolated Rabbit Aorta to Transmural Electrical Stimulation

Satoru Fukuda, M.D.,* Hiroshi Takeshita, M.D.,† and Noboru Toda, M.D., Ph.D.‡

Contractile responses of rabbit aortic strips to transmural stimulation and to exogenously applied norepinephrine (NE), potassium chloride (KCl), and histamine were studied in the presence of lidocaine or its metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (GX). Lidocaine, 10⁻⁴ and 5 x 10⁻⁴ M, attenuated the contractile response to transmural stimulation, whereas MEGX, 2 x 10⁻⁵ and 10⁻⁴ M, potentiated, but 5 x 10⁻⁴ M suppressed the response. GX, 2 x 10⁻⁵ to 5 x 10⁻⁴ M, potentiated the response to transmural stimulation. The suppression induced by lidocaine and MEGX was not reversed by excess calcium, 2.2 and 4.4 mm, but was partially reversed by cocaine, 5 x 10⁻⁴ M. Lidocaine, 5 x 10⁻⁴ M, and MEGX, 2 x 10⁻⁴ M, shifted the dose-response curve of NE to the right, whereas GX, 5 x 10⁻⁴ M, shifted the curve to the left. The maximum tension developed by K⁺ was attenuated by lidocaine, 5 x 10⁻⁴ M, MEGX, 5 x 10⁻⁴ and 2 x 10⁻³ M, and GX, 2 x 10⁻³ M. It may be concluded that lidocaine attenuates the response to stimulation of sympathetic nerves innervating the arterial wall by interfering with the release of NE. In contrast, the metabolites, MEGX and GX, potentiate the response, possibly by increasing the release of NE. MEGX in high concentrations appears to have the same mechanism of inhibitory action as does lidocaine. (Key words: Anesthetics, local; lidocaine, metabolites. Arteries; transmural stimulation. Metabolism: lidocaine metabolites. Sympathetic nervous system: catecholamines, norepinephrine.)

LIDOCAINE IS DEGRADED INTO SEVERAL METABOLITES, OF WHICH MONOETHYLGLYCINEXYLIDIDE (MEGX) AND GLYCYNEXYLIDIDE (GX) HAVE BEEN STATED TO HAVE THE SAME ANTIARRHYTHMIC, 1,2 LOCAL ANESTHETIC, 3,4 AND TOXIC CENTRAL NERVOUS SYSTEM ACTIONS 2,4,5 AS LIDOCAINE. MODIFICATION BY LIDOCAINE OF VASCULAR RESPONSIVENESS TO VASOCONSTRICTING AGENTS IN VITRO HAS BEEN INVESTIGATED BY FLEISCH AND TITUS 6 AND BY ALTURA AND ALTURA. 7 FURTHER STUDIES OF THE EFFECTS OF THE PHARMACOLOGICALLY ACTIVE METABOLITES, MEGX AND GX, MAY PROVIDE DATA FOR BETTER UNDERSTANDING OF CIRCULATORY CHANGES INDUCED BY INJECTIONS OF LIDOCAINE IN VIVO. THE LACK OF KNOWLEDGE ABOUT THE

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number of electrical pulses was kept constant (200 pulses) by changing the period of stimulation (100, 40, and 10 s for frequencies of 2, 5, and 20/s, respectively). Transmural stimulation was applied repeatedly until steady responses were obtained. In four preparations the response to transmural stimulation was tested in the presence of phenolamine, $10^{-6} \text{M}$, or bretylium, $2 \times 10^{-5} \text{M}$. The effects of $\text{Ca}^{++}$, 2.2 and 4.4 mm, or cocaine, $3 \times 10^{-6} \text{M}$, on the response to transmural stimulation in the preparation treated with lidocaine, MEGX, or GX, $5 \times 10^{-4} \text{M}$, were studied. In seven preparations the response to transmural stimulation by cocaine, $3 \times 10^{-6} \text{M}$, alone, was tested. It was ascertained that the altered responses of the preparation treated with lidocaine or its metabolites were returned to the control state by repeated washing of preparations.

Fig. 2. Modification by MEGX of the response to transmural stimulation and the dose–response curve of norepinephrine (NE). Mean values of the tension developed at 20/s and of the maximum contraction induced by NE in control medium were $0.45 \pm 0.07$ (n = 7) and $4.54 \pm 0.24$ (n = 13) g, respectively. MEGX slightly potentiated the tension developed at $2 \times 10^{-5}$ and $10^{-4} \text{M}$, but had a suppressive effect at $5 \times 10^{-4} \text{M}$.

Cumulative dose–response curves for NE, KCl, and histamine were obtained in both the absence (control) and the presence of $2 \times 10^{-5}$ to $2 \times 10^{-3} \text{M}$ lidocaine, MEGX, or GX. After 20-min exposure of preparations to test drugs, the responses to transmural stimulation or the dose–response relationship for NE, KCl, or histamine were obtained. The tension developed by NE, $5 \times 10^{-5} \text{M}$, KCl, $5 \times 10^{-2} \text{M}$, or histamine, $2 \times 10^{-4} \text{M}$, in control medium was taken as 100 per cent. Values presented in the text and figures are mean values ± SE. The data were analyzed.
of aortic strips was not altered by lidocaine, MEGX, or GX in concentrations ≤ 2 × 10⁻³ M.

Treatment with lidocaine, 2 × 10⁻⁵ M, did not alter the response to transmural stimulation at frequencies of 2, 5, and 20/s, whereas lidocaine, 10⁻⁴ M, significantly attenuated the response to transmural stimulation at 20/s. Further increase in the concentration to 5 × 10⁻⁴ M suppressed the response to stimulation at all frequencies used (fig. 1). The inhibitory effect of lidocaine was reversed by repeated washing of preparations. Treatment with MEGX, 2 × 10⁻⁵ and 10⁻⁴ M, slightly potentiated the response to transmural

Fig. 3. Modification by GX of the response to transmural stimulation and the dose–response curve of norepinephrine (NE). Mean values of the tension of contraction at 20/s and of the maximum contraction in control medium were 0.47 ± 0.07 (n = 6) and 4.48 ± 0.17 (n = 13) g, respectively. GX potentiated the tension developed and shifted the dose–response curve of NE to the left at 5 × 10⁻⁴ M.

statistically by the Student t test unpaired for data; P < 0.05 was considered significant.¶

Results

Contractile responses of aortic strips to transmural stimulation were abolished by pretreatment with bretylium, 2 × 10⁻⁴ M, and phentolamine, 10⁻⁶ M, in four of four preparations. The resting tension of the aortic strips was not altered by lidocaine, MEGX, or GX in concentrations ≤ 2 × 10⁻³ M.

¶ Drugs used and sources were: lidocaine hydrochloride, Fujisawa Pharmaceutical Co.; monoethylglycylxylidide hydrochloride, Fujisawa Pharmaceutical Co.; glycylxylidide hydrochloride, Fujisawa Pharmaceutical Co.; dl-norepinephrine hydrochloride, Sankyo Co.; histamine hydrochloride, Nakarai Chemical, Ltd.; cocaine hydrochloride, bretylium tosylate, Wellcome Pharmaceutical Co.; phentolamine mesylate, Giba-Geigy Ltd.

Fig. 4. Modification by Ca²⁺, 2.2 and 4.4 mM, and cocaine, 3 × 10⁻⁴ M, of the inhibitory effects of lidocaine at 5 × 10⁻⁴ M (upper panel) and MEGX at 5 × 10⁻⁴ M (lower panel) on the tension developed. The response at a frequency of 20/s in control medium was taken as 100 per cent. Mean values of contraction in the upper and lower panels were 0.44 ± 0.03 (n = 13) and 0.39 ± 0.03 (n = 11) g, respectively. The inhibitory effects of lidocaine and MEGX were not affected in the presence of Ca²⁺, but were incompletely reversed by cocaine at 20/s with potentiation at 2/s.
stimulation, while MEGX, 5 × 10⁻⁴ M, suppressed the response (fig. 2). Treatment with GX in concentrations ranging from 2 × 10⁻⁵ to 5 × 10⁻⁴ M significantly potentiated the response to transmural stimulation (fig. 3). The potentiating effect was reversed by repeated washing of preparations.

The inhibitory effect of lidocaine or MEGX, 5 × 10⁻⁴ M, on the response to transmural stimulation was not affected by the addition of Ca⁺⁺, 2.2 and 4.4 mM (fig. 4). Cocaine, 3 × 10⁻⁸ M, incompletely reversed the inhibitory effects of lidocaine and MEGX, 5 × 10⁻⁴ M, at 20/s, but significantly stimulated the response to transmural stimulation over the control at 2/s (fig. 4).

Treatment with cocaine alone significantly potentiated the response to transmural stimulation, and combined treatment with cocaine, 3 × 10⁻⁸ M, and GX, 5 × 10⁻⁴ M, caused an additional increase in the response (fig. 5).

The dose–response curve of NE was shifted to the right by lidocaine, 5 × 10⁻⁴ M (fig. 1) and, in contrast, was shifted to the left by GX, 5 × 10⁻¹ M (fig. 3). The response to NE was not influenced by treatment with MEGX in concentrations ≤ 5 × 10⁻⁴ M (fig. 2). Concentrations of NE sufficient to produce the same magnitude of contractions as that with transmural stimulation at frequencies of 5 and 20/s were 5.5 × 10⁻⁸ and 9.5 × 10⁻⁸ M, respectively. Lidocaine, 5 × 10⁻⁴ M, reduced the responses to these concentrations of NE by 11.6 ± 9.1 and 9.6 ± 7.0 per cent (n = 5), respectively; this represented markedly less than average inhibitions of the responses to transmural stimulation at 5 and 20/s (65.9 ± 9.6 and 92.9 ± 2.2 per cent, n = 8, respectively).

Effects of lidocaine, MEGX, and GX in concentrations from 2 × 10⁻⁵ to 2 × 10⁻⁸ M on the maximum contractions induced by NE, histamine, and K⁺, and the ED₅₀ of these agents, are listed in tables 1–3. The maximum response to K⁺ was attenuated by lidocaine, 5 × 10⁻⁴ M, MEGX, 5 × 10⁻⁴ M, and GX, 2 × 10⁻⁵ M. The inhibitory effect was greater with lidocaine. The contractile response to histamine was also attenuated by 2 × 10⁻³ M lidocaine or MEGX.

Discussion

The present study clearly demonstrated different effects of lidocaine and its metabolites on helically cut strips of rabbit aorta.

The contractile response to transmural stimulation applied under experimental conditions used in the present study is considered to result from NE released by excitation of adrenergic nerves, since the response is abolished by alpha-adrenoceptor blocking agents, adrenergic neuron blocking agents, or tetrodotoxin. Lidocaine, 10⁻⁴ M, or MEGX, 5 × 10⁻⁴ M, in concentrations insufficient to attenuate the contractile response to exogenous NE, reduced the response to transmural stimulation, and the attenuation of the response to transmural stimulation by lidocaine, 5 × 10⁻⁴ M, was appreciably greater than that of the response to exogenous NE. In contrast, it is known that alpha-adrenoceptor blocking agents reduce the response to exogenous NE more effectively than the response to adrenergic nerve stimulation. It may therefore be concluded that the attenuation by lidocaine and MEGX appears to be due mainly to an interference with the release of NE from adrenergic nerve terminals.

Concentrations of lidocaine used in this study are within a range in which the amplitude and the maximum rate of rise of action potentials of an isolated nerve preparation are significantly depressed. These alterations may be associated with slowed conduction and prolonged refractory periods. The threshold concentration of MEGX for inducing nerve blockade is greater than that of lidocaine. The lesser attenuation of the response to transmural stimulation by MEGX than by lidocaine may be associated with less susceptibility of nerves to MEGX.

That the inhibitory effect of lidocaine was related directly to frequencies of transmural neural stimulation, as seen with frog sciatic nerve, may also indicate the involvement of depression of nerve action potentials in the interference with the release of NE. Extracellular Ca⁺⁺ affects the membrane-stabilizing...
Table 1. Effects of Lidocaine on Responses of the Rabbit Aorta to Norepinephrine, KCl, and Histamine

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine Concentration (μM)</th>
<th>Control</th>
<th>2 x 10⁻⁴</th>
<th>10⁻⁴</th>
<th>5 x 10⁻⁴</th>
<th>2 x 10⁻³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine ED₅₀ (×10⁻⁷ M)</td>
<td></td>
<td>3.6 ± 0.5 (n = 11)</td>
<td>3.8 ± 0.5 (n = 7)</td>
<td>3.6 ± 0.5 (n = 6)</td>
<td>5.8 ± 0.8* (n = 5)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>100.7 ± 1.3 (n = 7)</td>
<td>99.8 ± 2.1 (n = 6)</td>
<td>102.2 ± 0.9 (n = 5)</td>
<td>—</td>
</tr>
<tr>
<td>KCl ED₅₀ (×10⁻³ M)</td>
<td></td>
<td>21.5 ± 0.9 (n = 8)</td>
<td>20.5 ± 1.0 (n = 5)</td>
<td>22.3 ± 1.3 (n = 5)</td>
<td>23.7 ± 0.6 (n = 4)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>101.6 ± 1.3 (n = 5)</td>
<td>101.5 ± 3.3 (n = 5)</td>
<td>85.1 ± 1.2† (n = 4)</td>
<td>—</td>
</tr>
<tr>
<td>Histamine ED₅₀ (×10⁻⁵ M)</td>
<td></td>
<td>5.2 ± 0.6 (n = 10)</td>
<td>5.5 ± 0.9 (n = 5)</td>
<td>5.2 ± 0.8 (n = 5)</td>
<td>5.4 ± 0.9 (n = 4)</td>
<td>21.6 ± 2.3† (n = 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>102.8 ± 1.1 (n = 5)</td>
<td>104.8 ± 4.8 (n = 5)</td>
<td>102.8 ± 1.6 (n = 4)</td>
<td>94.8 ± 2.9† (n = 5)</td>
</tr>
</tbody>
</table>

* Different from control, P < 0.05.
† Different from control, P < 0.01.

The effect of local anesthetics on isolated lobster axons, but does not influence the effect on myelinated nerves or squid axons. Thus, the finding that the addition of Ca²⁺ (2 and 3 times normal) to isolated aortic strips did not reverse the inhibitory effect of lidocaine or MEGX does not necessarily exclude the possibility that the local anesthetic stabilizes the autonomic nerve membrane. Further, inhibition of the transmembrane influx of Ca²⁺ may not be involved in the depressant effect of lidocaine and MEGX.

As shown in figure 1, the tension developed at higher frequencies was more susceptible to lidocaine. This is specific to local anesthetics, as reported by Covino and Vassallo. Toda reported that the tension developed at 5 or 20/s was attenuated by bretylium, and that this inhibitory effect was reversed with resulting potentiation by cocaine. Such potentiation can be explained either by active extrusion of bretylium accumulated within nerve terminals or by some other mode of inactivation of the bretylium by cocaine. Failure to demonstrate potentiation or reversal at 5 and 20/s by cocaine in the presence of lidocaine may be due to more susceptibility of the tension developed to lidocaine at higher frequencies. These considerations suggest that lidocaine possesses a bretylium-like inhibitory action in addition to action specific to local anesthetics at the nerve terminals.

Treatment with MEGX, 2 x 10⁻⁵ and 10⁻⁴ M, and GX, 2 x 10⁻⁵, 10⁻⁴, and 5 x 10⁻⁴ M, potentiated the response to transmural stimulation. Similar potentiation of the responses to transmural stimulation and to exogenous NE has been shown with cocaine, desipramine, and pyrogallol, but not with monoamine oxidase inhibitors. In the present study, dose-re-

Table 2. Effects of MEGX on Responses of the Rabbit Aorta to Norepinephrine, KCl, and Histamine

<table>
<thead>
<tr>
<th></th>
<th>MEGX Concentration (μM)</th>
<th>Control</th>
<th>2 x 10⁻⁴</th>
<th>10⁻⁴</th>
<th>5 x 10⁻⁴</th>
<th>2 x 10⁻³</th>
</tr>
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<tbody>
<tr>
<td>Norepinephrine ED₅₀ (×10⁻⁷ M)</td>
<td></td>
<td>3.7 ± 0.4 (n = 13)</td>
<td>3.6 ± 0.6 (n = 4)</td>
<td>3.6 ± 0.8 (n = 4)</td>
<td>3.6 ± 0.5 (n = 6)</td>
<td>5.9 ± 0.4† (n = 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>100.5 ± 1.8 (n = 4)</td>
<td>101.0 ± 1.1 (n = 4)</td>
<td>100.7 ± 2.2 (n = 6)</td>
<td>96.8 ± 2.7 (n = 5)</td>
</tr>
<tr>
<td>KCl ED₅₀ (×10⁻³ M)</td>
<td></td>
<td>20.4 ± 1.0 (n = 9)</td>
<td>—</td>
<td>20.4 ± 1.8 (n = 5)</td>
<td>22.6 ± 2.0 (n = 6)</td>
<td>24.4 ± 1.7* (n = 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>—</td>
<td>99.0 ± 0.8 (n = 5)</td>
<td>94.9 ± 2.0* (n = 6)</td>
<td>86.6 ± 2.8† (n = 5)</td>
</tr>
<tr>
<td>Histamine ED₅₀ (×10⁻⁵ M)</td>
<td></td>
<td>5.2 ± 0.5 (n = 9)</td>
<td>—</td>
<td>5.1 ± 0.7 (n = 6)</td>
<td>11.6 ± 2.7* (n = 5)</td>
<td>17.2 ± 2.2† (n = 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>—</td>
<td>102.1 ± 1.6 (n = 6)</td>
<td>101.7 ± 5.6 (n = 5)</td>
<td>101.1 ± 2.8 (n = 5)</td>
</tr>
</tbody>
</table>

* Different from control, P < 0.05.
† Different from control, P < 0.01.
Table 3. Effects of GX on Responses of the Rabbit Aorta to Norepinephrine, KCl, and Histamine

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>2 x 10^{-4}</th>
<th>10^{-4}</th>
<th>5 x 10^{-4}</th>
<th>2 x 10^{-3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine ED_{50} (×10^{-7} m)</td>
<td>3.9 ± 0.3 (n = 13)</td>
<td>4.1 ± 0.3 (n = 6)</td>
<td>3.4 ± 0.7 (n = 4)</td>
<td>2.4 ± 0.2† (n = 5)</td>
<td>4.2 ± 0.8 (n = 5)</td>
</tr>
<tr>
<td>Norepinephrine maximal response (per cent)</td>
<td>100 (n = 13)</td>
<td>104.4 ± 0.6 (n = 6)</td>
<td>101.8 ± 0.9 (n = 4)</td>
<td>105.5 ± 1.7* (n = 5)</td>
<td>97.5 ± 2.7 (n = 5)</td>
</tr>
<tr>
<td>KCl ED_{50} (×10^{-3} m)</td>
<td>20.6 ± 1.0 (n = 7)</td>
<td>— (n = 6)</td>
<td>19.1 ± 0.9 (n = 4)</td>
<td>20.6 ± 2.3 (n = 4)</td>
<td>23.5 ± 1.1 (n = 4)</td>
</tr>
<tr>
<td>KCl maximal response (per cent)</td>
<td>100 (n = 7)</td>
<td>106.8 ± 2.6 (n = 7)</td>
<td>109.9 ± 1.8 (n = 6)</td>
<td>98.9 ± 1.8 (n = 4)</td>
<td>82.9 ± 1.5† (n = 4)</td>
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<tr>
<td>Histamine ED_{50} (×10^{-6} m)</td>
<td>5.6 ± 0.6 (n = 10)</td>
<td>— (n = 6)</td>
<td>5.0 ± 0.8 (n = 4)</td>
<td>4.3 ± 0.5 (n = 4)</td>
<td>4.9 ± 0.8 (n = 4)</td>
</tr>
<tr>
<td>Histamine maximal response (per cent)</td>
<td>100 (n = 10)</td>
<td>99.7 ± 2.3 (n = 4)</td>
<td>101.7 ± 0.6 (n = 4)</td>
<td>102.1 ± 2.2 (n = 4)</td>
<td>102.1 ± 2.2 (n = 4)</td>
</tr>
</tbody>
</table>

* Different from control, P < 0.05.
† Different from control, P < 0.01.

Response curves of NE were not significantly influenced by MEGX or GX, 2 x 10^{-3} and 10^{-4} m, which were sufficient to potentiate the response to transmural stimulation. Furthermore, the potentiating effects of GX and cocaine were additive. Cocaine in the concentration used here (3 x 10^{-6} m) is sufficient to produce the maximum potentiation in association with an inhibition of neuronal uptake of NE. These findings suggest that the potentiation induced by MEGX and GX is related to an increase in the release of NE from nerve terminals, rather than an amine-uptake inhibition. In the highest concentration used (5 x 10^{-4} m), GX potentiated the response to exogenous NE, suggesting that this concentration interferes with inactivation processes of NE.

According to Hudgins et al.,* vasoconstricting agents, including NE, histamine, and KCl, interact with Ca^{2+} via different mechanisms. Fleisch and Titus* have postulated that lidocaine blocks α-adrenoceptors in rat aortic strips. However, in the present study, we could not demonstrate an α-blocking action of lidocaine on rabbit aortic strips. The responses to lidocaine, 5 x 10^{-4} m, are not necessarily attributable to α-adrenergic blockade, because lidocaine, 5 x 10^{-4} m, also attenuated the response to K+. MEGX has a similar action but is less active than lidocaine.

Increases of systemic vascular resistance during intravenous infusion of lidocaine have been reported to occur in man* and in the dog. In this study, lidocaine, 2 x 10^{-5} m (4.68 μg/ml), which is close to plasma levels attained for therapy of arrhythmias in clinical practice, did not affect the tension developed. Plasma concentrations of MEGX and GX during lidocaine infusion in man reach as high as 4.2 (2.1 x 10^{-5} m) and 4.5 μg/ml (2.6 x 10^{-5} m), respectively.* These concentrations were proved to be sufficient to significantly potentiate the contractile response of arterial smooth muscle to adrenergic nerve stimulation in this study. Therefore, an increased vascular resistance could be explained, at least in part, by an increased release of NE at the nerve terminals by the metabolites. The present study suggests that the metabolites play a significant role in changing cardiovascular function during lidocaine infusion in vivo.

The authors thank the Fujisawa Pharmaceutical Co. for the supplies of lidocaine, MEGX, and GX.

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