Sympathoadrenal Response to Eledoisin-induced Hypotension in Normotensives and Hypertensives

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Blood pressure response to infusion of synthetic eledoisin was carefully evaluated in 8 normotensives. There was tachyphylaxis to the hypotensive effect of this peptide. This tachyphylaxis is partly accounted for by the overactivity of the sympathoadrenal system, because urinary excretion of catecholamines was found to increase during the hypotension induced by eledoisin. In contrast, the sympathoadrenal response was lacking in 13 hypertensive patients. The latter responded to eledoisin infusion with a profounder hypotension than the former, and this hypersensitivity was considered to be due to the lack of sympathoadrenal overactivity.

Eledoisin is a biologically active polypeptide discovered by Erspamer\(^1\) in 1949 in the posterior salivary gland of *Eledone moschata*. Its structure has been elucidated by the same author\(^2\) as an endecapeptide with the following amino acid sequence: Pyr-Pro-Ser-Lys-Asp(OH)-Ala-Phe-Ileu-Gly-Leu-Met. Eledoisin dilates the peripheral vessels, causes hyperemia, enhances the capillary permeability, and increases local blood flow; it elicits contraction of isolated smooth muscle of organs such as guinea pig's gut, rat's uterus, etc. In the human body, eledoisin is much more resistant to enzymatic inactivation than other polypeptides with similar biological properties, i.e., bradykinin and kallidin. For this reason, several investigators\(^3\)--\(^5\) suggested a therapeutic use of eledoisin in the diseases in which an increase in regional blood flow is desirable, for instance, angina pectoris or vertebro-basilar blood flow insufficiency.

In the course of our study on the therapeutic use of eledoisin, it has been impressive that the blood pressure of patients, once lowered promptly with intravenous infusion of eledoisin, tended to rise gradually toward the preinfusion level, though the infusion rate was kept constant. This phenomenon may be accounted for in several ways, but the most probable explanation is that the sympathoadrenal system is activated in response to the hypotension induced by eledoisin to constrict the dilated vessels and restore the circulation. If this is the case, it would be expected that the overactivity of the sympathoadrenal system...
system would be reflected by an increased excretion of catecholamines in the
urine. Accordingly, urinary catecholamines were estimated before and after
infusion of eledoisin. The catecholamines were found to increase during the
hypotension by eledoisin in the normotensive patients, but not in the hypertensives.
In the latter, the depressor response was greater than in the former. The present
study suggested that the sympathoadrenal response to the depressor stimulus
seemed to be different between the normotensives and hypertensives.

MATERIALS AND METHODS

Patients: Thirteen patients with essential hypertension and 8 adults with
various diseases but without any evidence of cardiovascular disorders were studied.
Two-thirds of them were hospitalized patients, while the others were out-patients.

Eledoisin infusion: Before infusion of eledoisin, patients were asked to
empty their bladder and then to lie quietly in bed for one hour. Urine sample
was collected in a bottle containing 2 ml of 2N hydrochloric acid and served as
the control. Similarly, urine was collected just after the infusion had been
stopped and blood pressure had returned to the preinfusion level.

The volumes of the acidified urine samples were measured, and 30 ml
aliquot was extracted and analyzed for their content of catecholamines according
to the method of Euler and Floding,6 slightly modified by Yoshinaga.7 Briefly,
30 ml aliquot of each urine specimen was stirred with 0.8 g of activated
alumina at pH 8.4, and poured into a column. After washing the column
with 10 ml of water, the absorbed amines were eluted with 10 ml of 0.2 N
acetic acid. The catecholamines in the eluate were measured fluorimetrically
against internal standards. The content of epinephrine was estimated after its
oxidation at pH 3.5, and that of norepinephrine was calculated by subtracting
the epinephrine value from that of total catecholamines which had been simul-
taneously oxidized at pH 6.0.

RESULTS

Course of blood pressure change during eledoisin infusion

Fig. 1 illustrates the typical response in blood pressure and pulse rate during
the infusion of eledoisin. At the onset of infusion, blood pressure dropped
promptly with an increase in pulse rate. As the infusion continued, the blood
pressure and pulse rate tended to return to the preinfusion levels. When the
infusion rate was increased, blood pressure dropped again to a level lower than
that observed during the first infusion period. When the infusion rate was
stepwise increased, blood pressure was depressed also stepwise, but with a tendency
to return to the preceding levels at each time. After the cessation of infusion,
blood pressure and pulse rate returned promptly, sometimes with a transient
overshoot, to the original levels within a few minutes.

The basic pattern of changes in blood pressure and pulse rate on infusion of eledoisin was similar in both the normotensives and hypertensives, though the magnitude of blood pressure depression was profounder in the latter than in the former, as will be described later.

Shortly after the initiation of eledoisin infusion, the face, neck, arms and chest of patients became hyperemic, and a warm or tingling sensation was felt over these areas. Palpitation and other symptoms were scarcely complained of; sometimes nasal stuffiness appeared. All of these signs and symptoms quickly disappeared in a few minutes after stopping the infusion.

Hyperresponsiveness to eledoisin infusion in hypertensives

In the course of the study, it has soon become clear that the hypotension caused by eledoisin was greater in degree in the hypertensives than in the normotensives, as illustrated in Fig. 2. In this figure, systolic blood pressure is shown on the abscissa, and infusion rate in nanograms of eledoisin per kg body weight per minute on the ordinate. The steeper the line for a given patient, the higher the sensitivity to eledoisin. In general, the solid lines for the hypertensives, are steeper than the broken lines for the normotensives. Fig. 3 shows the results on diastolic blood pressure. In contrast to systolic changes, the
Fig. 2. Change of systolic blood pressure induced by eledoisin infusion in normotensives and hypertensives.

Fig. 3. Change of diastolic blood pressure induced by eledoisin infusion in normotensives and hypertensives.
diastolic ones were not significantly different between the two groups. There was also proved no difference in the changes in pulse rate between the two groups.

*Sympathoadrenal response to eledoisin-induced hypotension*

Urinary catecholamines were determined before and during the eledoisin infusion in 4 normotensive subjects. As shown in Fig. 4, urinary epinephrine and norepinephrine increased during the infusion in all but one, in whom only norepinephrine was increased.

Six patients with essential hypertension were studied in the same fashion, and the results are given in Fig. 5. In a sharp contrast to the normotensives, no significant changes were observed in the hypertensive patients except one, in whom the excretion of norepinephrine increased during the eledoisin-induced hypotension, while the excretion of epinephrine did not. Minor differences in catecholamines between pre- and post-infusion urines are not significant, since an error of 10–20 per cent was inherent in the assay procedures.

**DISCUSSION**

When eledoisin is infused intravenously in man, the hypotensive effect becomes gradually weakened even though the infusion continues at a constant rate. This phenomenon, tachyphylaxis, is partly accounted for by the counteraction of the sympathoadrenal system, which liberates catecholamines in response to the hypotension to restore the blood pressure. But the tachyphylaxis is not wholly explained by this mechanism, because it is also observed in hypertensive patients, in whom the sympathoadrenal response to eledoisin-induced hypotension is missing. Complex mechanisms might underlie this phenomenon.

In hypertensive patients, eledoisin induces hypotension to an exaggerated degree. This hyperresponsiveness is explainable by the fact that the sympathoadrenal system is not called into operation to counteract the hypotension, though nothing is known about the reason for the absence of sympathoadrenal response in hypertensive patients.

It has been generally ascertained that hypertensive patients have higher sensitivity than the normal to pressor stimuli such as norepinephrine, tyramine, angiotensin, etc. We have also verified this hypersensitivity in patients with hypertension. In the present study, we have experienced in these patients the same behavior against the opposite, depressor, stimulus. It may be a general rule that blood pressure response in hypertensives is excessive to all stimulations of either direction, pressor or depressor.

It is evident that one of the pressor mechanisms against drug-induced hypotension is the mobilization of sympathoadrenal system. But the regulatory action against hypertension due to pressor agents is entirely unknown. The
Fig. 4. Urinary excretion of catecholamines before and during eledoisin infusion in normotensives.

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<thead>
<tr>
<th>Subjects</th>
<th>Epinephrine (µg/h.)</th>
<th>Norepinephrine (µg/h.)</th>
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- □ Pre-infusion
- ■ Post-infusion

Fig. 5. Urinary excretion of catecholamines before and during eledoisin infusion in hypertensives.

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- ■ Post-infusion
exact mechanism regulating drug-induced hyper- or hypotension is a problem to be elucidated in future.

Sundin\(^9\) reported in 1956 that when patients are tilted to \(75^\circ\) no increase takes place in norepinephrine excretion in hypertensives, while a marked increase is regularly observed in normotensives under the same condition. We also confirmed this deficiency in sympathoadrenal response to the postural change in hypertensive patients (Yoshinaga, unpublished observation). It may be concluded that the function of the sympathoadrenal system is less active in hypertensives than in normotensive controls.

Acknowledgment

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References