SQ 14225 on the blood pressure and heart rate of conscious normotensive rabbits and measured baroreceptor reflex sensitivity.

SQ 14225 (1.0 mg kg^{-1}) had no effect on the pressor action of angiotensin II, but produced a profound inhibition of the pressor response to angiotensin I and potentiation of the depressor response to bradykinin for at least two hours. SQ 14225 (0.1–10 mg kg^{-1}) had no consistent dose related effect on mean arterial pressure but caused a small increase in heart rate at all doses.

Plasma noradrenaline was not changed 45 min after vehicle injection but was significantly increased from 0.400 ± 0.067 μg/l before to 0.545 ± 0.105 μg/l after SQ 14225 ($P < 0.05$). Similar increases in noradrenaline have been reported after the angiotensin II antagonist, saralasin in man (McGrath, Ledingham & Benedict, 1977). The effects on heart rate and plasma noradrenaline could be baroreceptor reflex mediated or a result of direct release of catecholamines (Peach, 1971).

Baroreceptor sensitivity was assessed by measuring the heart period (heart $rate^{-1}$) after pharmacological manipulation of mean arterial pressures. Blood pressure was increased using bolus intravenous doses of phenylephrine (10–50 μg) and reduced by sodium nitroprusside (100–500 μg). There was a highly significant linear relationship between heart period and mean arterial pressure in each animal (r = 0.83–0.96). The slope of the linear regression of heart period against mean arterial pressure was used as an index of baroreceptor reflex sensitivity.

Mean baroreceptor sensitivity was 3.7 ms mm Hg^{-1} before C.E.I. ($n = 7$). 45–75 min after SQ 14225 1 mg/kg, there was a significant reduction in baroreflex sensitivity to 2.3 ms mm Hg^{-1} ($P < 0.001$). In a further group of 5 rabbits baroreflex sensitivity was determined before and after the same volume of 0.9% saline vehicle. There was no significant difference in slope (3.2 and 3.0 ms mm Hg^{-1} before and after). The present experiments, however, do not permit a precise localization of this effect nor can they distinguish between effects of angiotensin II formation, bradykinin degradation or other unidentified actions of the agent. Resetting of baroreceptor reflex sensitivity may be therapeutically useful in reducing tachycardia resulting from a pressure fall after this drug.

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The effect of SQ 14225 on fluid intake in DOCA/salt hypertensive rats

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SQ 14225 (2-D-methyl-3-mercaptopropanoyl-L-proline; Captopril), an orally active inhibitor of angiotensin I-converting enzyme has been shown to reduce blood pressure in 2 kidney Goldblatt hypertension in rats (Leffan, Goldberg, High, Schaeffer, Waugh & Rubin, 1978) and to produce enzyme inhibition in man (Ferguson, Brunner, Turini, Gavras and McKinstry, 1977). We have examined this compound on fluid intake and on the development of hypertension in DOCA/salt rats.

Male Wistar rats (200 g) were made hypertensive by implanting a DOCA pellet (25 mg s.c.) and providing them with 1% w/v NaCl solution (saline) to drink; eight rats were given SQ 14225 (10 mg/kg p.o.) once daily for 14 days (20 mg/kg on the 12th day only) while nine control rats were given equivalent volumes of water p.o. Other animals were sham-operated and drank water; 8 of them were treated with SQ 14225 as above and 7 controls received water. Three to five rats were kept in each cage and mean daily fluid intake was estimated from the total consumption of each group. Systolic b.p. was measured by a tail cuff method.

In all DOCA/salt rats the blood pressure began to rise on the 6th day after implantation, no significant effect being produced by SQ 14225. By contrast, SQ 14225 had a marked effect on fluid intake in these rats. The mean (± s.e. mean) daily intake of saline,

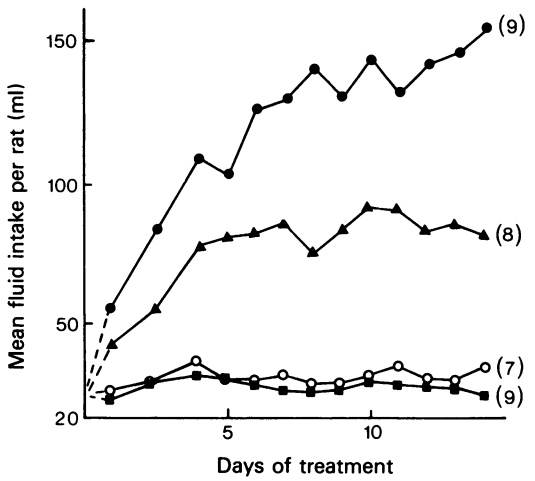

Figure 1 Daily fluid consumed by rats treated with (●) DOCA/salt, (▲) DOCA/salt and SQ 14225, (□) SQ 14225 alone and (○) control. Numbers of animals in parentheses.

averaged between days 6 to 14, was 139.2 ± 3.2 and 86.1 ± 1.7 ml for control and drug-treated rats respectively; these figures are significantly different ($P < 0.001$). A similar trend towards reduced fluid intake was seen when the drug was given to sham operated rats (Figure 1).

We think it unlikely that the effect on fluid intake of SQ 14225 results from peripheral actions since renin release has been reported to be 99% inhibited in DOCA/salt rats (Campbell & Pettinger, 1975). It is possible that SQ 14225 has some direct action on drinking unrelated to this inhibition of converting enzyme but it seems most likely that the effect of this compound on drinking is due either to inhibition of converting enzyme in the brain iso-renin system or to the potentiation of kinins.

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An inhibitory role for the adrenals in the cardiovascular effects of propranolol in the spontaneously hypertensive rat

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The anti-hypertensive effect of propranolol in different types of hypertension in man has been well documented (see Simpson, 1974). In rats with experimental hypertension however, the blood pressure lowering effect is less clear (Roba, Lambelin & De Schaepdryver, 1972; Fernandes, Onesti, Fiorentini, Gould, Kim & Swartz, 1977). We investigated the cardiovascular effects of (±)-propranolol in the unanesthetized spontaneously hypertensive rat (SHR). Blood pressure was recorded from a cannula in the caudal artery at the base of the tail in male rats 11–15 weeks of age. Heart rate was computed from the blood pressure recordings.

Different doses of propranolol (1 and 5 mg/kg subcutaneously) failed to decrease blood pressure during 2 h of measurement. At the highest dose heart rate decreased significantly (−50 ± 6 beats/min, $n = 6$) ($P < 0.01$). After central administration into a lateral ventricle (1.5 mg/kg), no cardiovascular changes were observed except a small hypertensive effect within the first 10 minutes. Peripheral administration of propranolol to animals which were subjected to bilateral adrenalectomy 4 h previously however, induced a profound decrease in blood pressure and heart rate. The effects were dose-dependent. Maximal effects were observed 15–30 min after the injection (−34 ± 6 mm Hg and −140 ± 8 beats/min respectively after 5 mg/kg, $n = 7$). Individual values for decreases in blood pressure and heart rate were not correlated ($r = 0.25$), indicating independent mechanisms for both parameters. In order to investigate whether the adrenal cortex or the adrenal medulla was responsible for the observed effects, rats were demedullated 2 days prior to the experiment. In these rats propranolol (5 mg/kg s.c.) caused no cardiovascular changes. After treatment of adrenalectomized animals with corticosterone (100 μg 100 g^{-1} h^{-1}) the decrease in blood pressure and heart rate due to propranolol were completely abolished. Substitution with 30 μg 100 g^{-1} h^{-1} corticosterone did not prevent the hypotensive action and bradycardia. Adrenal corticosteroids therefore seem to be responsible for the absence of