Functional Antagonism between Calcium-Antagonists and Noradrenaline on Isolated Guinea-Pig Atria*

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Summary. In the isolated electrically driven guinea-pig atrium the influence of D 600 and nifedipine on the action of noradrenaline was investigated.

1. The calcium-antagonists caused a dose-dependent negative inotropic effect. 10^{-7} M of D 600 or nifedipine inhibited the contractile amplitude by 75 and 55\% respectively.

2. In spite of the pronounced negative inotropic effect evoked by the two calcium-antagonists, the maximal response to noradrenaline was not changed. The sensitivity of the myocardium to noradrenaline was only slightly diminished i.e. by a factor of 4.6 and 3 as calculated from the pD_{2}-values.

3. The functional antagonism between noradrenaline and calcium-antagonists, therefore, offers the possibility to overcome cardiac side-effects of calcium-antagonists.

Key words: Guinea-Pig Atrium — Negative Inotropic Effect — Calcium-Antagonists — Noradrenaline — Functional Antagonism.

Drugs with calcium-antagonistic effects are of increasing importance in the long-term therapy of coronary diseases. D 600 and nifedipine (Bay a 1040), for example, are strongly acting drugs of this group. However, they do not act specifically on vascular musculature but influence the function of smooth muscles everywhere and consequently the myocardial performance, too. For instance, already low concentrations of D 600 or nifedipine (10^{-8}—10^{-6} M) cause relaxation of the smooth muscles of the vessels (Grün and Fleckenstein, 1972) and of the uterus (Fleckenstein et al., 1971) while causing pronounced negative inotropic effects on the heart (Fleckenstein et al., 1969; Vater et al., 1972). The calcium-antagonists are thought to inhibit specifically the excitation-contraction coupling in the smooth muscle. That might be true also for the excitation-secretion coupling of the noradrenaline-efflux from sympathetic nerve endings although it is inhibited only by high concentrations (Starke and Schümann, 1973).

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The negative inotropic effect of nifedipine was antagonized by a high concentration of the β-sympathomimetic agent isoprenaline (Fleckenstein et al., 1972).

It was therefore of interest to determine whether the negative inotropic effect of calcium-antagonists on the isolated guinea-pig atrium can be reversed by the physiological transmitter, noradrenaline. In addition we attempted to analyse the nature of this antagonism.

Materials and Methods

Adult male guinea pigs were killed by a blow on the head. The hearts were quickly removed and the left atria were suspended in Krebs-Henseleit solution bubbled with 95% O₂ and 5% CO₂ at 30°C.

The Krebs-Henseleit solution contained in addition 5.7 × 10⁻⁵ M ascorbic acid and 10⁻³ M glucose.

The resting tension was adjusted to 1 g. The atria were driven electrically by square wave impulses of 3 msec duration at a frequency of 2 Hz with twice the threshold voltage (2.4 ± 0.2 V). An equilibration time of 1 hr was allowed before cumulative dose-response curves were determined with noradrenaline. D 600 and nifedipine were added 30 min before the dose-response curves for noradrenaline were determined. Control experiments were conducted in order to determine the resting amplitude before the first and the second dose-response curve, the values obtained did not differ and amounted to 570.4 ± 60.2 mg and 513 ± 54 mg (N = 13), respectively.

The pD₂-value calculated from the second dose-response curve amounted to 6.67 ± 0.04 (N = 13) and differed significantly (P < 0.005) from 6.85 ± 0.03 as calculated from the first dose-response curve. Since this decrease of the pD₂-value is small, the pD₂-values for noradrenaline obtained under the influence of calcium-antagonists have not been corrected. The difference was 0.18 log units corresponding to 2.6% of the pD₂-value of the first control curve. Therefore, in each preparation two dose-response curves for noradrenaline were determined, the first one in the absence and the second one in the presence of a calcium-antagonist.

pD₂-values of noradrenaline were calculated according to van Rossum (1963). They are given as means ± S.E.

Drugs Used. (−)-Noradrenaline (Farbwerke Hoechst), D 600 (Knoll AG), nifedipine (Baya 1040, Farbenfabriken Bayer). Nifedipine was dissolved in cremophor (100 mg ad 100 g cremophor) and diluted with isotonic NaCl.

The experiments with nifedipine were performed under sodium-light (Starke and Schümann, 1973).

The concentration of drugs are given as their molarities.

Results and Discussion

In 32 experiments the resting tension of the atria amounted to 407 ± 42 mg. The calcium-antagonists D 600 as well as nifedipine induced a dose-dependent inhibition of the resting tension. At concentrations of 10⁻⁹, 10⁻⁸ and 10⁻⁷ M D 600 reduced the resting amplitude by 22.7, 35.2 and 75.2%, respectively (Table). Nifedipine in concentrations of 10⁻⁸ and 10⁻⁷ M caused an inhibition of the control amplitude by 36.5