Effects of Semotiadil (SD-3211), a Benzothiazine Calcium Antagonist, on Blood Pressure and Atrioventricular Conductivity in Anesthetized Dogs

Masaaki Kageyama, Hiroaki Yamada, Keisuke Satoh and Norio Taira*

*Department of Pharmacology, Tohoku University School of Medicine, Sendai 980, Japan*

ABSTRACT—We investigated the effects of semotiadil (SD-3211), a novel calcium antagonist, on blood pressure and the atrioventricular (AV) conduction time and functional refractory period (FRP) of the AV conduction system (AV conductivity) in anesthetized open-chest dogs. The heart was electrically stimulated at a constant rate. In dogs with an intact nerve supply to the heart, i.v.-injections of semotiadil (0.03 to 0.3 mg/kg) produced a fall of blood pressure in a dose-dependent manner. AV conduction time and FRP were prolonged by rather higher doses (0.3 mg/kg), and second-degree AV block occurred only with the highest dose (1 mg/kg). In dogs with the nerve supply to the heart interrupted, the vasodepressor effects and suppressant effects of semotiadil on AV conductivity were slightly enhanced. The suppressant effects on AV conductivity became marked as pacing rates were increased. These results suggest that semotiadil at appropriate doses produces a vasodepressor effect without affecting AV conductivity even in the heart deprived of nervous control, e.g., the heart with β-adrenoceptors blocked. The frequency-dependent suppressant effect on FRP of semotiadil is also noteworthy in the treatment of reentrant supraventricular tachycardia that involves the AV node.

Keywords: Atrioventricular conduction, Blood pressure, Calcium antagonist, Semotiadil, Open-chest dog (anesthetized)

Semotiadil fumarate (SD-3211, (+)-(R)-2-[5-methoxy-2-[3-[methyl-[2-[3,4-(methylenedioxy)phenoxy]ethyl]-amino]propoxy]phenyl]-4-methyl-2H-1,4-benzothiazine-3(4H)-one hydrogen fumarate, whose chemical structure is shown in Fig. 1, decreased the plateau of the fast action potential without affecting the maximum upstroke velocity and depressed the slow action potential induced by isoproterenol in isolated guinea pig papillary muscles (1). The result suggested that semotiadil can be classified as a calcium antagonist (1). The view was confirmed by a recent electrophysiological study, which indicated that semotiadil inhibited unitary calcium currents through voltage-dependent calcium channels (2). Oral administration of semotiadil produced long-lasting antihypertensive effects in hypertensive dogs and rats (3, 4) and antianginal effects in rats (5, 6).

In a previous study using isolated blood-perfused dog hearts (7), we characterized the cardiovascular profile of semotiadil as follows: semotiadil is nearly equieffective in producing coronary vasodilation and in suppressing atrioventricular (AV) conduction, but is less effective in suppressing sinoatrial (SA) nodal and ventricular automaticity, intraventricular conduction and cardiac muscle contractility. This profile of semotiadil raised the possibility that it would produce undesirable
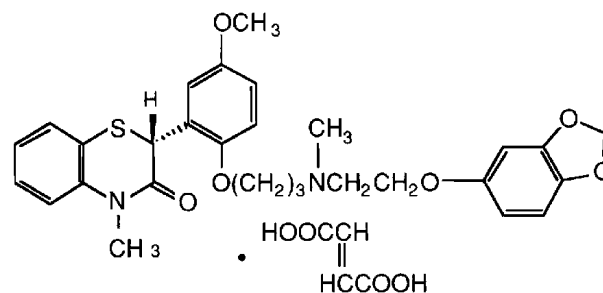
Fig. 1. Chemical structure of semotiadil.

*To whom all correspondence should be addressed.

effects on AV conduction in the treatment of hypertension and angina pectoris. Conversely, semotiadil may suppress reentrant supraventricular tachyarrhythmia that involves the AV node. Thus, we felt it necessary to obtain detailed information about the effects of semotiadil on AV conductivity (AV conduction time and functional refractory period of the AV conduction system (FRP)) in whole animals.

For this purpose, we investigated the effects of semotiadil on blood pressure, AV conduction time and FRP in anesthetized open-chest dogs. Because changes in heart rate affect AV conductivity (8), the heart was electrically paced.

MATERIALS AND METHODS

Mongrel dogs of both sexes weighing 7 – 17 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.), which was supplemented when necessary. Under artificial respiration, the chest was opened by midsternal thoracotomy, and the heart was kept in position with the pericardial cradle. Bipolar stimulating electrodes were sutured onto the epicardial surface of the right appendage. Two pairs of bipolar recording electrodes were sutured onto the epicardial surface of the right atrium and the apex to obtain atrial and ventricular electrograms, respectively. Catheters were inserted into the right femoral artery and vein to measure blood pressure and to administer drugs, respectively. The SA node activity was eliminated by injections of 70% ethanol into the sinus node artery and then the right appendage was paced at a basal rate of 150 stimuli/min. In some animals, the nerve supply to the heart was left intact (dogs with the nerve-intact heart); and in others, the vagus nerves were cut bilaterally and the stellate ganglia were extirpated bilaterally (vagotomized and stellectomized dogs).

AV conduction time was measured by an AV interval counter (Data-Graph, NH-110); and FRP was measured by an apparatus, which consisted of a programmed stimulator (Data-Graph, HT-1), an interval counter (Data-Graph, HT-11) and a display unit (Nihon Kohden, VC-7A). Details of the apparatus which measures FRP automatically have been described elsewhere (9, 10). Briefly the programmed stimulator delivered extrastimuli S' after every 7th regular (pacing) stimulus (S), and the interval between S and S' was shortened following the program. Blood pressure was measured by a pressure transducer (Gould-Statham, P23ID). Blood pressure, AV conduction time and FRP were recorded on a rectilinear recorder (San-ei Instrument, 8S).

In the absence of drugs, the pacing rate was reduced

from 150 (the basal rate) to 120 stimuli/min. After AV conduction time had become stable, AV conduction time and FRP were measured. Subsequently, the pacing rate was elevated stepwise from 120 up to 200 stimuli/min; and at each rate, the measurements were made. The pacing rates employed were as follows: 120, 130, 150, 170, 190 and 200 stimuli/min. All these measurements were completed within 15 min. After control measurements, semotiadil at 0.2 mg/kg was injected i.v. When drug effects on AV conduction time reached a maximum, the measurements of AV conduction time and FRP were started in the same way as the control. The effects of these drugs on AV conductivity lasted at least 15 min. In some experiments, the order of changing pacing rates was reversed.

Semotiadil fumarate, ($+$)-(R)-2-[5-methoxy-2-[3-[methyl-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]-propoxy]phenyl]-4-methyl-2H-1,4-benzothiazine-3(4H)-one hydrogen fumarate, was dissolved in saline containing 20% dimethyl sulfoxide (DMSO) to give a concentration of 10 mg/ml. When the drug was given at doses of less than 1 mg/kg, the stock solution was diluted with saline. In dogs with the nerve-intact heart and in vagotomized and stellectomized dogs, i.v.-injection of 20% DMSO, a vehicle of semotiadil, had no effect on blood pressure, AV conduction time and FRP.

Each value represents the mean $\pm$ S.E. Statistical significance between predosing and postdosing values was determined by Student's t-test. If $P < 0.05$, the value was considered statistically significant.

RESULTS

Effects of semotiadil on blood pressure and AV conduction time in dogs with the nerve-intact heart

Figure 2 shows the effects of semotiadil injected i.v. on systolic blood pressure (SBP), diastolic blood pressure (DBP) and AV conduction time in dogs with the nerve-intact heart, which was paced at 150 stimuli/min. The vasodepressor effect of semotiadil was more marked on DBP than on SBP; DBP was decreased significantly by 0.03 mg/kg or more, whereas no significant decrease in SBP was seen. The decrease in DBP reached a nadir at about 1 min, and wore off within 5 min. Semotiadil at relatively low doses (0.01 to 0.1 mg/kg) did not affect AV conduction time. However, after 0.3 mg/kg of semotiadil, AV conduction time gradually increased, and the increase amounted up to about 30 msec at about 4.5 min and lasted longer than 10 min. At 1 mg/kg of semotiadil, second degree AV block occurred in 5 of 6 dogs.
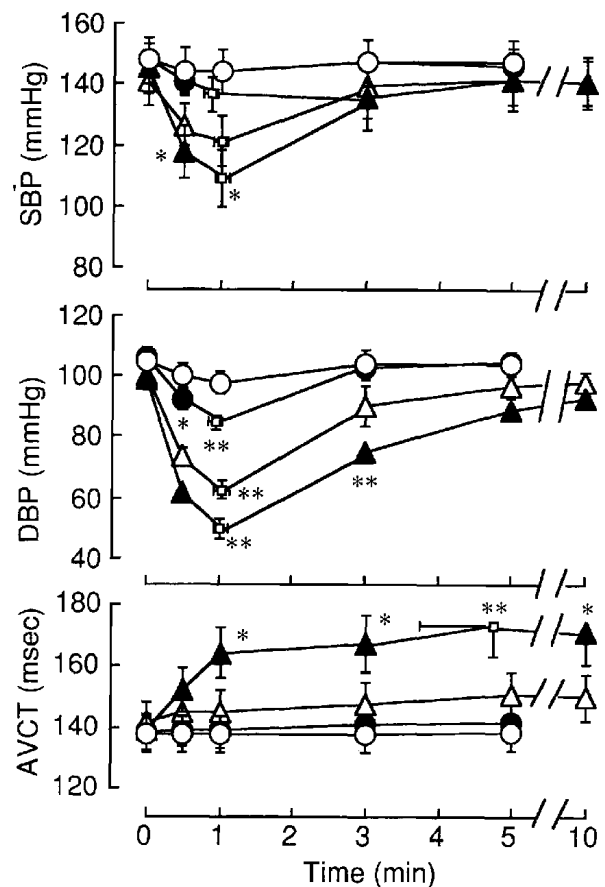
Effects of semotiadil on blood pressure and AV conduction time in vagotomized and stellectomized dogs

The effects of semotiadil on SBP, DBP and AV conduction time in vagotomized and stellectomized dogs, in which the heart was paced at 150 stimuli/min, are shown in Fig. 3. In these dogs, predosing values of blood pressure were not different from those in dogs with the nerve-intact heart. However, predosing values of AV conduction time in vagotomized and stellectomized dogs was greater by about 20 msec than that in dogs with the nerve-intact heart. i.v.-Injection of semotiadil (0.01 to 0.3 mg/kg) resulted in a greater decrease in blood pressure, particularly SBP, than that observed in dogs with the nerve-intact heart. The decrease in

SBP and DBP induced by semotiadil reached a nadir in about 1 min. The decrease in DBP produced by 0.3 mg/kg of semotiadil lasted about 5 min. In vagotomized and stellectomized dogs, no change in AV conduction time was observed with low doses of semotiadil. However, with 0.3 mg/kg of semotiadil, AV conduction time increased rather rapidly, reached a plateau in about 1 min and still remained increased at 10 min after administration of the drug; this prolongation of AV conduction time caused by 0.3 mg/kg of semotiadil was greater than that in dogs with the nerve-intact heart. With 1 mg/kg of semotiadil, AV conduction time was prolonged progressively so that second-degree AV block occurred in all of 6 dogs.
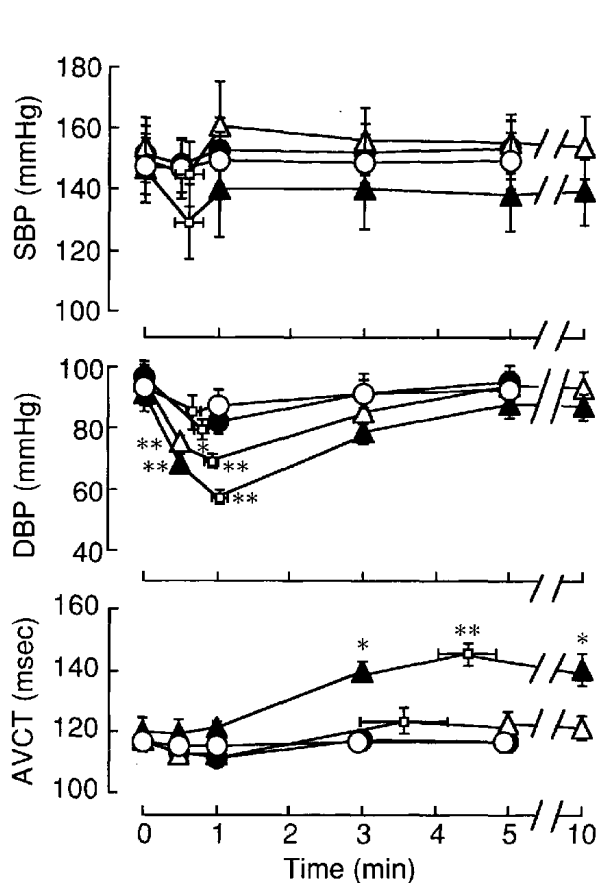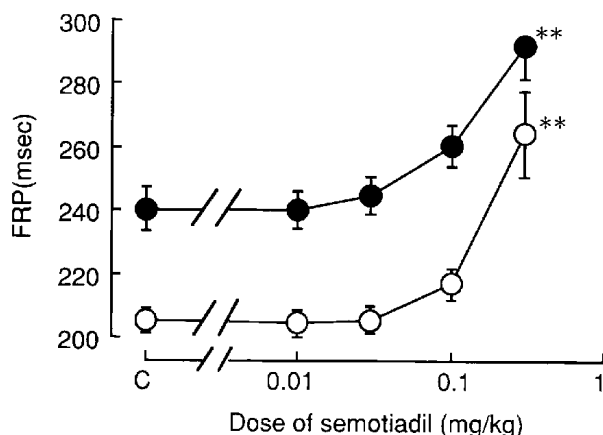

Fig. 2. Effects of semotiadil on systolic blood pressure (SBP), diastolic blood pressure (DBP) and atrioventricular conduction time (AVCT) in anesthetized open-chest dogs in which the nerves supplying the heart were left intact. The right appendage was paced at a rate of 150 stimuli/min. Open circles, 0.01 mg/kg; closed circles, 0.03 mg/kg; open triangles, 0.1 mg/kg; closed triangles, 0.3 mg/kg; small squares, peak responses. Each value represents the mean ± S.E. of 6 dogs. Second-degree AV block occurred in 5 of 6 dogs with 1 mg/kg. $^{*}P < 0.05$, $^{**}P < 0.01$, compared with predosing values.

Fig. 3. Effects of semotiadil on systolic blood pressure (SBP), diastolic blood pressure (DBP) and atrioventricular conduction time (AVCT) in anesthetized open-chest dogs in which the nerve supply to the heart was interrupted by bilateral vagotomy and extirpation of the stellate ganglia. Heart rate was maintained at 150 beats/min. Open circles, 0.01 mg/kg; closed circles, 0.03 mg/kg; open triangles, 0.1 mg/kg; closed triangles, 0.3 mg/kg; small squares, peak responses. Each value represents the mean ± S.E. of 6 dogs. Second-degree AV block occurred in all 6 dogs with 1 mg/kg. $^{*}P < 0.05$, $^{**}P < 0.01$, compared with predosing values.

Effects of semotiadil on FRP in dogs with the nerve-intact heart and in vagotomized and stellectomized dogs

Dose-response curves for the effects of semotiadil on FRP in dogs with the nerve-intact heart and in vagotomized and stellectomized dogs are shown in Fig. 4. FRP was measured when changes in AV conduction time reached maximum levels after administration of drugs at each dose. In dogs with the nerve-intact heart, semotiadil given i.v. at 0.3 mg/kg prolonged FRP significantly. The effects of semotiadil on FRP were slightly enhanced in vagotomized and stellectomized dogs.

The suppressant effect of semotiadil on AV conductivity became pronounced as pacing rates were increased. When semotiadil was given i.v. at 0.2 mg/kg, AV conduction time was prolonged from the respective predosing value of 129.2 ± 2.4 and 134.8 ± 3.1 msec to 151.0 ± 7.2 and 162.0 ± 7.5 msec at 120 and 150 stimuli/min. At 190 and 200 stimuli/min, second-degree AV block occurred in 2 and 3 of 6 dogs, respectively. Semotiadil also prolonged FRP from the respective predosing value of 249.3 ± 7.8 and 242.2 ± 8.3 msec to 291.2 ± 16.5 and 292.5 ± 14.8 msec at 120 and 150 stimuli/min.
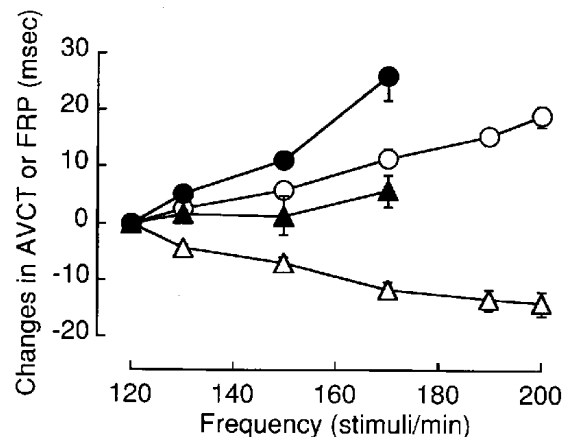

Fig. 4. Effects of semotiadil on functional refractory period (FRP) in anesthetized open-chest dogs. Animals in which the nerve supply to the heart was intact and deprived are indicated by open circles and closed circles, respectively. Each value represents the mean ± S.E. of 6 dogs. **$P < 0.01$, compared with predosing values (C).

Fig. 5. Effects of semotiadil on atrioventricular conduction time (AVCT, circles) and functional refractory period (FRP, triangles) in anesthetized open-chest dogs in which the heart was paced at various rates. The nerve supply to the heart was deprived. Open symbols, control; closed symbols, semotiadil 0.2 mg/kg. Each value represents the mean ± S.E. of 6 dogs. Each value obtained at each frequency is expressed as a difference from that obtained at 120 stimuli/min. Second-degree AV block occurred with semotiadil in 2 and in 3 of 6 dogs at 190 and 200 stimuli/min.

Effects of semotiadil on AV conduction time and FRP at various pacing rates in vagotomized and stellectomized dogs

Figure 5 shows the effects of semotiadil on AV conduction time and FRP in vagotomized and stellectomized dogs, in which pacing rates were varied in the range of 120 to 200 stimuli/min. In the absence of the drug, AV conduction time at 150 stimuli/min was 134.8 ± 3.1 msec. When a pacing rate was reduced to 120 stimuli/min, AV conduction time shortened to 129.2 ± 2.4 msec. An elevation of the pacing rate to 200 stimuli/min increased AV conduction time to 148.2 ± 4.1 msec. In contrast, FRP decreased from 249.3 ± 7.8 msec to 242.2 ± 8.3 and 235.2 ± 7.6 msec as pacing rates were elevated from 120 to 150 and 200 stimuli/min. Thus, AV conduction time was prolonged, whereas FRP was shortened as pacing rates were increased.

DISCUSSION

In agreement with a previous study (11), semotiadil, which is classified as a calcium antagonist (1, 2), produced a fall of blood pressure in anesthetized open-chest dogs when administered i.v. in the present study. When administered at relatively higher doses, semotiadil prolonged AV conduction time and FRP. Its vasodepressant effect was observed at lower doses than those producing prolongation of AV conductivity even in dogs with the nerve supply to the heart interrupted. Thus, semotiadil at appropriate doses produced the vasodepressant effect without affecting AV conductivity even in the heart deprived of autonomic control.

Nondihydropyridine calcium antagonists affect car-

diac functions, particularly sinus node activity, AV conductivity and contractility at vasodilatory doses (12, 13). In clinical settings, cardiodepression such as bradycardia and AV block has been observed with the antagonists as adverse effects (14, 15). Particularly, the cardiodepression appears to become more severe when patients are being treated with β-adrenoceptor blockers (16, 17). In our previous study (7), semotiadil suppressed sinus node activity, cardiac contractility and AV conduction at a coronary vasodilator dose when administered into the coronary circulation. Semotiadil was nearly equipotent in increasing blood flow and in prolonging AV conduction time (first-degree AV block) in the isolated, blood-perfused AV node preparation of dogs. The agent was less effective in suppressing sinus nodal activity and cardiac contractility. Therefore, it is possible that semotiadil produces an adverse effect such as negative dromotropic effects. In the present study, semotiadil indeed produced a prolongation of AV conduction time by about 25 msec at its peak effect at 0.3 mg/kg and second-degree AV block in 5 of 6 preparations at 1 mg/kg in anesthetized open-chest dogs with the nerve-intact heart. However, at 0.1 mg/kg of semotiadil, which caused a sizable fall of blood pressure, particularly DBP, there occurred no prolongation of AV conduction time. The vasodepressor effect of semotiadil was enhanced in dogs with the nerve supply to the heart interrupted, but even in these dogs, there occurred no significant prolongation of AV conduction time at 0.1 mg/kg. Therefore, semotiadil given at appropriate doses can be used as a safe antihypertensive drug even in patients with β-adrenoceptor blockade, as has been suggested (3). In the previous study (3) on conscious renal hypertensive dogs, the combination of semotiadil and propranolol produced antihypertensive effects without affecting heart rate and AV conduction time. However, precautions on the negative dromotropic effect of semotiadil are necessary when the agent is used at extremely high doses.

As clearly demonstrated in the present study, semotiadil prolonged AV conduction time and FRP in a parallel manner, which is characteristic of calcium antagonists (7). The suppressant effects on these two variables were frequency-dependent as had been demonstrated on AH intervals in Langendorff heart preparations from rabbits (1). The frequency-dependence of the prolonging effect of semotiadil was more marked on FRP than on AV conduction time. This characteristic is favorable for the treatment of paroxysmal supraventricular tachycardia that involves reentry in the AV node. It has been established that non-vasoselective calcium antagonists like verapamil and diltiazem are effective in the treatment of the reentrant supra-

ventricular tachycardia (18). Thus, semotiadil would be usable for similar purposes.

In conclusion, semotiadil at lower doses produced the vasodepressor effect without affecting AV conduction time and FRP even in dogs with deprived autonomic control of heart rate. These results suggest that semotiadil at appropriate doses is available for the treatment of hypertensive patients whose hearts are in a state deprived of nervous control, e.g., β-adrenoceptor blockade, without producing adverse effects on AV conductivity. Clearly, caution is needed when semotiadil is used at higher doses because of its prolonging effect on AV conductivity. Conversely, a frequency-dependent prolonging effect of semotiadil on FRP may be useful for the controlling reentrant supraventricular tachycardias that involve the AV node.

REFERENCES

1 Miyawaki, N., Furuta, T., Shigei, T., Yamauchi, H. and Iso, T.: Electrophysiological properties of SD-3211, a novel putative Ca^{2+} antagonist, in isolated guinea pig and rabbit hearts. J. Cardiovasc. Pharmacol. 16, 769–775 (1990)

2 Teramoto, N., Kitamura, K. and Kuriyama, H.: Inhibitory actions of semotiadil, a novel Ca channel blocker, on the voltage-dependent Ca channel in smooth muscle cells of the rabbit portal vein. Japan. J. Pharmacol. 58, Supp. I, 286P (1992)

3 Kageyama, M., Nishimura, K., Takada, T., Miyawaki, N. and Yamauchi, H.: SD-3211, a novel bezothiazine calcium antagonist, alone and in combination with a beta-adrenoceptor antagonist, produces antihypertensive effects without affecting heart rate and atrioventricular conduction in conscious renal hypertensive dogs. J. Cardiovasc. Pharmacol. 17, 102–107 (1991)

4 Takada, T., Miyawaki, N., Kageyama, M., Matsuno, K., Ishida, N., Yamauchi, H. and Iso, T.: Antihypertensive effect of a novel calcium antagonist, SD-3211, in experimental hypertensive rats. J. Cardiovasc. Pharmacol. 18, 855–862 (1991)

5 Mori, T., Irie, K., Ishi, F. and Ashida, S.: Prevention of coronary vasospasm by a novel Ca^{++} antagonist, SD-3211 (sesamodil) in rats. Japan. J. Pharmacol. 52, Supp. I, 213P (1990)

6 Mori, T., Irie, K. and Ashida, S.: Inhibitory effects of SD-3211, a novel long-acting Ca^{++} antagonist, on vasopressin induced ST segment depression in rats. Japan. J. Pharmacol. 55, Supp. I, 328P (1991)

7 Yoneyama, F., Yamada, H., Satoh, K. and Taira, N.: Cardiac versus coronary dilator effects of SD-3211, a new non-

dihydropyridine calcium antagonist, in isolated, blood-perfused dog hearts. Cardiovasc. Drugs Ther. **4**, 1469–1476 (1990)

8   Hashimoto, K., Iijima, T., Hashimoto, K. and Taira, N.: The isolated and cross-circulated AV node preparation of the dog. Tohoku. J. Exp. Med. **107**, 263–275 (1972)

9   Taira, N., Motomura, S., Narimatsu, A. and Iijima, T.: Experimental pharmacological investigations of effects of nifedipine on atrioventricular conduction in comparison with those of other vasodilators. In 2nd International Adalat[R] Symposium. New Therapy of Ischemic Heart Disease, Edited by Lochner, W., Braasch, W. and Kroneberg, G., p. 40–48, Springer-Verlag, Berlin, Heidelberg and New York (1975)

10 Taira, N., Iijima, T., Narimatsu, A., Satoh, K. and Yanagisawa, T.: Effects on atrio-ventricular conduction of propranolol, pindolol and carteolol in the dog heart in situ as assessed by automated devices. Japan. J. Pharmacol. **28**, 473–483 (1978)

11 Takada, T., Miyawaki, N., Nishimura, K., Nakata, K., Matsuno, K., Ishida, N., Yamauchi, H. and Iso, T.: Cardiohemodynamic effect of a novel calcium antagonist, SD-3211, in the dog. Arch. Int. Phamacodyn. Ther. **309**, 75–87

(1991)

12 Taira, N.: Differences in cardiovascular profile among calcium antagonists. Am. J. Cardiol. **59**, 24B–29B (1987)

13 Millard, R.W., Lathrop, D.A., Grupp, G., Ashraf, M., Grupp, I.L. and Schwartz, A.: Differential cardiovascular effects of calcium channel blocking agents: Potential mechanisms. Am. J. Cardiol. **49**, 499–506 (1982)

14 Krebs, R.: Adverse reactions with calcium antagonists. Hypertension **5**, Supp. **II**, II-125–II-129 (1983)

15 Russell, R.P.: Side effects of calcium channel blockers. Hypertension **11**, Supp. **II**, II-42–II-44 (1988)

16 Dahlöf, B., Eggertsen, R. and Hansson, L.: Calcium antagonists combined with β-blockers or ACE inhibitors in the treatment of hypertension. J. Cardiovasc. Pharmacol. **12**, Supp. **6**, S104–S108 (1988)

17 Waller, P.C. and Inman, W.H.W.: Diltiazem and heart block. Lancet **18**, 617 (1989)

18 Mitchell, L.B., Schroeder, J.S. and Mason, J.W.: Comparative clinical electrophysiologic effects of diltiazem, verapamil and nifedipine: a review. Am. J. Cardiol. **49**, 629–634 (1982)