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Effect of Propranolol on Plasma Renin Activity, Renal Cortex Renin, and Adrenal and Brain Isorenins in Rats[1] (39069)

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The widespread use of propranolol and its effectiveness in many hypertensive patients, especially those with high plasma renin activity, have provoked great interest as to its possible mode of action. Its antihypertensive effect has been attributed to a decrease in plasma volume (1), to a suppression of plasma renin activity (2), and more recently to a central action (3). Because of the recent claim that adrenergic β-blockers should be used in all patients with a high plasma renin activity (2), we decided to investigate the effect of propranolol on plasma renin activity, renal renin content, and the isorenin content of adrenal and brain (frontal cortex) tissues in rats.

Materials and methods. Sprague–Dawley rats weighing 200–250 g were maintained on Purina Chow and received water *ad libitum*. Propranolol (kindly donated by Dr. Richard Davis, Ayerst Laboratories, Montreal) was diluted in isotonic saline in appropriate concentrations and 0.2 ml portions of the solutions was used for intraperitoneal injection. The rats were divided into three groups: (a) a control group of 11 rats which received 0.2 ml of isotonic saline intraperitoneally three times a day for 15 days (group 1), (b) 12 rats which received propranolol at 6 mg/kg of body weight per day (in three equal doses at 8.00, 14.00, and 20.00 hr) for 15 days (group 2), (c) a third group of 12 rats which received propranolol similarly, but at 30 mg/kg per day for 15 days (group 3).

Blood pressure and pulse were recorded one hour after administration of propranolol at the level of the caudal artery by means of a cuff on the tail connected to a strain-gauge and a Grass Polygraph, on the seventh and the fifteenth day of the experiment.

On the fifteenth day, the rats were anesthetized with sodium pentobarbital (60 mg/kg ip). Aortic blood was immediately taken and centrifuged in the cold (4°) at 10,000 rpm for 10 min; the plasma was immediately frozen. Kidneys, adrenals and brain were also immediately frozen.

Plasma renin activity was measured by the micromethod of Boucher *et al.* (4), plasma being incubated for 15 hr. Kidneys were homogenized in a Polytron with the tubes kept in ice. After centrifugation, 1 g of homogenate was diluted in 200 ml of doubly distilled water and 100 μl of the diluted homogenate was used for measurement of renal renin content by the Boucher *et al.* procedure. Isorenins from brain frontal cortex and adrenals were measured by a modification of the above method (5, 6).

Results. Rats in groups 2 and 3 gave no evidence of toxicity or side effects during propranolol administration. There were no significant differences in weight or blood pressure between the three groups. Pulse rate was significantly lower in group 2 than in controls and even lower in group 3 (Fig. 1). There was no significant difference in renal renin content or in adrenal or frontal cortex isorenins. Plasma renin activity was slightly, but not significantly, lower in groups 2 and 3, than in group 1. If one examines the results for each rat in the two groups (Table I), it becomes clear that the rats responded in two completely different ways: (a) 10 out of 24 rats had a total suppression of plasma renin activity, whereas (b) there was no significant difference from controls in the 14 other rats. (It is to be noted that 1 of the 11 control rats had undetectable PRA after 15 hr of plasma incubation).

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TABLE I. EFFECTS OF PROPRANOLOL IN RATS ON ISORENIN CONTENTS OF ADRENAL AND BRAIN TISSUES, RENAL CORTEX RENIN, AND PLASMA RENIN ACTIVITY.

		Isorenin content			
		Adrenal (ng/g/hr)	Brain frontal cortex (ng/g/hr)	Renal cortex renin (ng/mg/hr)	Plasma renin activity (ng/ml/hr)
Group 1, controls	1	—	3.04	335	2.5
	2	56.1	4.44	273	2.5
	3	76.0	1.62	79.9	2.5
	4	70.1	3.60	86.4	4.5
	5	82.6	1.47	189	1.6
	6	45.2	4.16	229	2.5
	7	35.5	5.62	183	3.3
	8	41.1	4.17	186	2.5
	9	61.6	4.08	927	1.6
	10	33.3	4.78	125	0
	11	42.2	4.52	154	1.6
	12				
Mean ± SE		54 ± 5.5	3.8 ± 0.4	252 ± 71	2.28 ± 0.34
Group 2, 6 mg/kg/day	1	33.2	1.59	203	1.6
	2	69.2	2.37	161	1.6
	3	79.3	2.24	85.8	2.5
	4	48.5	2.81	191	2.5
	5	58.3	1.69	150	2.5
	6	66.6	4.36	187	2.5
	7	33.2	7.47	209	0
	8	30	2.85	294	1.6
	9	33.7	3.80	200	1.6
	10	25.8	3.79	478	0
	11	26.7	3.16	228	0
	12	27.0	2.51	93.2	0
Mean ± SE		44 ± 5.5	3.2 ± 0.5	207 ± 29	1.36 ± 0.3
Group 3, 30 mg/kg/day	1	82.1	2.18	384	2.5
	2	24.8	3.37	119	3.3
	3	66.8	2.45	319	3.3
	4	83.3	2.24	303	0
	5	145.2	5.83	231	4.5
	6	33.5	5.78	126	0
	7	33.4	4.90	156	2.5
	8	41.7	3.40	85.6	0
	9	32.9	3.70	140	3.3
	10	25	0.95	254	0
	11	33.1	1.51	176	0
	12	27.9	5.25	110	0
Mean ± SE		52.5 ± 10	3.4 ± 0.5	201 ± 28	1.6 ± 0.5

Discussion. The lack of any hypotensive effect of propranolol in normal rats has been previously reported (7). On the other hand, in spontaneously hypertensive rats, Vavra *et al.* (7) have reported a fall in blood pressure after 10 weeks of oral propranolol administration at 1 mg/kg/day and after 6 weeks with 5 mg/kg/day. On the other hand, in DOCA-hypertensive rats, Farmer and Levy (8) have noted an antihypertensive effect of propranolol only when the dose had reached 50 mg/kg, given twice a day subcutaneously. In 1972, Roba *et al.* (9) reported no change or a slight decrease in pulse rate

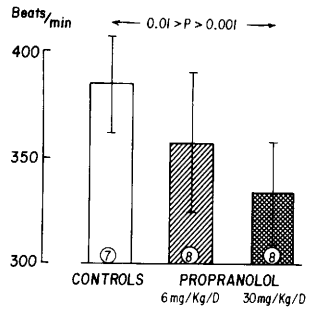

FIG. 1. Effects of propranolol on pulse rate in rats at 6 mg/kg/day and at 30 mg/kg/day for 2 weeks. Mean ± SD.

with doses of propranolol that produced a significant decrease in blood pressure in normal or hypertensive rats, whereas Vavra *et al.* (7) with doses of 20–100 mg/kg/day found a significant decrease in pulse rate without change in blood pressure. These differences in results emphasize the importance of taking the pulse rate one hour after administration of propranolol, since the half-life of this drug after intramuscular injection is only 78 min (10).

PRA during propranolol administration showed either no difference from control rats, or a total suppression. The absence of any significant decrease in renal renin content strongly suggests that propranolol, which suppresses plasma renin reactivity in two-fifths of the treated rats, inhibits the release of renin rather than its synthesis or secretion. It is of interest that the adrenal and brain isorenin contents behave in the same way as the renal renin content. These experiments are in accord with the clinical observations reported by many workers of the lack of any consistent effect of chronic propranolol administration on plasma renin of hypertensive patients, whether their blood pressure was decreased or unchanged by the drug (11–17). This is in contrast to the usually good correlation of the fall in blood pressure and in PRA produced by administration of propranolol in patients with acute hypertensive conditions accompanied by high PRA, and in the 3% of patients with essential hypertension, who have high PRA (18). Nevertheless, one must not forget that a coincidence of two effects does not necessarily mean that one is the cause of the other.

Summary. Propranolol administration to rats was studied for its effects on plasma renin activity, renal renin content, and adrenal and brain isorenins. Propranolol was given intraperitoneally at 6 and 30 mg/kg/day for a 15-day period. Pulse rate was significantly decreased. There were no effects on the isorenin content of adrenal or brain tissue or on renal renin content. Rats responded in two completely different ways with respect to plasma renin activity. Two-fifths had a total suppression of plasma renin activity; the rest had concentrations similar to those in controls. These observations are consistent with those seen during chronic administration of propranolol to hypertensive patients and suggest that its antihypertensive effect may in some patients be through the suppression of renin release. Its mechanism of action in most patients remains at present unclear.

1. Julius, S., Pascual, A. V., Abrecht, P. H., and London, R., Proc. Soc. Exp. Biol. Med. **140,** 982 (1972).
2. Böhler, F. R., Laragh, J. H., Baer, L., Vaughan, E. B. Jr., and Brunner, H. R., New Engl. J. Med. **287,** 1209 (1972).
3. Reid, J. L., Lewis, P. J., Myers, M. G., and Dollery, C. T., J. Pharmacol. Exp. Ther. **188,** 394 (1974).
4. Boucher, R., Ménard, J., and Genest, J., Canad. J. Physiol. Pharmacol. **45,** 881 (1967).
5. Ganten, D., Minnich, J., Granger, P., Hayduk, K., Brecht, H. M., Barbeau, A., Boucher, R., and Genest, J., Science **173,** 64 (1971).
6. Ganten, D., Marquez-Julio, A., Granger, P., Hayduk, K., Karsunky, K. P., Boucher, R., and Genest, J., Amer. J. Physiol. **221,** 1733 (1971).
7. Vavra, I., Tom, H., and Greselin, E., Canad. J. Physiol. Pharmacol. **51,** 727 (1973).
8. Farmer, J. B., and Levy, G. P., Brit. J. Pharmacol. **34,** 116 (1968).
9. Roba, J., Lambelin, G., and De Schaepdryver, A. F., 1972. Arch. Int. Pharmacodyn. **200,** 182 (1972).
10. Forman, B. H., and Mulrow, P. J., Circ. Res. **35,** 215 (1968).
11. Bravo, E. L., Tarrazzi, R. C., and Dustan, H. P., J. Lab. Clin. Med. **83,** 119 (1974). New Engl. J. Med. **292,** 66
12. Michelakis, A. M., McAllister, R. G., J. Clin. Endocr. **34,** 386 (1972).
13. Hansson, L., Acta Med. Scand. Suppl. **550,** 32 (1972).

14. Stokes, G. S., Weber, M. A., and Thornell, L. R., Brit. Med. J. January 12, p. 60 (1974).
15. Esler, M. D., Clin. Pharmacol. Ther. **15,** 484 (1974).
16. Safar, M., Corvol, P., Weiss, Y., Folliot, A., and Ménard, J., Nouv. Presse Med. **3,** 871 (1974).
17. Gysling, E., and de Wurspemberger, B., Schweiz. Med. Wochenschr. **104,** 1797 (1974).
18. Genest, J., Boucher, R., Kuchel, O., Nowaczynski, W., Can. Med. Ass. J. **109,** 475 (1973).

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