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# Sumatriptan provokes coronary artery spasm in patients with variant angina: Possible involvement of serotonin 1B receptor

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**Abstract**

*Background:* Serotonin (5HT) can induce coronary artery spasm (CAS) in patients with variant angina (VA). We have previously reported that $5HT_{1B}$ and $5HT_{2A}$ receptors gene were expressed in human coronary arterial smooth muscle cells and that isolated coronary artery from a patient with VA showed the supersensitivity to sumatriptan (SMT), a $5HT_{1B/1D}$ receptor agonist. The aim of the present study was to determine whether SMT can provoke CAS directly or indirectly through platelet aggregation in patients with VA.
*Methods:* We evaluated the effects of intracoronary infusion of graded concentrations of SMT on coronary arteries in 9 patients, including 5 documented VA and 4 participants with atypical chest pain as control.
*Results:* SMT provoked CAS in all patients with VA. SMT could not induce CAS in control. SMT ($10^{-4}$ M) caused significant contractions (%diameter of baseline; median [interquartile range], 0 [0–18.4]% in VA, as compared with control (proximal segments; 92.6 [77.9–118.9]%, $p<0.05$ vs. VA, distal segments; 92.9 [65.3–158.5]%, $p<0.01$ vs. VA). In control, minor dilation occurred at SMT concentration up to $10^{-5}$ M. SMT could induce in vitro platelet aggregation neither in healthy subjects nor in patients with VA.
*Conclusions:* These findings suggest that activation of $5HT_{1B}$ receptor by SMT can induce CAS directly in patients with VA without platelet activation. This is the first report directly demonstrating the effect of $5HT_{1B}$ receptor activation on human coronary arteries in vivo.


*Keywords:* Serotonin; Coronary artery spasm; Variant angina; Sumatriptan; Platelet aggregation

## 1. Introduction

Coronary artery spasm (CAS) plays a pivotal role in the pathogenesis of a variety of coronary artery diseases (CAD) including not only variant angina (VA) but also rest angina, unstable angina, myocardial infarction, and sudden death [1–3]. However, the precise mechanism of CAS remains to be elucidated.

Serotonin (5-hydroxytryptamine; 5HT), which is locally released from aggregated platelets, is one of the most important intrinsic vasoactive substances and has been implicated in the genesis of CAS [4–6]. We and others have shown that intracoronary infusion of 5HT can provoke CAS in patients with VA [7–9]. In pharmacological characterization of receptor systems using 5HT receptor agonists and antagonists in vitro, 5HT has been found to contract human large coronary arteries through $5HT_1$-like receptor as well as $5HT_2$ receptor. Kaumann et al. [10] showed that the $5HT_1$-like receptor pharmacologically resembles the $5HT_{1B}$ receptor and predominates over $5HT_2$ receptor in mediating 5HT-induced contractions in isolated human coronary arteries. We have previously demonstrated by using ribonuclease protection assay that not only $5HT_{2A}$ but $5HT_{1B}$ mRNAs are predominantly expressed and no $5HT_{1D}$ signal is detected in human

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coronary arteries [11]. Furthermore, we demonstrated the supersensitivity of isolated coronary artery to sumatriptan (SMT), a $5HT_{1B/1D}$ receptor agonist, in a patient with VA. We also detected gene expression of $5HT_{1B}$ and $5HT_{2A}$ receptors in spastic coronary artery, but not $5HT_{1D}$ receptor [12]. These findings strongly suggest that (1) $5HT_{1B}$ receptor is expressed functionally, (2) SMT is $5HT_{1B}$ receptor agonist in human coronary bed, and (3) $5HT_{1B}$ receptor may involve in the supersensitivity to SMT in spastic coronary arteries, since SMT is devoid of agonist properties at the $5HT_{2A}$ receptor [12]. In addition, the 5HT-induced coronary contraction was not completely eliminated by ketanserin, a selective $5HT_{2A}$ receptor antagonist, in patients with VA in vivo [13,14]. The aim of this study is to determine whether SMT, $5HT_{1B}$ receptor agonist, may be a trigger for CAS in patients with VA in vivo.

Moreover, we evaluated whether SMT could induce CAS indirectly through platelet aggregation. In vitro platelet aggregation in response to SMT was evaluated by using a novel laser-light scattering (LS) method [15,16]. This method is particularly useful for studying small aggregates formation after stimulation with weak agonist such as 5HT, which could not be evaluated by the previous methods [17].

## 2. Materials and methods

### 2.1. Study subjects

Between December 2000 and February 2003, 916 patients were referred to the Kobe University Hospital for diagnostic coronary angiography. Patients with myocardial infarction, left ventricular dysfunction, cardiomyopathy, valvular heart disease, or history of coronary intervention were excluded. 221 patients were consecutively enrolled. All patients gave informed consent in accordance with the guidelines of the Institutional Committee on Human Research at Kobe University Hospital before participation in the study. All participants underwent exercise testing, Holter monitoring electrocardiography (ECG), and non-invasive provocative examinations (hand grip, cold pressor and hyperventilation tests) for CAS, while receiving no medication. No patients had taken aspirin, clopidogrel or ticlopidine. Patients were excluded from the study if they had coronary artery stenosis $\geq$75%. Finally, we evaluated 9 patients (8 men, 1 woman; age, median [interquartile range], 50 [40–59] years) who did not have significant stenosis of coronary artery and could be received spasm provocation tests by SMT.

Patients were considered to have hypertension if they met the criteria of The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [18] or already treated with antihypertensive agents. They were considered to have hypercholesterolemia if they met the criteria of Adult Treatment Panel III (ATP III) [19] or were already under treatment for hypercholesterolemia. They were defined as having diabetes if they met the diagnostic criteria of American Diabetes Association (ADA) [20] or were already under treatment for diabetes. The clinical characteristics of these patients are shown in Table 1. The patients were classified into two groups based on their characteristics.

Control: Four patients, who had atypical chest pain, sufficiently severe to require further investigation, negative results on exercise testing, Holter ECG, and non-invasive provocation tests for CAS were classified.

VA: This group comprised five patients. All had a history of spontaneous, predominantly early-morning angina, accompanied with transient ECG change (ST elevation >2 mm). Three patients had negative results on exercise testing. Non-invasive provocative examinations induced myocardial ischemia in two patients.

The current investigation conforms with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Institutional Committee on Human Research at Kobe University Hospital.

### 2.2. Drug preparations

Sumatriptan succinate (3.0 mg/ml: $10^{-2}$ M, Imigran®, GlaxoSmithKline, Tokyo) stock solution was diluted with

Table 1
Clinical characteristics of patients

| Group | Patient No. | Age | Sex | Angina type | Exercise test | Holter ECG | Provocative test | ECG change during angina attack | Risk factors | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Smoking | DM | HT | HC |
| Control | 1 | 62 | M | E | N | N | N | NR | + | – | + | + |
| | 2 | 50 | M | R | N | N | N | NR | + | – | – | – |
| | 3 | 37 | M | R | N | N | N | NR | + | – | – | + |
| | 4 | 36 | M | R | N | N | N | NR | + | – | – | – |
| VA | 5 | 45 | M | R | N | N | N | ST↑ at II, III, aVF | + | – | – | + |
| | 6 | 62 | M | R+E | P | P | N | ST↑ at II, III, aVF | + | – | – | + |
| | 7 | 41 | F | E | N | N | P | ST↑ at II, III, aVF, $V_{1-4}$ | – | – | – | – |
| | 8 | 58 | M | R+E | P | N | P | ST↑ at II, III, aVF | + | + | + | – |
| | 9 | 53 | M | R | N | N | N | ST↑ at $V_{5-6}$ | + | – | – | – |

↑, elevation; DM, diabetes mellitus; E, effort; HC, hypercholesterolemia; HT, hypertension; N, negative for ischemia; NR, no electrocardiogram during anginal attack was recorded; P, positive for ischemia; R, rest; VA, variant angina.