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The influence of β-blocking agents on the kinin system in rat plasma

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The hypotensive effect of β-blocking agents has been reported in man (Buhler, Laragh & others, 1972, 1973; Doyle, 1974; Simpson, 1974) and in normotensive or spontaneously hypertensive animals (Roba, Lambelin & Schaepdryver, 1972; Vavra & Greselin, 1973; Lloyd & Nanol, 1975; Sweet & Wenger, 1976) but the mechanism is not clear. An effect on the renin-angiotensin system was postulated and the inhibition of the renin secretion was suggested to be responsible (Weber, Thornell & Stokes, 1974). But according to Rocha e Silva (1963) the renin-angiotensin system can have an antagonistic action towards the kinin system. Therefore we have investigated the influence of β-blocking drugs on the kinin system by estimating in the rat the concentration of kininogen *in vivo* and the activation of prekallikrein *in vitro*.

The β-blocking drugs used were: propranolol (Polfa), alprenolol (Astra), sotalol (Mead. Johnson), Kö 1366—bunitrolol (Boehringer), practolol (Polfa), pindolol—Visken (Sandoz). Phentolamine (Regitine—Ciba), an α-receptor blocking agent was also studied. Male Wistar rats weighing 180–220 g were injected with the β-blocking drugs intraperitoneally. Two h later animals were anaesthetized with ether and blood was collected from the inferior vena cava. The pooled blood from 8 rats was used for the preparation of batches of rat plasma. The concentration of kininogen was estimated according to Briseid, Dyrud & Öie (1970). Kinin was released from kininogen by a plasma and urine kallikrein preparation. The kinin determinations were carried out on the isolated rat uterus as 'bracketing assays' with the standard dose ratio 3:2. Bradykinin (Sandoz) was used as standard.

Activation of prekallikrein *in vitro* was estimated according to Briseid & others (1970) with a small modification. Prekallikrein preparations (0·9 ml) were incubated for 45 min at 37° with propranolol, Kö 1366 or phentolamine added at several concentrations in a constant volume of 0·1 ml. Incubate (0·5 ml) was then added to 0·5 ml of kininogen preparation. After incubation at 37° for exactly 10 min, a 0·5 ml sample was transfered to 2·5 ml of boiling saline. The mixture was boiled for 5 min cooled and its volume was adjusted to 5 ml with saline. The released kinins were assayed as described above.

Table 1. *The influence of β-blocking drugs and phentolamine on the kininogen concentration* (μg ml^{-1} ± s.e.) *in rat plasma.*

Drug	Dose mg kg^{-1}, i.p.	n	Kininogen concn μg ml^{-1} ± s.e.	% decrease
Solvent	—	16	2·00 ± 0·036	—
Propranolol	1	5	1·87 ± 0·08	7
	10	10	1·58 ± 0·048	21**
Phentolamine	5	10	1·99 ± 0·07	—
	10	5	1·99 ± 0·07	—
	15	5	2·00 ± 0·10	—
Solvent	—	13	1·90 ± 0·07	—
Propranolol	20	9	1·50 ± 0·04	25**
Kö 1366	20	7	1·47 ± 0·12	27**
Alprenolol	20	12	1·70 ± 0·05	15*
Sotalol	20	8	1·27 ± 0·06	37**
Pindolol	20	7	1·47 ± 0·12	27**
Practolol	20	17	1·90 ± 0·10	5
	60	5	1·47 ± 0·10	27**

*P <0·01. ** P <0·001.

Propranolol (1 mg kg^{-1}) did not influence the plasma kininogen, concentration but at 10 and 20 mg kg^{-1} it decreased it by about 21 and 25%, respectively. Alprenolol, sotalol, pindolol and Kö 1366 at 20 mg kg^{-1} also reduced the concentration of kininogen in plasma by 15, 37, 27 and 27% respectively. Practolol (20 mg kg^{-1}) appeared without effect while 60 mg kg^{-1} decreased the kininogen concentration by about 27% (Table 1).

Propranolol and Kö 1366, 1×10^{-5}, 1×10^{-4} or 1×10^{-3} g induced dose-dependent activation of prekallikreine. Phentolamine up to 1×10^{-3} g did not produce such an effect.

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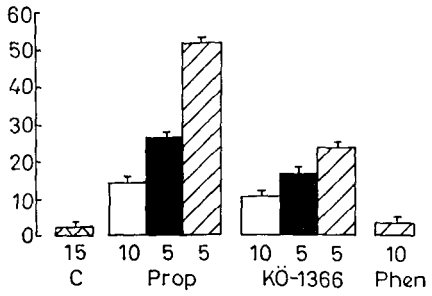

FIG. 1. The influence of propranolol (Prop), KÖ-1366 and phentolamine (Phen) on the prekallikrein activity in rat plasma. Concentrations (g ml^{-1}) of administered drugs; open columns 1×10^{-5}; closed columns 1×10^{-4}; hatched columns 1×10^{-3}. Crossed hatched column is the saline control (C). Figures under the columns refer to the number of estimations. Ordinate: Liberated kinins (ng).

We have previously reported a decrease of kininogen and prekallikrein in rat plasma after propranolol (Szurska, 1976). These findings are confirmed for five other β-blocking drugs. The decrease in plasma kininogen concentration *in vivo* and activation of prekallikrein *in vitro* may be evidence that β-adrenoceptor blocking agents induce activation of the kinin system leading to the release of free kinins. This effect may be responsible for the inhibition of renin secretion. The idea of mutual antagonism of both systems (kinin-renins) originating from α-2-globulins of plasma appeared in 1963 (Rocha e Silva) and has been supported by subsequent findings (Alabaster & Bakhle, 1972; Cziernuch & Gomazkow, 1976) though there are also contrary findings (Stokes, 1974; Takeda, Sakurai & Imai, 1975). In contrast to propranolol, pindolol, another β-blocking drug, does not affect renin activity in plasma (Castania & Rothschild, 1974; Weber & others, 1974) but, as we report here, it induces the activation of the kinin system.

The activation of the kinin system in rat plasma seems to be a specific effect of β-blocking drugs as it does not appear after phentolamine (Szurska, 1976; *vide infra*) but occurred with the six compounds in *in vivo* experiments and for the two used *in vitro*. But it should be emphasized that for activation of the kinin system *in vivo* the doses are several times higher than those needed for β-blockade in pharmacological experiments.

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