Effect of Ketanserin on Proximal and Distal Coronary Constrictor Responses to Intracoronary Infusion of Serotonin in Patients With Stable Angina, Patients With Variant Angina, and Control Patients

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Background. Serotonin, released by aggregating platelets, may contribute to or cause myocardial ischemia by constricting epicardial vessels. Experimental studies suggest that this constriction is mediated by two distinct serotonin receptor subtypes: 5-hydroxytryptamine-

Methods and Results. To determine the relative contribution of S1-like and S2 receptors to the vasoconstrictor effects of serotonin, we studied the effect of ketanserin (0.75 mg, intracoronary), a selective S2 receptor antagonist, on the constrictor response of human coronary vessels to intracoronary infusions of serotonin. In control patients (n=7), serotonin (10^-7 mol/l) caused significant (p<0.05) constriction only in distal segments, which was significantly (p<0.05) inhibited by ketanserin. In stable angina patients (n=8), serotonin (10^-7 mol/l) caused significant constriction in proximal (p<0.01) and distal (p<0.01) segments, which was significantly inhibited by ketanserin in proximal (p<0.05) but not distal (p=0.30) segments. In patients with variant angina (n=3), epicardial occlusion at the site of preexisting stenoses in proximal locations occurred at infused concentrations of 10^-6 (one patient) or 10^-5 (two patients) mol/l. The infusion of the same concentration of serotonin after ketanserin again caused epicardial occlusion.

Conclusions. Our results suggest that functionally important S1-like receptors that mediate vasoconstriction exist in the epicardial vessels of patients with stable or variant angina. Their activation, either at hyperreactive sites in patients with variant angina or in the distal epicardial vessels of patients with chronic stable angina, may contribute to or cause myocardial ischemia when serotonin is released after the intracoronary activation of platelets. (Circulation 1992;86:187-195)

KEY WORDS • 5-hydroxytryptamine • ischemia, myocardial • receptors • coronary vasospasm

A ccumulating evidence suggests that unstable angina frequently results from platelet aggregation or thrombus formation at the site of fissured atheromatous plaques that may occur even at sites without significant preexisting coronary arterial narrowing.1,2 Studies in animals have shown that the intracoronary activation of platelets may contribute to or cause myocardial ischemia both by causing mechanical obstruction of the arterial lumen and by releasing potent vasoconstrictor substances such as serotonin3,4; recent studies support a role for these mechanisms in humans.5,6

The intracoronary infusion of serotonin causes intense vasoconstriction in atherosclerotic arteries.7,8 In isolated human coronary arteries, serotonin-induced constriction is mediated by 5-hydroxytryptamine2 (S2) receptors and by 5-hydroxytryptamine1-like (S1-like) receptors on smooth muscle9-11; the relative contribution of S1-like receptors is significantly greater in segments adjacent to a discrete atheromatous stenosis.11 In addition, although the intracoronary infusion of serotonin induces profound vasoconstriction in patients with variant angina, S2 receptor antagonists have proved ineffective in the treatment of this condition.12,13

To elucidate the relative contribution of S1-like and S2 receptors to the vasoconstrictor effects of serotonin in humans, we examined (with use of quantitative angiography) the effect of ketanserin, a selective antagonist at S2 receptors, on the vasoconstrictor response of vessel

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segments to intracoronary infusions of serotonin in patients with differing clinical presentations of coronary atherosclerosis and in control patients with normal coronary arteries.

Methods

Patients

We studied 25 patients admitted for routine cardiac catheterization. The study protocol was approved by the Research Ethics Committee of the University of Lille. Informed consent for the discontinuation of therapy and the intracoronary administration of serotonin and ketanserin was obtained from all patients. Regular antianginal medication was discontinued at least 24 hours before catheterization. All the patients were taking aspirin 100–300 mg daily, which was continued. Patients were allowed to use sublingual nitroglycerin as needed, but no study was performed within 3 hours of its administration. No premedication was given.

Drugs

Serotonin creatinine sulfate was prepared for human use by the Hammersmith Hospital Pharmacy (London) and stored at −20°C in ampules containing 5 ml of 10−2 mol/l solution until just before use. The stock solution was diluted with normal saline (0.9%) to achieve final infused concentrations of 10−6 to 10−4 mol/l. Ketanserin (as ketanserin tartrate, Serapress) was a gift from Formenti S.r.l. (Milan, Italy). Ampules containing 10 mg of ketanserin were diluted in saline to a concentration of 0.375 mg/ml.

Invasive Protocol

Two ECG leads were monitored continuously throughout the study. Femoral arterial pressure, heart rate, and two ECG leads were recorded during the last 30 seconds of the infusions. After the diagnostic study, an optimal view was chosen to visualize the coronary artery to be studied, and the position of the camera subsequently remained unchanged. Heparin was not routinely administered. All infusions were administered through 8F Judkins catheters at room temperature at a rate of 1 ml/min with use of a syringe pump (Perfusor, Braun-Melsungen). We have previously shown that intracoronary infusion of saline or injection of contrast medium is not associated with a significant change in coronary diameter.14 The patients therefore received a single 2-minute infusion of vehicle solution (0.9% saline) followed by 2-minute infusions of serotonin creatinine sulfate or ketanserin (0.375 mg/ml) according to the protocols outlined below. Finally, an intracoronary bolus dose of isosorbide dinitrate (ISDN) (2 mg in 2 ml of saline) was administered. Angiography was performed at baseline and after each infusion after the hand injection of 6–8 ml of contrast (Omnipaque, Nycomed). Before each angiogram, the catheter was emptied to avoid the effects of bolus administration of serotonin.

Study Protocols

Reproducibility of vasoconstriction. Tachyphylaxis to the effects of serotonin is frequently observed in animal models; therefore, we initially compared the degree of vasoconstriction induced by repeated infusion of the same concentration of serotonin. We studied seven patients (four men and three women) with a mean±SEM age of 50.0±9.8 years who had angiographic evidence of atherosclerosis. Four patients had chronic stable angina with positive results on exercise testing. Three had previously undergone successful coronary angioplasty and had atypical chest pain with negative results on exercise testing. Infusions were performed in nondilated arteries without significant (>50%) stenoses. Three left and four right coronary arteries were studied. Each patient received an infusion of saline, followed by an infusion of serotonin (10−4 mol/l). An arteriogram was performed at baseline, after the infusion of saline, and immediately after the initial infusion of serotonin. Another arteriogram was performed 5 minutes later. The infusion of serotonin was then repeated, and another arteriogram was performed. Finally, an intracoronary bolus dose of ISDN (2 mg in 2 ml of saline) was administered, and an arteriogram was performed 2 minutes later.

Effects of ketanserin. To investigate the effect of ketanserin on the constrictor response to serotonin, we studied a group of patients with stable angina, a group with variant angina, and a control group with atypical chest pain. Serotonin was infused at a concentration (10−4 mol/l) that we have previously shown to constrict normal and atheromatous coronary vessels.7

Group 1, Control Patients

We studied seven patients (four men and three women) with a mean±SD age of 51.9±10.6 years who presented with atypical chest pain, who had negative results on exercise testing, and normal coronary arteriograms. All the patients had at least one conventional risk factor for coronary disease, and angiography was performed at the request of the referring physician. Each patient received an infusion of saline followed by an infusion of serotonin (10−4 mol/l) in the left coronary artery. Five minutes later, ketanserin (0.375 mg/ml) was infused for 2 minutes. The infusion of serotonin was repeated 5 minutes later. An arteriogram was obtained at baseline and immediately after each infusion. Finally, an intracoronary bolus dose of ISDN (2 mg in 2 ml of saline) was administered, and an arteriogram was obtained 2 minutes later.

Group 2, Stable Angina

We studied eight patients (five men and three women) with a mean±SD age of 58.1±11.9 years who presented with stable effort angina and positive results on exercise testing. All had discrete atherosclerotic lesions on coronary arteriography. Infusions were performed in the less-diseased artery, which was the left coronary artery in five patients and the right coronary artery in three. The sequence of infusions was identical to that performed in group 1.

Group 3, Variant Angina

We studied three patients (two men and one woman) with a mean age of 50.7 years. All presented with spontaneous, predominantly early-morning angina and had negative results on exercise testing. Provocation testing with ergonovine caused angina associated with a marked shift of the ST segment (elevation in leads V1 through V4 in patient 1, depression in leads V3 and V4 in patients 2 and 3). All three patients had isolated
Table 1. Reproducibility of Constrictor Effects of Serotonin

<table>
<thead>
<tr>
<th>Group</th>
<th>Control 1</th>
<th>Saline</th>
<th>Ser 1</th>
<th>Control 2</th>
<th>Ser 2</th>
<th>ISDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>3.52±0.35</td>
<td>3.55±0.40</td>
<td>2.98±0.36*</td>
<td>3.54±0.36</td>
<td>2.99±0.44*</td>
<td>3.91±0.40*</td>
</tr>
<tr>
<td>Distal</td>
<td>1.86±0.41</td>
<td>1.88±0.43</td>
<td>1.18±0.34*</td>
<td>1.87±0.41</td>
<td>1.19±0.42*</td>
<td>2.15±0.48*</td>
</tr>
</tbody>
</table>

Mean±SD diameters of proximal and distal arterial segments (mm) in patients who underwent a repeat infusion of the same dose of serotonin are shown at baseline (Control 1), after a 2-minute infusion of saline, after a 2-minute infusion of serotonin (Ser 1), 5 minutes later (Control 2), after repeat infusion of the same dose of serotonin (Ser 2), and after intracoronary injection of isosorbide dinitrate (ISDN).

Table 2. Effect of Ketanserin on Constrictor Effects of Serotonin

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Saline</th>
<th>Ser 1</th>
<th>Ketanserin</th>
<th>Ser 2</th>
<th>ISDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Proximal segment</td>
<td>3.53±0.53</td>
<td>3.52±0.53</td>
<td>3.23±0.58</td>
<td>3.52±0.54</td>
<td>3.44±0.56</td>
</tr>
<tr>
<td></td>
<td>Distal segment</td>
<td>2.05±0.43</td>
<td>2.04±0.39</td>
<td>1.43±0.53*</td>
<td>2.01±0.38</td>
<td>1.88±0.42</td>
</tr>
<tr>
<td>Group 2</td>
<td>Proximal segment</td>
<td>3.33±0.37</td>
<td>3.32±0.35</td>
<td>2.69±0.18*</td>
<td>3.35±0.43</td>
<td>3.22±0.39*</td>
</tr>
<tr>
<td></td>
<td>Distal segment</td>
<td>2.00±0.40</td>
<td>1.99±0.39</td>
<td>1.24±0.31*</td>
<td>2.01±0.38</td>
<td>1.43±0.29*</td>
</tr>
</tbody>
</table>

Mean±SD diameters of proximal and distal arterial segments (mm) in control patients (group 1) and in patients with stable angina (group 2) are shown at baseline, after a 2-minute infusion of saline, after a 2-minute infusion of serotonin (Ser 1), after infusion of ketanserin, after repeat infusion of the same dose of serotonin (Ser 2), and after intracoronary injection of isosorbide dinitrate (ISDN).

*Significant (p<0.05) change from baseline.
†Significant (p<0.05) change from corresponding value before ketanserin.
measuring the minimal diameter in the stenotic segment and the reference diameter proximal to the stenosis at baseline and after each intervention. The severity of stenosis was expressed as a percentage according to the following formula: the severity of stenosis equals the minimum diameter of the stenosis subtracted from the reference diameter and the result divided by the reference diameter. Finally, all measurements were made by a single investigator who was unaware of the design of the study protocol.

**Statistical Analysis**

All data are expressed as mean±SD. Sequential data (hemodynamic variables and coronary artery diameters in millimeters) were compared by one-way ANOVA with an allowance for repeated measures. Two-tailed Student's *t* tests with the Bonferroni correction were used to compare paired observations. A value of *p*<0.05 was considered to indicate statistical significance.

**Results**

There were no significant changes in heart rate or systolic arterial blood pressure associated with the intracoronary infusion of saline, ketanserin, or serotonin. The changes observed in the vessel segments we studied are detailed in Tables 1 and 2 and Figures 1 and 2. The intracoronary infusion of 0.9% saline was not associated with significant changes in epicardial luminal diameter. Dilatation was consistently observed in all groups after the injection of ISDN. The vasoconstrictor effect of serotonin was reproducible in the five patients who underwent repeated infusion of the same concentration (Table 1). The other two patients in this group did not have the second infusion performed because the patients experienced angina after the first infusion and ISDN was immediately injected.

**Group 1, Control Patients**

*Changes in coronary diameter.* Infusion of serotonin caused a significant (*p*<0.05) decrease in mean diameter only in the distal vessel segments. After infusion of ketanserin, the mean diameters of proximal or distal segments were not significantly different from baseline. The decrease in mean distal diameter that occurred after repeat infusion of serotonin was significantly (*p*<0.05) less than that observed after the initial infusion (Figure 1 and Table 2). No patient developed symptoms or ECG changes.

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**FIGURE 1.** Graphs showing luminal diameter changes in proximal (left panel) and distal (right panel) vessel segments from control patients (group 1). Responses in individual patients, expressed as a percentage of the baseline diameter (CTL), are shown after a 2-minute infusion of serotonin (10⁻⁴ mol/l) before (SER 1) and 5 minutes after (SER 2) infusion of ketanserin (KET) and after intracoronary injection of isosorbide dinitrate (ISDN). Solid symbols with error bars indicate mean±SD.

**FIGURE 2.** Graphs showing luminal diameter changes in proximal (left panel) and distal (right panel) vessel segments from the patients with stable angina (group 2). Responses in individual patients, expressed as a percentage of the baseline diameter (CTL), are shown after a 2-minute infusion of serotonin (10⁻⁴ mol/l) before (SER 1) and 5 minutes after (SER 2) infusion of ketanserin (KET) and after intracoronary injection of isosorbide dinitrate (ISDN). Solid symbols with error bars indicate mean±SD.
Group 2, Stable Angina

Symptoms and ECG changes. Three patients developed chest pain immediately after the initial infusion of serotonin, with ST segment depression in two who were immediately given intracoronary nitrates and did not complete the protocol; the other patient had no ECG changes and the pain resolved spontaneously. The pain recurred in two patients after the subsequent infusion of serotonin but without ECG changes. Therefore, six patients completed the protocol.

Changes in coronary diameter. Infusion of serotonin caused a significant decrease in mean diameter in proximal (p<0.01) and distal (p<0.01) vessel segments. After infusion of ketanserin, the mean diameters of proximal or distal segments were not significantly different from baseline. The decrease in mean proximal diameter that occurred after repeat infusion of serotonin was significantly (p<0.05) less than that observed after the initial infusion, whereas the decrease in mean distal diameter was not significantly different (p=0.30) from that observed after the initial infusion (Figures 2 and 3 and Table 2).

Group 3, Variant Angina

Symptoms and ECG changes. All three patients developed angina at an infused concentration of 10^{-6} mol/l (one patient) or 10^{-5} mol/l (two patients) with ST segment shift similar to that seen during ergonovine provocation before catheterization. The pain and ECG changes resolved after inhalation of amyl nitrite but recurred during subsequent infusion of the same concentration of serotonin after ketanserin.

Changes in coronary diameter. Epicardial occlusion occurred at the site of the preexisting stenosis at an infused concentration of 10^{-6} mol/l in patient 3 and at an infused concentration of 10^{-5} mol/l in patients 1 and 2. The infusion of the same concentration of serotonin after ketanserin again caused epicardial occlusion (Figures 4 and 5).

Discussion

Our results suggest that the activation of S_{1}-like receptors contributes to the epicardial vasoconstrictor effect of serotonin in patients with coronary atherosclerosis, at the site of hyperreactive stenoses in patients with variant angina, and in the distal epicardial vessels in patients with stable effort angina.

Control Patients

In the control patients, serotonin caused significant constriction in distal epicardial vessels that was signifi-
FIGURE 4. Angiographic findings in a patient with variant angina (patient 3, group 3) at baseline (panel A), after intracoronary infusion of serotonin (10^{-6} mol/l), before (panel B) and after (panel C) intracoronary infusion of ketanserin, and 2 minutes after injection of isosorbide dinitrate (panel D). Epicardial occlusion occurred at the site of a preexisting stenosis in the circumflex coronary artery (arrow) before (panel B) and after (panel C) infusion of ketanserin.

cantly inhibited by ketanserin. Vasodilation did not occur after the infusion of ketanserin or after the subsequent infusion of serotonin.

These results are consistent with the results of studies in vitro that suggest that serotonin has a direct vasoconstrictor effect on normal human epicardial vessels. Isolated human coronary vessels, even when preconstricted, do not relax when exposed to serotonin or to 5-carboxamidotryptamine, a selective S_{1}-like receptor agonist; however, the constrictor response of vessels studied at basal tension is markedly enhanced by endothelial removal, which suggests that normal endothelium attenuates a direct constrictor effect on smooth muscle.

The results of experimental studies with vasoactive agents in vitro cannot necessarily be extrapolated to the intact coronary circulation. With intraluminal infusion, the first interaction is with the endothelium, whereas in isolated rings, effects on the endothelium and on vascular smooth muscle occur simultaneously; furthermore, in vivo, other factors such as an effect on coronary blood flow may independently affect epicardial diameter. However, epicardial constriction also occurs when serotonin is directly infused into the coronary circulation of the dog, which demonstrates the existence of a direct epicardial constrictor effect in vivo. In fact, epicardial constriction occurs despite a concomitant increase in coronary blood flow, suggesting that serotonin has opposite effects on epicardial and resistance vessels. This has been directly demonstrated by a recent study that showed that serotonin constricts feline epicardial vessels >90-μm diameter but dilates arterioles with a smaller caliber.

Golino et al recently showed that intracoronary infusion of serotonin in patients without atherosclerosis causes a dose-dependent increase in coronary blood flow. They also observed a dose-dependent increase in epicardial vessel diameter, which was more marked after the intravenous administration of ketanserin and was similar in magnitude to that produced by the intracoronary injection of nitrates. In a similar study in patients without coronary atherosclerosis, we observed small, nonsignificant increases in epicardial diameter at infused doses of 10^{-7}–10^{-5} mol/l but constriction most marked in the distal vessels at 10^{-4} mol/l. The results of the present study confirm that the intracoronary infusion of serotonin 10^{-4} mol/l constricts angiographically normal distal coronary vessels. Two factors may explain
the discrepancy between the studies. First, the highest dose by Golino et al that evoked a vasodilator response was approximately one quarter of that infused in the present study. This difference may be important because in the forearm, the infusion of lower doses of serotonin causes an increase in blood flow, whereas at high concentrations, a vasoconstrictor effect occurs. Second, their control group was all women without a history of chest pain, whereas the control patients in the present study had atypical chest pain syndromes and at least one conventional risk factor for coronary atherosclerosis. This difference in patient characteristics may also be important, because in animal models, factors such as hypertension or induced hypercholesterolemia have a marked potentiating effect on the constrictor effects of serotonin even in the absence of histologically demonstrable atherosclerosis.

Chronic Stable Angina Pectoris

In this group, serotonin caused significant vasoconstriction in both proximal and distal vessel segments, but ketanserin significantly inhibited serotonin-induced vasoconstriction only in the proximal vessel segments. The more marked constriction observed in atherosclerotic vessels is consistent with previous experimental studies in animals that suggest that endothelial dysfunction enhances the constrictor effect of serotonin and with observations on isolated human vessels that demonstrate that the constrictor effect of serotonin is markedly enhanced by pretreatment with methylene blue, an inhibitor of nitric oxide. The demonstration that serotonin significantly constricts distal vessels after S receptor blockade suggests that the activation of S-like receptors on epicardial vessels contributes to the vasoconstriction observed after intracoronary infusion of serotonin in patients with stable angina.

This conclusion is consistent with previous observations of isolated human coronary vessels that demonstrate that the constrictor effect of serotonin is mediated by S-like and S receptors, as it is only partially antagonized by ketanserin, a selective S receptor antagonist, but completely abolished by methiothepin, an antagonist at S-like and S receptors. Furthermore, sumatriptan and 5-carboxamidotryptamine, which are selective S-like agonists, also constrict isolated human coronary vessels.

In the control patients and those with stable angina, the constrictor effects of serotonin were more marked in the distal epicardial vessels; however, the inhibitory effects of ketanserin on distal constriction were significant only in the vessel segments from the control patients. The reasons underlying these differences are unclear and cannot be completely defined from the data obtained in the present study. It is possible that in normal vessels, when S receptor-mediated constriction is blocked by ketanserin, an endothelium-dependent S-like receptor-mediated release of relaxant factor(s) masks a direct S-like-mediated component of smooth muscle constriction, a hypothesis that is consistent with the results of studies in animals and with the findings reported by Golino et al in patients with normal arteries; the constrictor response to serotonin, observed in atherosclerotic vessels after S receptor blockade, may reflect the inability of a dysfunctional endothelium to synthesize or release adequate amounts of endothelium-dependent relaxant factor(s), thus allowing a constrictor effect of S-like receptor stimulation on smooth muscle to predominate.

Golino et al reported that ketanserin completely inhibited the vasoconstrictor effects of serotonin on epicardial vessels (at an infused concentration of 2.8x10^-5 mol/l) in three patients with atherosclerosis. The fourfold higher dose of serotonin used in our study may explain the discrepancy between the studies.

Variant Angina

In patients with variant angina, ketanserin did not prevent serotonin-induced occlusive spasm in proximal epicardial vessels. This suggests that activation of S-like receptors at a spastic site is a sufficient stimulus to cause epicardial occlusion, whereas in nonspastic arteries, S-like receptor activation, as reflected by the constrictor response to serotonin after ketanserin infusion, produces only moderate constriction.

In a recent important study in a canine model of dynamic coronary stenosis created by inflating a microballoon in a proximal epicardial vessel, Ichikawa et al demonstrated that the intracoronary infusion of serotonin caused a dose-dependent decrease in coronary blood flow associated with an increase in stenosis resistance and an increase in left ventricular end-diastolic pressure. These effects were prevented by methysergide, a nonselective serotonin receptor antagonist, but not by ketanserin, which suggests that, in this model of dynamic stenosis, the constrictor effects of serotonin are predominantly mediated through S-like receptors.

In humans, the most reliable test to substantiate a clinical diagnosis of variant angina is the intravenous injection of ergonovine, a drug that has agonist activity at serotonin receptors and at α-receptors. However, neither ketanserin, an antagonist at α-receptors and S₂...
By guest on January 15, 2018

Study Limitations

First, the suggestion that S1-like receptors play a role in the vasoconstrictor effects of serotonin is of necessity based on indirect evidence, because no S1-like agonists are currently available for clinical use. Second, the design of our study does not allow us to exclude that ketanserin-resistant, serotonin-induced vasoconstriction is caused by the release of endothelium-derived constricting factors by serotonin rather than to the activation of S1-like receptors. However, the results of studies in vitro support the latter interpretation.9,11

Finally, we cannot exclude that the administration of ketanserin by the intracoronary route produces less effective S1 blockade than the intravenous route used by Golino et al.8 This seems unlikely, as the dose of ketanserin that we infused was relatively greater and has been shown to completely abolish serotonin-induced decreases in forearm blood flow.21

Clinical Implications

The potential therapeutic benefit of serotonin receptor antagonists in unstable angina is based on the assumption that local concentrations of serotonin, released by aggregating platelets in the coronary circulation, are sufficient to evoke detrimental effects, and that serotonin antagonists will prevent these effects. Clinical studies suggest that platelet activation occurs in unstable angina,29 and studies in vitro have shown that when platelets aggregate in numbers equivalent to those circulating in blood, the concentration of serotonin may reach 6×10^{-6} mol/l.30 The dose of serotonin infused in the present study would, if one allows for dilution by coronary blood flow, produce an effective intracoronary concentration of approximately 10^{-6} mol/l. The actual concentration in the artery may, however, be less because serotonin is rapidly removed from the bloodstream by active endothelial uptake and by adsorption onto circulating platelets.31 Caution must be advised in the extrapolation of these results, which were obtained during intracoronary infusions of serotonin. However, the demonstration that a functionally important population of S1-like receptors is present on atherosclerotic human epicardial coronary arteries suggests that blockade of S1 receptors alone may not be sufficient to inhibit the vasoconstrictor effects of serotonin in vivo, when serotonin is released after the intracoronary activation of platelets.

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References


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