Inhibition of Bradykinin Vasodilation and Potentiation of Norepinephrine and Angiotensin Vasoconstriction by Inhibitors of Prostaglandin Synthesis in Skeletal Muscle of the Rat

By Edward J. Messina, Richard Weiner, and Gabor Kaley

ABSTRACT
Recent reports have indicated that vascular responsiveness can be altered by exogenously administered or endogenously released prostaglandins. Furthermore, in certain tissues inhibitors of prostaglandin synthesis have been shown to limit the increase in blood flow in response to bradykinin and to enhance the reduction in blood flow in response to angiotensin and norepinephrine. These findings suggest an important local circulatory role for prostaglandins. We attempted to implicate further prostaglandins in local blood flow regulation by examining the effects of indomethacin (IND) and 5,8,11,14-eicosatetraynoic acid (ETA), inhibitors of prostaglandin synthesis, on microvascular arteriolar responses to bradykinin, prostaglandin E, (PGE,), prostaglandin E2 (PGE2), histamine, norepinephrine, and angiotensin. Male Wistar rats were anesthetized with sodium pentobarbital, and their cremaster muscle was exteriorized and prepared for in vivo microscopic observation of microvessels. Changes in arteriolar luminal diameters in response to topical administration of vasoactive agents were quantified with an imaging shearing measuring eyepiece in conjunction with a television microscope and recorder. Local administration of IND or ETA significantly reduced the arteriolar dilation elicited by bradykinin, whereas the responses to PGE1 and PGE2 remained unaltered. Responses to histamine, although somewhat reduced, were not significantly different from control. Vasoconstrictor responses of arterioles elicited by norepinephrine and angiotensin were potentiated by IND or ETA administration. These results indicate that prostaglandins synthetized in skeletal muscle microcirculation in situ (1) mediate, in part, vasodilator responses to bradykinin and (2) modulate vasoconstrictor responses to angiotensin and norepinephrine. Thus, these findings support the hypothesis that prostaglandins are local regulators of microvascular responsiveness.

Other evidence indicates that endogenous prostaglandins present in and released by the spleen (7) and the kidney (8) can contribute to the regulation of vascular tone. Additional interactions between prostaglandins and other vasoactive substances have been uncovered in the kidney where inhibition of prostaglandin synthesis diminishes the vasodilator effects of bradykinin (9) and enhances the vasoconstrictor effects of angiotensin and norepinephrine (10). Since circulating prostaglandins are essentially metabolized by the lungs (11, 12), it seems important to establish what role, if any, locally synthesized prostaglandins have on the regulation of blood flow at the microcirculatory level. To this end, we studied the responsiveness of single arterioles to vasodilator and vasoconstrictor agents in the presence of locally administered inhibitors of prostaglandin synthesis in the microcirculation of the rat cremaster muscle.

Methods
The present study was performed in the cremaster (skeletal) muscle of male Wistar rats weighing 80–130 g. All of the rats were anesthetized with an intramuscular (thigh muscle) injection of sodium pentobarbital (3.0
mg/100 g body weight). To ensure a free airway, the trachea was exposed and cannulated with a 2.5-3.0-cm length of polyethylene tubing (PE 240). Surgical exposure and preparation of the cremaster muscle were performed according to a previously described method (13) which permits the in vivo microscopic study of this thin sheet of skeletal muscle by transillumination.

The cremaster muscle was kept moist and warm by a continuous superfusion of Ringer's gelatin solution at a rate of 2 ml/min. The temperature of the solution was thermostatically maintained at 33.5 ± 0.5°C. The Ringer's gelatin solution contained 10 g/liter of gelatin, 154 mM NaCl, 5.63 mM KCl, and 2.16 mM CaCl₂. The pH of this solution was adjusted to 7.4 with dry sodium bicarbonate.

Changes in arteriolar luminal diameters in response to the various vasoactive substances were recorded with an image-shearing eyepiece and a television microscope (14). Arterioles selected for study ranged in size from 15 to 55μm in luminal diameter.

All vasoactive agents, including the prostaglandins, were applied topically to the cremaster muscle in 0.1-ml volumes with a calibrated syringe. During the administration of vasoactive substances, the flow of Ringer's gelatin solution was not halted so that these substances were further diluted with the superfusion fluid.

The following vasoactive agents were used: PGE₁, and PGE₂ (Upjohn), norepinephrine bitartrate (Levophed bitartrate, Winthrop), angiotensin amide (Hypertensin, Ciba), bradykinin (Sandoz), and histamine dihydrochloride (Fisher Chemical). The doses of all of the vasoactive substances except norepinephrine and angiotensin refer to the base. All vasoactive agents utilized in this study elicited reproducible changes in arteriolar diameters for a 3-4-hour testing period.

Prostaglandins were put into solution by the addition (to each milligram) of 0.1 ml of 95% ethanol (v/v) and 0.9 ml of a Na₂CO₃ solution (20 mg/100 ml). Standard stock solutions of the prostaglandins containing 100 or 200 μg/ml were prepared by further dilution with sterile isotonic saline and stored frozen for no longer than 2 months. Stock solutions of the various vasoactive substances were also prepared by dilution with sterile isotonic saline and stored frozen for no more than 1 week. On the day of the experiment, the agents to be used were thawed at room temperature, and final dilutions were made with Ringer's gelatin solution. Aliquots of these dilutions, which were kept cold, were warmed to 33°C prior to topical administration on the cremaster muscle.

Indomethacin (Indocin), an inhibitor of prostaglandin synthesis (15-17), was put into solution by the addition of 10 mg to 100 ml of Ringer's gelatin solution and stirring gently for 1-2 hours. Then, 10-ml aliquots were taken and further diluted to 100 ml with Ringer's gelatin solution, yielding a final concentration of 10 μg/ml of indomethacin (IND). The pH of this solution was then adjusted to 7.4 with sodium bicarbonate.

Another prostaglandin synthetase inhibitor, 5,8,11,14-eicosatetraynoic acid (ETA) (18, 19) was put into solution by adding the material to a 1% (v/v) solution of benzyl alcohol in water and adjusting the pH to 9-10 with 2-4 drops of a 1N sodium hydroxide solution to yield a final concentration of ETA of 1 mg/ml. An aliquot of this solution of ETA was then diluted with Ringer's gelatin solution, yielding a concentration of 10 μg/ml. Finally, the pH was adjusted to 7.4 with either sodium bicarbonate or 0.1N HCl.

The experiments with bradykinin were performed in the following manner. Control arteriolar responses to several doses of bradykinin were determined in a randomized fashion, in duplicate, during the superfusion of Ringer's gelatin solution at 2 ml/min and then again during superfusion of Ringer's gelatin containing 10 μg/ml of either IND or ETA. Studies with the other vasoactive agents were carried out in the following way. After the arteriole for the study had been selected, control arteriolar responses to several doses of a vasoactive substance (either histamine, PGE₁, PGE₂, norepinephrine, or angiotensin) were determined in a randomized manner, in duplicate, prior to IND or ETA administration. In addition, the response to 1 μg of bradykinin (test dose) was also determined. Then, during the administration of IND or ETA, the response to the test dose of bradykinin was redetermined at 5-minute intervals in the same arteriole. After the response was inhibited by 50% or more (an indirect measure of inhibition of prostaglandin synthesis, see Results), responses to the selected vasoactive agent were retested at 5-10-minute intervals.

Statistical analyses were performed using Student's t-test (20). A P value of 0.05 or less was considered statistically significant.

Results

EFFECTS OF INDOMETHACIN ON ARTERIOLAR VASODILATOR RESPONSES TO BRADYKININ, HISTAMINE, PGE₁, AND PGE₂

In a group of nine rats, a dose-response relationship was obtained for bradykinin-induced arteriolar dilation (0.001-1.0 μg) before and during superfusion of IND. Arterioles selected for study in this group of rats had a mean control diameter of 18.4 ± 0.3μ which increased during IND administration to 19.8 ± 0.4μ. This mean increase of 1.4μ or 7% constituted a significant change in diameter (P < 0.01). IND caused a statistically significant inhibition of bradykinin-induced vasodilator responses at each dose of bradykinin tested (P < 0.05) except at the 0.001-μg dose (P > 0.10) (Fig. 1). Inhibition of the vasodilator responses (for all doses tested) ranged from 58% to 70% of the control responses. Measuring from the start of IND superfusion, the onset of inhibition ranged from 10 to 45 minutes and averaged 20 minutes. These results were obtained at a time when the vasodilator responses to bradykinin were maximally inhibited. Maximum inhibition was determined by successive administration of all of the doses of bradykinin over a 90-minute period of IND administration. On cessation of the IND superfusion, vasodilator responses...
to bradykinin did not return to control levels for at least 1 hour, at which time the experiment was terminated.

**TABLE 1**

Effects of IND on Histamine-Induced Vasodilation of Rat Cremaster Muscle Arterioles

<table>
<thead>
<tr>
<th>Histamine (μg)</th>
<th>Before IND</th>
<th>During IND</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.003</td>
<td>3.6 ± 1.0</td>
<td>2.5 ± 0.9</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>0.03</td>
<td>5.3 ± 1.2</td>
<td>4.6 ± 0.8</td>
<td>&gt;0.30</td>
</tr>
<tr>
<td>0.3</td>
<td>7.8 ± 1.0</td>
<td>6.3 ± 0.6</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>3.0</td>
<td>9.7 ± 0.8</td>
<td>9.4 ± 0.8</td>
<td>&gt;0.35</td>
</tr>
<tr>
<td>30.0</td>
<td>11.5 ± 0.6</td>
<td>10.0 ± 0.8</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Values are mean increases in diameter from control ± se. \( P \) values were determined by Student's t-test.

In eight rats, arteriolar responses to histamine (0.003-30 μg) were determined before and during superfusion with IND. Table 1 summarizes the effects of IND on the histamine-induced vasodilator responses of arterioles in the rat cremaster muscle. Control arteriolar diameters averaged 18.1 ± 0.4μ prior to IND and 18.0 ± 0.5μ during IND superfusion (\( P > 0.45 \)). IND did not consistently influence the histamine responses, although there seemed to be a tendency toward a reduction of the vasodilator responses during its administration. However, these changes did not prove to be statistically significant.

Responses to PGE₁ were studied in six rats in doses ranging from 0.0001 to 0.1 μg. Arteriolar diameters averaged 19.2 ± 0.5μ before and 19.6 ± 0.7μ during IND superfusion (\( P > 0.30 \)). PGE₂ was studied in six different rats in doses ranging from 0.001 to 1.0 μg. In this group of rats, arterioles were 18.5 ± 0.4μ prior to and 18.5 ± 0.5μ during IND administration (\( P > 0.49 \)). Unlike the bradykinin responses, arteriolar vasodilator responses to either PGE₁ or PGE₂ were not inhibited by IND administration (Table 2). These responses to the prostaglandins were recorded after the bradykinin-induced vasodilation was maximally inhibited.

**EFFECTS OF INDOMETHACIN ON ARTERIOlar VASCOCONSTRICTOR RESPONSES TO NOREPINEPHRINE AND ANGIOTENSIN**

Arteriolar vasoconstrictor responses to norepinephrine were measured in seven rats. The effects of four different doses of norepinephrine, namely, 0.001, 0.01, 0.1, and 1.0 μg, were studied in each animal. Control diameters averaged 20.5 ± 0.3μ before IND and 20.7 ± 0.4μ during IND administration (\( P > 0.35 \)). IND potentiated the arteriolar vasoconstrictor responses at the three lower doses of norepinephrine studied (Fig. 2). Whether there was a potentiation of the vasoconstrictor responses at the highest dose of norepinephrine (1.0 μg) could not be determined, since arterioles were already maximally responding before IND administration.

**TABLE 2**

Effects of IND on PGE₁ and PGE₂-Induced Vasodilation of Rat Cremaster Muscle Arterioles

<table>
<thead>
<tr>
<th>PGE₁ (μg)</th>
<th>Before IND</th>
<th>During IND</th>
<th>( P )</th>
<th>PGE₂ (μg)</th>
<th>Before IND</th>
<th>During IND</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0001</td>
<td>3.7 ± 0.7</td>
<td>4.3 ± 0.7</td>
<td>&gt;0.25</td>
<td>0.001</td>
<td>2.8 ± 0.7</td>
<td>2.4 ± 0.7</td>
<td>&gt;0.30</td>
</tr>
<tr>
<td>0.001</td>
<td>6.3 ± 1.3</td>
<td>6.6 ± 1.2</td>
<td>&gt;0.40</td>
<td>0.01</td>
<td>4.9 ± 0.6</td>
<td>4.7 ± 0.5</td>
<td>&gt;0.35</td>
</tr>
<tr>
<td>0.01</td>
<td>10.8 ± 1.5</td>
<td>8.9 ± 1.5</td>
<td>&gt;0.20</td>
<td>0.1</td>
<td>5.7 ± 0.4</td>
<td>5.2 ± 0.5</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>0.1</td>
<td>12.5 ± 2.1</td>
<td>12.7 ± 2.3</td>
<td>&gt;0.45</td>
<td>1.0</td>
<td>9.9 ± 0.8</td>
<td>9.2 ± 0.7</td>
<td>&gt;0.25</td>
</tr>
</tbody>
</table>

Values are mean increases in diameter from control ± se. \( P \) values were determined by Student's t-test.
Potentiation by IND of norepinephrine-induced vasoconstriction in rat cremaster muscle arterioles. Values are mean decreases in diameter from control. Vertical lines represent ± SE. Indicated P values were determined by Student’s t-test. N.S. denotes no significant difference.

Potentiation of vasoconstrictor responses at the three lower doses represented a 124% (0.001 μg), 31% (0.01 μg), and 27% (0.1 μg) change from control.

The effects of IND on vasoconstrictor responses elicited by angiotensin were studied in seven rats. Angiotensin was applied to the cremaster muscle in four different doses, namely, 0.005, 0.05, 0.5, and 5.0 ng. Arteriolar diameters averaged 18.8 ± 0.3μ before IND and 19.3 ± 0.3μ during IND administration (P > 0.10). IND augmented the responses to angiotensin at all four doses tested (Fig. 3). Potentiation of vasoconstrictor responses represented increases from control of 109% (0.005 ng), 43% (0.05 ng), 15% (0.5 ng), and 24% (5.0 ng).

EFFECTS OF 5,8,11,14-EICOSATETRAYNOIC ACID ON ARTERIOLAR VASODILATOR RESPONSES TO BRADYKININ, HISTAMINE, PGE₁, AND PGE₂

Superfusion of the cremaster muscle with ETA was performed in seven rats. ETA had no apparent vasoactivity of its own on arterioles of the rat cremaster muscle in this or any of the other groups of rats studied. The vehicle for ETA was also without any effect. Arteriolar diameters averaged 19.4 ± 0.3μ before administration of the drug and 19.5 ± 0.5μ after administration (P > 0.40). In these rats, four doses of bradykinin (0.001, 0.01, 0.1, and 1.0 μg), PGE₁ (0.1 μg), and PGE₂ (1.0 μg) were tested before and during ETA administration. As shown in Figure 4, ETA consistently inhibited bradykinin-evoked vasodilator responses of rat cremaster muscle arterioles. These results were recorded when responses to bradykinin were maximally reduced. Onset of the inhibition of bradykinin responses occurred at 15–75 minutes, averaging approximately 45 minutes, after the start of ETA superfusion. Reduction of the bradykinin responses represented a 90% (0.001 μg), 86% (0.01 μg), 83% (0.1 μg), and 68% (1.0 μg) change from control. Bradykinin responses remained depressed for up to

Circulation Research, Vol. 37, October 1975
60 minutes (time when experiment was concluded) after the superfusion of ETA was halted.

Before the administration of the prostaglandin synthetase inhibitor, ETA, the mean increase in arteriolar diameter in response to PGE, (0.1 ng) was 12.9 ± 1.4μ and that to PGE₂ (1.0 μg) was 11.3 ± 1.3μ. When the arteriolar responses to bradykinin were maximally inhibited by ETA, responses to the two prostaglandins were once again determined. At this time, the mean increases in diameter were 12.4 ± 0.7μ (P > 0.35) after PGE₁, and 11.0 ± 0.8μ (P > 0.40) after PGE₂ responses which were not significantly different from control.

The effects of ETA on histamine-induced (0.003-30 μg) vasodilator responses were studied in five rats. ETA, like IND, did not significantly inhibit arteriolar responses to histamine (Table 3), although the responses were somewhat reduced. Control vascular diameters were 19.4 ± 0.6μ before ETA and 20.3 ± 0.5μ (P > 0.10) during ETA administration.

**EFFECTS OF 5,8,11,14-EICOSATETRAYNOIC ACID ON ANTERIOLAR VASOCONSTRICTOR RESPONSES TO NOREPINEPHRINE AND ANGIOTENSIN**

In six rats, the effects of several doses of norepinephrine (0.001–1.0 μg) on arteriolar diameters were studied (Fig. 5). At the two lower doses, responses to norepinephrine were significantly potentiated. Increases from control of arteriolar vasoconstrictor responses to norepinephrine at 0.001, 0.01, and 1.0 μg were 100%, 49%, and 17%, respectively. In this series of experiments, arteriolar diameters averaged 19.7 ± 0.4μ before administration of ETA and 20.3 ± 0.4μ after; this difference was not statistically significant (P > 0.10).

Experiments were performed in seven rats to determine the effects of ETA on angiotensin-induced (0.005-5.0 ng) vasoconstrictor responses. Figure 6 demonstrates that administration of ETA significantly potentiated the angiotensin-induced arteriolar vasoconstrictor responses in the rat cremaster muscle at all doses studied. Potentiation of vasoconstrictor responses represented changes from control of 131% (0.005 ng), 67% (0.05 ng), 32% (0.5 ng), and 37% (5.0 ng). Mean control arteriolar diameters before the superfusion of ETA (21.6 ± 0.6μ) and during the administration of this inhibitor of prostaglandin synthesis (21.0 ± 0.7μ) were not significantly different (P > 0.25).

**Discussion**

In 1960, Collier and Shorley (21) reported that some of the actions of bradykinin (i.e., bronchoconstriction and contraction of guinea pig ileum) could be antagonized by nonsteroidal, analgesic, antipyretic agents. Later it was reported that aspirin in the dog, rabbit, and guinea pig (22–24), IND in the rabbit (23), and meclofenamate in the guinea pig (24) could reduce the duration but not the depth of the systemic hypotension elicited by bradykinin. More recently, evidence has been presented which demonstrates that these nonsteroidal, anti-inflammatory agents can inhibit both the synthesis and the release of prostaglandins from a variety of tissues (15–17).

McGiff and his co-workers (25, 26), in a series of papers, have also reported that in the canine kidney bradykinin elicits a vasodilation which is associated with an increased release in the renal venous effluent of a PGE-like substance, as characterized by bioassay and thin-layer chromatogra-

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**TABLE 3**

<table>
<thead>
<tr>
<th>Histamine (μg)</th>
<th>Increase in diameter (μ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before ETA</td>
</tr>
<tr>
<td>0.003</td>
<td>3.2 ± 0.6</td>
</tr>
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</tbody>
</table>

Values are mean increases in diameter from control ± se. P values were determined by Student's t-test.
The renal vasodilator action of bradykinin is due to flow and prostaglandin release and attenuates the pharyngeal response. Administration of IND decreases renal blood flow significantly. Several studies have demonstrated that IND and ETA can reduce significantly skeletal muscle bradykinin vasodilator responses. This conclusion is supported by the fact that two chemically dissimilar substances whose known common biological action is inhibition of prostaglandin synthesis inhibit bradykinin-induced arteriolar dilator responses. Furthermore, that this inhibition is not the result of a nonspecific decrease in vascular responsiveness produced by IND or ETA is indicated by the fact that the responses to PGE1 and PGE2 are unaffected at a time when the bradykinin response is maximally inhibited. Our findings also suggest that the bradykinin-prostaglandin interaction is not limited to the renal vasculature and that it may represent a more widespread phenomenon which occurs in other microcirculatory beds as well. It would be interesting to speculate if other vasodilator responses are accompanied by or are dependent on prostaglandin synthesis and release. The lack of any significant effect of prostaglandin inhibition on histamine-induced vasodilation militates against this possibility, although histamine responses were also, albeit slightly, affected. Interestingly, in another study, aspirin was also ineffective in blunting the histamine-induced hypotension, a finding which complements our observation. Although in our experiments IND generally did not alter vascular diameters, in one series of experiments it was observed, prior to the testing of bradykinin responses, that IND in itself caused a small but nevertheless significant vasodilation (1.4 μm mean increase in arteriolar diameter from control). It might be argued that this increase could partially account for the inhibition of vasodilation which followed bradykinin administration. However, the initial vasodilation was quite small in comparison with the extent of the inhibition; consequently, it is unlikely that it had a major effect on the subsequent response. Then again, the effect may have been altogether a chance occurrence, since it was not observed in any of the other groups of rats receiving IND. Superfusion of ETA did not alter arteriolar diameters from control levels in any of the rats studied.

Prostaglandins have also been reported to be released from a variety of tissues in response to the administration of vasoconstrictor agents. A PGE-like substance has been reported to appear in the renal lymph of cats in response to norepinephrine infusion into the renal artery and in the renal venous blood of dogs in response to infusions of either norepinephrine or angiotensin. It has also been demonstrated that infusions of angiotensin into the renal artery of dogs causes both a dose-dependent decrease in renal blood flow and the release of a PGE2-like substance. Furthermore, inhibition of prostaglandin synthesis with either IND or meclofenamate prevents the release of the PGE2-like substance by angiotensin from the kidney and augments renal vasoconstriction. In rabbit kidney, IND inhibits the basal release of prostaglandins, causing an increase in perfusion pressure and an augmentation of the vasoconstrictor response to renal nerve stimulation. Similar effects have also been reported for IND in the cat spleen. ETA also potentiates pressure responses in the cat spleen to nerve stimulation at a time when prostaglandin release is inhibited; however, it does not increase resting perfusion pressure as does IND. In addition, in the blood-perfused dog's paw both IND and ETA are effective in potentiating the responses to norepinephrine and sympathetic nerve stimulation, and there is also a tendency for vasoconstriction to occur in the paw after administration of the prostaglandin synthetase inhibitors. On the basis of these findings it has been postulated that a prostaglandin synthesized in the dog's paw and released into the
cutaneous circulation by the adrenergic neurotransmitter noradrenaline antagonizes the vasocostrictror effect of this agent.

The present study demonstrated that locally administered IND or ETA potentiates significantly the arteriolar constrictor responses to noradrenaline and angiotensin in the rat cremaster muscle. One possible implication of this finding is that vasodilator prostaglandins, synthesized within the microcirculatory bed, normally accompany excitation of vascular smooth muscle by noradrenaline and angiotensin and that this release counteracts and tends to attenuate the constrictor responses. In this manner prostaglandins could be envisioned as functioning as local hormones in a negative feedback system to limit and moderate the degree and the duration of vasoconstriction. Although this hypothesis has not yet been proved, our findings strongly suggest a causal relationship between vasoconstrictor influences and prostaglandin release.

It is intriguing to speculate as to why in the present experiments IND (or ETA) per se did not bring about a vasoconstriction but, paradoxically, blunted certain vasodilator responses and also substantially enhanced the vasoconstriction induced by noradrenaline and angiotensin. It is possible that in skeletal muscle (unlike in kidney) the basal output of vasodilator prostaglandins is quite low and that the small amount of IND superfused locally either cannot interfere with this background release of prostaglandins or alternatively, if it does inhibit the release, does not result in a measurable increase in the tone of the small blood vessels. On the other hand, the sudden surge in prostaglandin release following the administration of a variety of vasoactive agents is appreciably modified in the presence of inhibitors of prostaglandin synthesis, hence the change in vascular responsiveness.

In conclusion, our findings and those of other authors suggest that endogenous synthesis and release of prostaglandins are perhaps essential in the maintenance of a balance between constrictor and dilator influences and that in this way prostaglandins contribute to the local regulation of blood flow.

References


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Circ Res. 1975;37:430-437  
doi: 10.1161/01.RES.37.4.430  

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