4.2 μg Hg/day compared with 0.6 μg/day in the untreated controls or the 1.9 μg/day in the animals treated only with penicillamine.

Sodium maleate reduced the non-protein but not the protein-bound thiol groups in the kidney. Neither did it change the amount and the pattern of thiol compound excretion in the urine after penicillamine. Thus its effect on the mercury excretion cannot be explained by its action as a thiol reagent nor by any modification of the penicillamine excretion. Probably its effect was due to metabolic or permeability changes which facilitated the withdrawal of mercury by penicillamine. The binding site for sodium maleate in the kidney responsible for these changes was probably not a protein thiol group because with thiols maleate should form irreversible (covalent) bonds. The binding site was likely to be another reactive group with which maleate formed a reversible (ionic) bond. The affinity of sodium maleate for this reactive group might be higher than its affinity for penicillamine, but lower than that for dimercaptopropanol. Thus dimercaptopropanol given either simultaneously or even 3 hr after sodium maleate would be able to break this reversible bond and so abolish the change responsible for the increase in the mercury excretion.

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Effect of different dopa decarboxylase inhibitors on the hypotensive response to α-methyldopa in rats

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In order to explain the antihypertensive properties of L-α-methyl-3,4-dihydroxyphenylalanine (α-methyldopa), Day & Rand (1964) suggested that α-methylnoradrenaline formed from α-methyldopa may serve as a false transmitter in place of noradrenaline in peripheral sympathetic nerves. The theory implies that inhibition of the synthesis of false transmitters from α-methyldopa should abolish the hypotensive effect.

Carotid blood pressure was recorded in conscious Sprague-Dawley rats, 180–250 g, with renal hypertension (Henning, 1967). All drugs were injected intraperitoneally. After α-methyldopa (200 mg/kg) the maximal decrease in arterial blood pressure occurred after 3–6 hr (mean decrease after 3 hr: 46 mm Hg, S.E. of mean=5.2, n=8). Pretreatment with Ro 4-4602 (seryl-1,2,3-trihydroxybenzylhydrazine), a potent inhibitor of dopa decarboxylase in peripheral tissues and in brain, completely prevented the fall in blood pressure after α-methyldopa. The inhibitor was given 4×200 mg/kg at 2 hr interval, first dose 30 min before α-methyldopa. Mean decrease in blood pressure 3 hr after α-methyldopa plus Ro 4-4602 was 1 mm Hg (S.E. of mean=6.1, n=6), differing significantly ($P<0.025$) from the value after α-methyldopa only. In control experiments, Ro 4-4602 alone had a slight hypotensive effect 12–24 hr after the first dose. The accumulation of α-methyldopamine 3 and 6 hr after α-methyldopa (200 mg/kg) was inhibited completely in the heart and femoral muscle and to about 75% in the brain following the same pretreatment with Ro 4-4602.

Unlike Ro 4-4602, the decarboxylase inhibitor MK-485 (hydrazinomethyldopa) does not penetrate into the brain. Pretreatment with MK-485 (5×100 mg/kg at 2 hr interval, first dose 30 min before α-methyldopa) did not prevent the decrease in blood pressure

after α-methyldopa (100 mg/kg). Mean decrease 3 hr after α-methyldopa alone was 35 mm Hg (S.E. of mean=6.5, n=13) and after α-methyldopa plus MK-485 39 mm Hg (S.E. of mean=8.0, n=8). The difference was not statistically significant. MK-485 alone lowered blood pressure slightly after 12–24 hr. The accumulation of α-methyldopamine was inhibited to 100% in heart and in femoral muscle but was unchanged in brain by pretreatment with MK-485.

Thus, inhibition of the synthesis from α-methyldopa of false transmitters in peripheral sympathetic nerves does not influence the hypotensive response of the drug, but this effect is abolished when the inhibition is extended to the central nervous system.

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Vasodilatation and oxygen uptake in skeletal muscle of the dog

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It is considered that oxygen uptake of a resting muscle can be increased by augmenting the blood flow and the number of open capillaries in the muscle. The oxygen uptake of the isolated gastrocnemius or gracilis muscle in dog was determined following vasodilatation caused by either nervous or humoral mechanisms, in order to study their point of action. The venous blood from the muscle was directed through a cuvette where oxygen saturation was continuously estimated by reflexion oximetry. The arterial oxygen saturation was also determined. Blood flow was measured by a silicone filled drop counter on either the arterial or the venous side.

Activation of the sympathetic cholinergic vasodilator nerves caused a vasodilatation lasting about 2 min. This vasodilatation led to an initial increase in oxygen uptake followed by a return to resting values even though the blood flow remained at the augmented level. This is somewhat at variance with the results of Rosell & Uvnas (1962), who, in skeletal muscle of cat, found a decrease in oxygen uptake after an initial increase following sympathetic cholinergic vasodilatation.

Acetylcholine, infused I.A. at 0.1–0.5 μg/min per 100 g muscle caused a dilatation. During the first 10–30 sec of this vasodilatation the oxygen uptake increased but then returned to resting values and remained there even when the vasodilatation was prolonged over 4–5 min.

Vasodilatation was further caused by inhibition of vasoconstrictor nervous tone. The carotid sinus nerve was stimulated and, to avoid the effect of the blood pressure fall, the muscle to be studied was cross-perfused from a donor dog. In this case oxygen uptake was increased during the whole period of stimulation, provided the blood flow was kept increased.

Some conclusions concerning the sites of action of vasodilatory mechanisms can be drawn from these experiments. The sympathetic cholinergic vasodilator nerves and acetylcholine seem to dilate preferentially at the arteriolar level. The increased blood flow caused by these mechanisms initially passes nutritional channels leading to increased uptake of oxygen, but are later directed through more non-nutritional pathways, a sort