Effects of Nitroglycerin on $\text{H}^3$-Catecholamine Metabolism

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The mechanism of anti-anginal effect of nitroglycerin on sclerotic coronary patients has been a mystery. The authors demonstrated an abrupt and remarkable decrease of the radioactivity of $\text{H}^3$-catecholamine during infusion after sublingual administration of nitroglycerin, and thus postulated that this drug acts as an accelerator of catecholamine inactivation.

It has been shown for about the last hundred years that nitroglycerin is one of the most favorable drugs for anginal attack. Many authors have found the increase of coronary blood flow following the use of this drug and therefore have believed for some time that the mechanism by which this drug acts upon anginal attack was due to the coronary dilating effect.

However, since our previous reports1)-3) and Gorlin's one4) showed that the effects on coronary flow of nitroglycerin were different between sclerotic coronary arteries and normal coronary vessels, the effects of this drug on the metabolism of myocardium have been studied.

On the other hand, the role of catecholamine on angina pectoris is very interesting, too. From our laboratory and clinic, some reports have been published about the role of catecholamine on the various kinds of cardiovascular diseases.5),6)

In this report, the effects of nitroglycerin on catecholamine metabolism as observed in patients with or without angina pectoris and in rabbits are given, and through these findings, an effort was made to clarify the mechanism of angina pectoris.

Material and Methods

Clinical trial: Eighteen cases were infused intravenously $\text{H}^3$-catecholamine for 30 to 60 min. Among these, 6 cases with angina pectoris were administered nitroglycerin sublingually 4 to 6 min. before the end of $\text{H}^3$-epinephrine or $\text{H}^3$-norepinephrine infusion. As reported previously,5),6) during and after the infusion of $\text{H}^3$-catecholamine continuous recording of electrocardiogram was made, blood pressure was taken at frequent intervals and the radioactivity of $\text{H}^3$-catecholamine

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in plasma and urine was estimated. The metabolites of H3-catecholamine were estimated at the same time in the urine. The estimation of H3-catecholamine and its metabolites of each sample was carried out by the methods previously reported.5)-7)

Experiments in animals: Six rabbits were used, including 3 non-treated as control and 3 pre-treated with nitroglycerin administered sublingually 3 min. before the experiment. H3-catecholamine was infused intravenously, and 3 min. after the infusion, the rabbits were killed with a blow. The radioactivity of H3-catecholamine and its metabolites in plasma and myocardium was estimated by similar methods as described before.

RESULTS

Table I. Patients with H3-CA Infusion (Total 18)

<table>
<thead>
<tr>
<th>Nitroglycerin</th>
<th>Infusion</th>
<th>Cases</th>
<th>Attack Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Epinephrine</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>Epinephrine</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**H3-EP INFUSION**

**H3-NEP INFUSION**

Fig. 1. Control.
Clinical experiment: In all of the 5 cases with previous anginal attacks, the infusion of H^3-epinephrine provoked a similar attack. On the other-hand, in cases without previous attack, the infusion of the same amount of H^3-epinephrine did not provoke any attack. Furthermore, H^3-norepinephrine did not provoke attack in both groups (Table I).

The responses of blood pressure and heart rate to H^3-epinephrine and norepinephrine, and the radioactivity of the H^3-catecholamine in plasma in normal control without the treatment of any drug, during and after the infusion of H^3-catecholamine are shown in Fig. 1 as typical cases. In these cases, the plasma level of H^3-epinephrine or H^3-norepinephrine became higher gradually during the infusion, followed by a rapid fall of the the radioactivity in plasma in the first 60 min. after the end of the infusion and then followed by a slower decrease of this level. The radioactivity in plasma still remained 6 hours later from the end of the infusion.

Fig. 2 shows the results of 2 of the patients who were administered nitroglycerin sublingually during the infusion of H^3-epinephrine or H^3-norepinephrine. In 6 cases, nitroglycerin caused a remarkable fall of the plasma level of H^3-epinephrine or H^3-norepinephrine mostly within 3 to 5 min. after the administration of this drug and even during infusion.
The results of the plasma level of H3-catecholamine in all cases of the nitroglycerin group are summarized in Fig. 3 (on the right). On the contrary, the plasma H3-catecholamine of the non-treated group increased gradually as the infusion continued. Therefore, the level of H3-catecholamine in plasma was maximum just before the end of the infusion.

A urine analysis was carried out to determine the fate of these infused H3-catecholamine just after the administration of nitroglycerin. In the urine,
the radioactivity of H³-catecholamine was less in patients with nitroglycerin than in patients without any drugs (Fig. 4). However, the excretion of these H³-acidic metabolites seemed to be increased in the nitroglycerin group as compared to the control group (Fig. 4). Further investigation is necessary concerning the urine analyses.

Animal experiments: H³-catecholamine in the plasma and myocardium was lower in the nitroglycerin group than in the non-pretreated rabbits (Fig. 5). However, no particular changes were revealed in the radioactivity of H³-metanephrine or H³-acidic metabolites.

Fig. 5. Effects of nitroglycerin on the H³-norepinephrine (rabbits).

**DISCUSSION**

It has been recognized for a long time that the nitrates, especially the nitroglycerin, are effective in relieving the pain of angina pectoris.

Nevertheless, the pathogenesis and indeed the etiology of angina pectoris continued to elude investigators. Furthermore, the physiological basis for the pharmacological treatment of such an attack or the mechanism of the anti-anginal drugs such as the nitrates is replete with paradox and remains a mystery.

Until a few years ago, the effects of the nitrates have been attributed to the increase of coronary blood flow.

In 1957, Yasuda¹) found the decrease of coronary blood flow in patients with coronary sclerosis through coronary catheterization, though the cases were few in number. Two years later, Gorlin and his associates¹) described similar findings as Yasuda in detail, comparing patients with coronary sclerosis and normal persons. They showed that the fixed coronary blood flow of patients with angina pectoris did not respond to nitrates, rather the coronary
flow was decreased by the administration of nitroglycerin, one of the nitrates, in contrast to the reaction of the coronary arteries in normal subjects.

After then, there were some reports, by Ito, et al., Hollander, et al. and Bing, et al. which confirmed the results described above. Henceforth, it has gradually become popular that the relief of angina attack by nitrates is not attributed to the increase of coronary blood flow but to other mechanisms, and that the effect of nitrates on the coronary flow is different between patients with coronary sclerosis and normal subjects. Recently, many workers postulate that the clinical effects of nitrates are attributed to the improvement of myocardial metabolism rather than the increase of coronary blood flow. In fact, nitroglycerin seems to have several pharmacological effects, namely the lowering of blood pressure, decrease of cardiac output, decrease of coronary flow in the sclerotic artery, slight diminution of oxygen consumption, coronary resistance and therefore decrease in cardiac work. Some investigators, such as Christensson or Case, et al. proposed the mechanism of this drug on the anginal pain as decrease of cardiac work due to the lowering of blood pressure or decrease of myocardial oxygen consumption.

Now, it has become most important to know how these drugs improve the myocardial metabolism. As to these points, there have been several reports made, proving that catecholamine plays an important role as a pathogenic factor in angina pectoris. It has been demonstrated as early as in 1930 that epinephrine initiates an attack in patients already suffering from angina pectoris. Our results (Table I) showed similar findings as that of Levine, in spite of the small dosage of epinephrine used in our clinical experiment. That is to say that in our studies also, epinephrine provoked anginal attack in patients with coronary sclerosis, but not in persons without coronary sclerosis.

Especially Raab and his associates advanced the theory that the attack of stenocardiac pain on efforts, cold or emotion is caused by a hypoxiating metabolic effect of sudden discharge of epinephrine upon cardiac muscle whose sclerotic arteries are incapable of dilating sufficiently to compensate for the increased oxygen consumption caused by epinephrine in the myocardium. In fact, it has been well known that the increase of cardiac oxygen consumption, cardiac contractility, cardiac output and therefore the increase of cardiac work and blood pressure were caused through the effects of the epinephrine on the heart muscle.

Also, the role of the sympathetic nervous system in coronary heart disease, as reflected by alteration in plasma level and urinary excretion of catecholamine, has been subjected to study for the last 2 decades.
Thus, it seems possible to suppose that the nitrates, at least in part, show their effect on angina pectoris through the inactivation, both in quality and quantity of catecholamine as derived from our suggestion that catecholamine is one of the most important triggers of angina pectoris and that nitroglycerin improves the myocardial disturbance.

Some workers suppose that nitroglycerin provides their anti-adrenergic effects of improving myocardial metabolism due to catecholamine. Namely, there are many proofs to show that this drug prevents the hypoxic change of electrocardiogram produced by exercise, sympathetic stimulation or the injection of catecholamine. They all supposed that these effects of nitroglycerin were attributed to the anticatecholamine action. Of course, there are a few who did not agree with this opinion. However, we can suggest that the decrease of cardiac work, at least in part, correlate with the inactivation of catecholamine.

Through the findings of this study, the rapid disappearance of H^3-epinephrine and H^3-norepinephrine in plasma just after the use of nitroglycerin was observed. The disappearance was not due to the rapid excretion of catecholamine in the urine (Fig. 4). Rather, it is supposed that nitroglycerin accelerates the inactivation of catecholamine from our findings on the excretion of H^3-acidic metabolites. However, further study is needed and is at present continued for resolution of these points in our laboratory and clinic. At present, though Unghrany, et al. found the diminution of plasma catecholamine by the use of nitroglycerin, using the measurement of non-radioactive catecholamine at frequent intervals, there is no proof to show the fate of the catecholamine.

Thus, despite existing uncertainties regarding the underlying mechanism, a direct influence of nitroglycerin and other coronary dilator on myocardial metabolism may be considered as partially responsible for the sympathetic effect in patients with angina pectoris and non-dilatable sclerotic coronary arteries.

Summary

During the infusion of H^3-epinephrine or H^3-norepinephrine (0.15µg./Kg./min.) for 30 to 60 min. in 18 patients, nitroglycerin was administered to 6 cases with angina pectoris. The radioactivity of H^3-epinephrine or H^3-norepinephrine in plasma and urine and its H^3-acidic metabolites in urine were estimated in all cases. Similar measurements in the myocardium and plasma were carried out in 6 rabbits (3 non-treated and 3 pre-treated with nitroglycerin 3 min. before the infusion of H^3-norepinephrine).
From these studies, it is postulated that this drug acts as an accelerator of catecholamine inactivation. Further investigation will be needed.

References