INTRINSIC β -SYMPATHOMIMETIC ACTIVITY OF DILEVALOL, *R, R*-ISOMER OF LABETALOL

KAZUKI MATSUNAGA, KIMIKO NAKAMURA AND MOTOHIKO UEDA

Department of Pharmacology, Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka, 553, Japan

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The potency and selectivity of the intrinsic β -sympathomimetic activity (ISA) of dilevalol were studied with isolated guinea-pig trachea and pithed rat. This drug relaxed the contracture of isolated guinea-pig tracheal preparation induced by histamine in a dose-dependent manner. The dose-response curves of dilevalol and labetalol were shifted to the right with propranolol pretreatment. The relaxing potency of dilevalol was approximately 4.7 times more potent than that of labetalol. Dilevalol markedly reduced the diastolic blood pressure with only a slight increase of heart rate in pithed rats, while isoproterenol and pindolol caused moderate to marked positive chronotropic effects in proportion to their hypotensive effects. These results suggest that dilevalol has more potent ISA than labetalol and shows more β_2 -adrenoceptor selectivity than pindolol.

Keywords — intrinsic β -sympathomimetic activity; β_2 -selectivity; dilevalol; labetalol; guinea-pig isolated trachea; pithed rat

Dilevalol is the *R, R*-isomer of labetalol, an α - and β -adrenoceptor blocking agent with intrinsic β -sympathomimetic activity (ISA).¹⁾ ISA of dilevalol and labetalol is assumed to be one of the essential properties for their antihypertensive effect with simultaneous α - and β -adrenoceptor blocking properties, since the acute hypotensive effects of these drugs in conscious spontaneously hypertensive rats (SHR) were inhibited by propranolol pretreatment.²⁾ Although labetalol relaxed isolated guinea-pig trachea²⁾ and rat uterine preparations,⁴⁾ only negligible effects were observed on the heart rate of ganglion-blocked dogs⁵⁾ and isolated guinea-pig atria.⁶⁾ Dilevalol is a more potent β -blocker but a less potent α -blocker than labetalol,¹⁾ but not much is known about its ISA.

Thus, this study examined the potency and β -adrenoceptor selectivity of ISA of dilevalol using isolated guinea-pig trachea and pithed rat.

MATERIALS AND METHODS

Measurement of Tension in Isolated Guinea-pig

Tracheal Preparation — Male guinea-pigs weighing 330 to 450 g were pretreated with reserpine (2.5 mg/kg, *s.c.*) 24 h before use. Tracheal chain preparations⁷⁾ from these guinea-pigs were vertically mounted in a 30-ml organ bath filled with Krebs-Ringer solution at 37°C under an initial resting tension of 1 g. Tensions were isometrically recorded with a Medicalcor-der (DMP-3004, Nihon Koden) with an F-D pick up (SB-1T, Nihon Koden). After a stable contracture had been obtained with histamine (10^{-6} M), the relaxing effects of dilevalol and labetalol were compared. The effects of propranolol (10^{-6} M) pretreatment for 5 min on the responses to cumulative administrations of dilevalol and labetalol were also examined. The relaxing responses were calculated as the percentage of maximal relaxation induced by papaverine (10^{-4} M) at the end of each experiment. The drug concentration causing 50 percent relaxation to the response induced by papaverine (10^{-4} M) was determined as the EC_{50} . The Krebs-Ringer bicarbonate solution contained

119 mM NaCl, 4.7 mM KCl, 25 mM NaHCO₃, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄ and 11 mM glucose and the solution was aerated with a mixture of 95% O₂ + 5% CO₂.

Measurements of Blood Pressure and Heart Rate in Pithed Rats—Twelve weeks old male Slc-Wistar rats weighing 240 to 280 g were pithed following the procedure of Gillespie and Muir.⁸⁾ The rat was pithed through the right orbit into the entire length of the spinal canal with a stainless steel rod (2 mm in diameter) under ether anesthesia and placed under artificial respiration. Carotid blood pressure (BP) and heart rate (HR) were recorded on a polygraph (RM-6000, Nihon Kodan) with an electronic manometer (MP-25S, Nihon Kodan) and a pulse rate tachometer (AT-600G, Nihon Kodan), respectively. The hemodynamic effects of dilevalol were compared with those of isoproterenol and pindolol. Isoproterenol was cumula-

tively administered, while dilevalol and pindolol were administered as single doses to an individual pithed rat to avoid autoblockade.

Drugs Used—Dilevalol·HCl (Schering-Plough), labetalol·HCl (Schering-Plough), pindolol·HCl (Shionogi), propranolol·HCl (sigma), isoproterenol·HCl (Nikken Chemicals), reserpine (Daiichi), histamine·2HCl (Wako Pure Chemical). Doses are expressed in terms of the salt forms. Student's *t*-test was used to determine the significant differences.

RESULTS AND DISCUSSION

Relaxation of the Tracheal Preparation

Dilevalol and labetalol dose-dependently relaxed histamine-induced contracture of the tracheal chain preparation. The relaxing action proceeded much more slowly than that of isoproterenol. Dilevalol showed a more potent relaxing effect than labetalol at concentrations lower than 10⁻⁶ M. EC₅₀ values of dilevalol and labetalol were 10⁻⁷ and 4.7 × 10⁻⁷ M, respectively. This may show why the acute hypotensive effect of dilevalol in conscious SHR is somewhat more potent than labetalol at lower doses.²⁾ Pro-

FIG. 1. *Effect of Propranolol Pretreatment on the Relaxation Caused by Dilevalol and Labetalol in the Isolated Guinea-pig Tracheal Preparations*

○ — ○, dilevalol (6); △ — △, labetalol (6);
● — ●, propranolol 10⁻⁶ M + dilevalol (6);
▲ — ▲, propranolol 10⁻⁶ M + labetalol (6).

Numerals in parentheses show the number of preparations. Each point represents the mean ± S.E. a) indicate significantly different values from those of labetalol. a) *p* < 0.05.

FIG. 2. *Hypotensive and Positive Chronotropic Effects of Isoproterenol, Pindolol and Dilevalol in Pithed Rats*

○, isoproterenol (7); ◇, pindolol (4); ●, dilevalol (5–6).

Numerals in parentheses show the number of rats. Each point represents the mean ± S.E.

pranolol pretreatment shifted the dose-response curves of both dilevalol and labetalol to the right within the dose-range tested. This suggests that these tracheal relaxations by dilevalol and labetalol are due to the β -adrenoceptor agonistic activity. The equipotent relaxing effects of dilevalol and labetalol above 3×10^{-6} M may be related to the β -adrenoceptor autblockage (Fig. 1).

BP and HR in Pithed Rat

In forty-one pithed rats, mean $\pm$ S.E. of the resting diastolic BP and HR were 62 ± 2 mmHg and 342 ± 6 beats/min, respectively. Dilevalol markedly decreased diastolic BP with a slight increment of HR, while isoproterenol and pindolol caused a marked positive chronotropic effect in proportion to hypotension in pithed rats (Fig. 2). Hypotensive and positive chronotropic changes (23 ± 2 mmHg and 20 ± 5 beats/min) produced by dilevalol at 0.1 mg/kg *i.v.* were significantly inhibited (0 ± 1 mmHg and 6 ± 3 beats/min) by propranolol at 1 mg/kg *i.v.* pretreatment for 5 min in each six pithed rats. Intravenous injection of propranolol transiently caused slight hypotension and a negative

FIG. 3. Correlation between the Positive Chronotropic and Hypotensive Effects of Isoproterenol, Pindolol and Dilevalol in Pithed Rat

Changes of heart rate and diastolic blood pressure are derived from the same experiment shown in Fig. 2.

○, isoproterenol; ◇, pindolol; ●, dilevalol.

Concentrations of drugs used (*i.v.*): 10^{-8} – 10^{-7} g/kg isoproterenol, 10^{-5} – 10^{-4} g/kg pindolol, 10^{-4} – 10^{-3} g/kg dilevalol.

chronotropic effect, but these effects always disappeared before the administration of dilevalol. The diastolic BP and HR immediately before the administration of dilevalol were 58 ± 3 mmHg and 352 ± 20 beats/min, respectively. These changes are assumed to be due to the β -adrenoceptor agonistic activity. Labetalol was previously reported to show relative β_2 -adrenoceptor selectivity.^{3–6} In our experiments, dilevalol also showed β_2 -adrenoceptor selectivity in pithed rats and a negligible chronotropic effect in rat isolated right atria of rats (unpublished). In contrast, pindolol seemed to possess non-selective β -adrenoceptor agonistic activity⁵) (Fig. 3).

These results show that dilevalol has a more potent ISA than labetalol and more β_2 -adrenoceptor selectivity than pindolol.

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