# Potentiation by Alpha-Methyldopa of Pressor Responses to Angiotensin[1] (34689)

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(Introduced by T. E. Gaffney)

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Vascular responses to exogenous angiotensin have been shown to be influenced by the level of endogenous renin activity in experimental animals and in humans. Systemic pressor responses to angiotensin are augmented in conditions associated with low plasma renin activity, *e.g.*, primary aldosteronism (1, 2) and after nephrectomy (3, 4). Conversely, a reduction in the pressor response to angiotensin has been observed in conditions associated with increased plasma renin activity, *e.g.*, sodium deprivation, renovascular hypertension, malignant hypertension, Bartter's syndrome, and secondary aldosteronism due to cirrhosis of the liver (1, 5–8).

Recent studies in our laboratory (9) have shown that chronic treatment with alpha-methyldopa reduces plasma renin activity in humans. In view of this observation, it was of interest to determine whether chronic treatment with methyldopa is associated with an augmented pressor response to angiotensin. This possibility was studied in the denervated hindleg of dogs.

*Methods.* Mongrel dogs, 10.2 to 17.0 kg, were used. Experiments were performed on seven control dogs and eight dogs pretreated for 4 to 7 days with methyldopate hydrochloride, 150 mg/kg/day, iv. Morphine sulfate (3 mg/kg) and 30 min later a mixture of chloralose (50 mg/kg) and urethane (500 mg/kg) were given iv as anesthetic agents. A cuffed endotracheal tube was inserted into the trachea and artificial ventilation was carried out with a Harvard respirator after bilateral cervical vagotomy.

[1] This research supported by USPHS Grants HE-07392 and HE-05622.

The left hindleg of the dog was prepared for constant-flow perfusion by a previously described technique (10). Briefly, the technique involved exposing the abdominal aorta through a midline incision and inserting a polyethylene cannula into its lower portion via the left femoral artery. Blood obtained via this cannula was led through a Sigmamotor pump to the peripheral segment of the ligated left femoral artery in the upper thigh. Acute denervation of the left hindleg was performed by sectioning the left abdominal sympathetic, left femoral, and left sciatic nerves. Initially, the flow rate was adjusted to give a perfusion pressure approximately equal to the mean systemic arterial pressure; it was then held constant throughout the experiment. The absence of a reflex increase in perfusion pressure in response to bilateral carotid occlusion was taken as evidence of complete denervation.

Perfusion pressure was measured from a sidearm in the tubing between the pump and the perfused femoral artery, while the systemic arterial pressure was obtained from a brachial artery. These pressures were measured with Statham transducers and were recorded with a Grass polygraph. Mean pressures were obtained by electrical integration.

Hindleg pressor responses to intra-arterial (ia) angiotensin II amide, 0.1 to 3 $\mu$g, and norepinephrine bitartrate, 0.1 to 10 $\mu$g, were obtained in control and methyldopa-pretreated dogs. In addition, pressor responses to these drugs were measured 2 hr after a single iv injection of methyldopate HCl, 150 mg/kg, in each of the seven control dogs.

Student's test was used for statistical analyses and $p$ values under 0.05 were consid-

ered significant. Means ± 1 SE are shown in Fig. 1 and 2.

*Results and Discussion.* After chronic treatment with methyldopa, 150 mg/kg/day for 4 to 7 days, the pressor responses to ia angiotensin were significantly augmented ($p < .05$) at each dose tested (Fig. 1A). In contrast, vasoconstrictor responses to ia norepinephrine were the same in control and methyldopa-treated dogs (Fig. 1B).

The administration of a single iv injection of methyldopa, 150 mg/kg, to control dogs had no effect on hindleg pressor responses to either angiotensin or norepinephrine during the 2-hr observation period after drug administration (Fig. 2).

These results demonstrate that chronic treatment with methyldopa was associated with augmented vasoconstrictor responses to angiotensin in dogs. Potentiation of the pressor effect of angiotensin also occurs in patients with primary aldosteronism and in nephrectomized animals (1, 4); in both of these conditions plasma renin activity is low. Although plasma renin activity was not measured in the present study, Mohammed *et al.* (9) have found that treatment with methyldopa leads to a reduction in plasma renin activity in human subjects. It is possible, therefore, that the enhanced pressor responses to angiotensin seen in the present study are related to a suppression of the renin–angiotensin system by methyldopa.

Potentiation of certain responses to norepinephrine has been observed in animals treated with methyldopa (11–13); this effect is presumably due to the adrenergic neuronal blocking effect of methyldopa. The hindleg

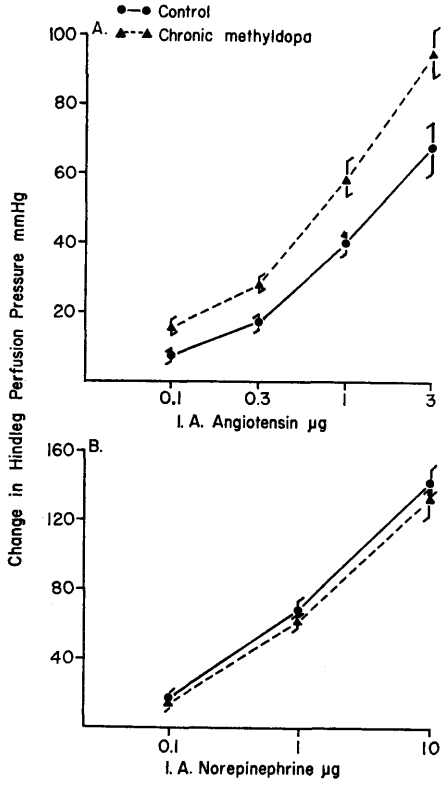


FIG. 1. The effect of chronic treatment with methyldopa (150 mg/kg/day iv for 4–7 days) on pressor responses to ia injections of angiotensin (A) and norepinephrine (B) in the denervated hindlegs of dogs.

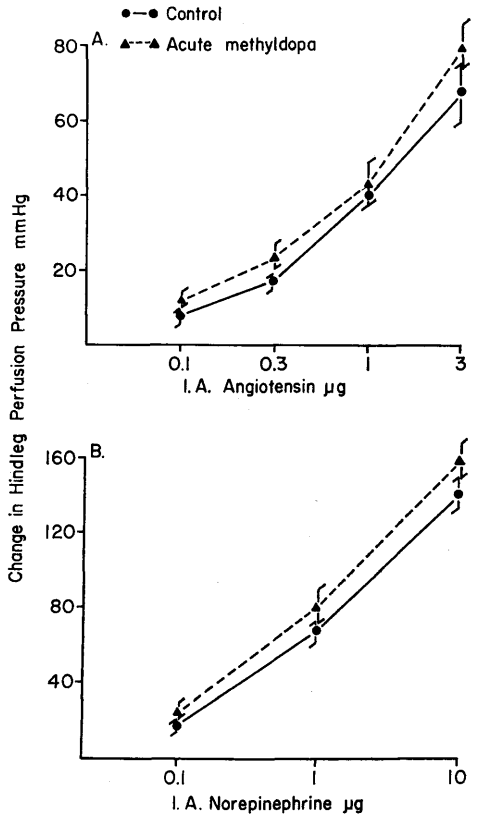


FIG. 2. The hindleg pressor responses to ia injections of angiotensin (A), and norepinephrine (B), before (●), and 2 hr after (▲), a single iv injection of methyldopa, 150 mg/kg.

vasoconstrictor effect of norepinephrine, however, was not enhanced after treatment with methyldopa in the present study.

It is well established that the sympathetic nervous system contributes to the vasoconstrictor action of angiotensin. Acute sympathectomy reduces the pressor response to angiotensin in the hindleg of the dog (14) and the rat (15). Likewise, adrenergic neuronal blocking agents such as reserpine, bretylium, and guanethidine reduce the vasoconstrictor effect of angiotensin (16, 17). Since treatment with methyldopa led to a potentiation, rather than an inhibition, of the vasoconstrictor responses to angiotensin in the present study, it is unlikely that this phenomenon was related to a blocking effect of methyldopa on the adrenergic neurones; furthermore, the sympathetic nerves to the hindleg were cut at the outset of the experiments.

The augmentation by methyldopa of the pressor responses to an endogenous vasoactive peptide, angiotensin, is of particular interest since this effect might tend to counteract the hypotensive effect of methyldopa. The development of tolerance to the hypotensive effect of methyldopa is known to occur in some hypertensive patients (18) and it is possible that this phenomenon may be in part related to the development of potentiation, not only of the vascular responses to catecholamines (11), but also of those to angiotensin.

*Summary.* Chronic treatment with methyldopa, for 4 to 7 days, produced augmentation of pressor responses to angiotensin in the denervated hindleg of dogs, whereas vasoconstrictor responses to norepinephrine were unaffected. The administration of a single iv injection of methyldopa did not alter the hindleg pressor responses to either angiotensin or norepinephrine. Since chronic treatment with methyldopa has been shown to decrease plasma renin activity in man, it is possible that the potentiation of the vasoconstrictor effect of angiotensin seen in dogs after chronic treatment with methyldopa may be related to an effect of this drug on the renin–angiotensin system.

The authors are indebted to Mr. John Brubaker and Miss Barbara Anderson for assistance during this study, and to Dr. W. H. Wilkinson of Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania for the generous supply of methyldopate hydrochloride.

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Received Dec. 3, 1969. P.S.E.B.M., 1970, Vol. 133.