In vitro study of mutual antagonism between α- and β-adrenoceptor blocking agents

Many unrelated drugs cause a reappearance of the adrenaline-pressor response that is blocked by α-adrenoceptor blocking agents (Osswald, 1969). An antagonism of α-receptor blockers by β-receptor blocking agents, *in vivo* and *in vitro*, has been widely reported (see, Krell & Patil, 1969) though the mechanism of this interaction is not clear.

One explanation assumes that blockade of β-adrenoceptors after administration of α-receptor blockers mainly unmasks residual α-effects (Garrett, Malafaya-Baptista & Osswald, 1966; Nickerson, 1970). The concept finds a strong support in the findings that the antagonism of α- by the β-adrenergic blocker is seen only if a test preparation exhibiting functionally opposed α- and β-adrenoceptors is used together with an agonist that excites both the receptor species. Also, the pressor activity of a sympathomimetic drug exerted at a time when a β-blocker has antagonized α-receptor blockade never quite reaches its control magnitude.

On testing this concept *in vitro*, however, we found that pronethalol and tolazoline antagonize each other even though relatively pure agonists, isoprenaline and phenylephrine, were used with rabbit isolated ileum and perfused heart of frog (ambient temperature, 18°–22°). In these preparations the sympathomimetic excitation of either α- or β-receptor results in a similar overt effect (Furchgott, 1960; Buckley & Jordon, 1969).

Phenylephrine produced a concentration-related relaxation of the rabbit ileum the curves for which were unaffected by pronethalol (5 ng/ml, n = 5, Fig. 1) but were parallelly shifted to the right by tolazoline (0·5 μg/ml); pronethalol now shifted the curves back to their control position on the concentration-axis despite the presence of tolazoline in the bath (n = 11, Fig. 1). Again, tolazoline (0·5 μg/ml, n = 7) which had no major effect on the relaxant action of isoprenaline (Fig. 1) totally reversed the blockade of isoprenaline provoked by pronethalol (5 ng/ml). A similar mutual antagonism between α- and β-adrenergic blockers was reported *in vivo* by Ahlquist & Levy (1959) who studied responses of canine ileum.

The inotropic effect of agonists on frog heart (perfused as described by Buckley & Jordon, 1969) was recorded using a light spring lever. Pronethalol (100 ng/ml of perfusion fluid) nearly blocked the inotropic effect of submaximal doses of isoprenaline (2 to 5 μg, tested at 7 min intervals). Within 5 to 20 min of perfusion with fluid to which tolazoline (20 μg/ml) was also added the response to isoprenaline recovered up to 80 to 100% of the control (n = 10); tolazoline alone had no significant effect on the response to isoprenaline. The blockade, however, supervened again totally (n = 3) or partially (n = 7) in the following 30 min of continued perfusion. Doubling the strength of tolazoline in the fluid at this stage again produced a comparable recovery of response to isoprenaline. In another series of experiments (n = 6), pronethalol (75 ng/ml of fluid) did not alter the inotropic effect of submaximal doses of phenylephrine (100 to 275 μg, tested at 10 min intervals), but partially reversed the block provoked by tolazoline (10 μg/ml in the fluid). At the time of maximal recovery, the response to phenylephrine was 50 to 70% of the control.

Allowing that isoprenaline stimulated the α-receptors at a time when pronethalol had blocked the β-receptors, tolazoline was expected to block the residual relaxation of the ileum or the stimulation of the heart caused by isoprenaline. Hence, recovery from pronethalol-induced blockade due to tolazoline, occurring in a test sytem exhibiting parallelly functioning α- and β-receptors should have some basis other than that proposed by Garrett & others (1966). The contention is further supported by the finding that action of phenylephrine, blocked by tolazoline, reappeared totally

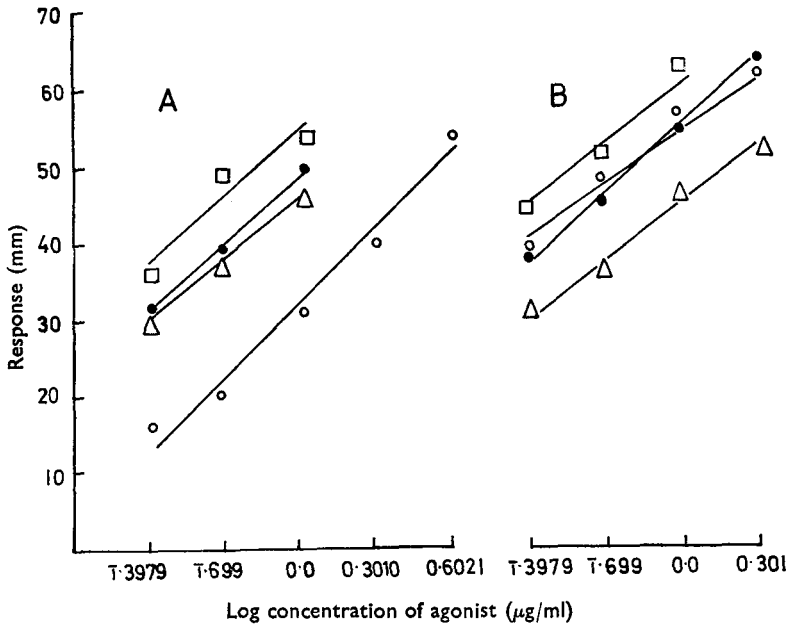

FIG. 1. Rabbit isolated ileum (Tyrode solution at 33° ± 1°, gassed with 5% CO_2 in O_2). Concentration-response curves for (A) isoprenaline HCl (tested at 6 min intervals) and (B) phenylephrine HCl (tested at 10 min intervals) in absence and in presence of antagonists added 5 min before. —●— Control. —△— Tolazoline 0·5 μg/ml. —○— Pronethalol 5 ng/ml. —□— Pronethalol 5 ng and tolazoline 20 μg/ml.

(ileum experiments) or partially (heart experiments) after administration of pronethalol.

Pronethalol and tolazoline (in concentrations used in this study) did not sensitize the tissues to phenylephrine and isoprenaline, respectively. This seems to exclude further that sensitization by one blocker of receptors spared from blocking activity of their regular, specific blocker (Osswald, 1960) can explain the observed antagonism between pronethalol and tolazoline.

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