Light has now been shown to have a marked effect on two enzymatic processes in the rat pineal gland. It stimulates the activity of 5-HTPD, an enzyme which makes serotonin, and inhibits the activity of hydroxy-indole-O-methyl transferase, an enzyme localized only in the pineal gland¹⁷ which makes melatonin. It is interesting that the enzymatic synthesis of serotonin, a precursor of melatonin, is out of photic phase with the enzymatic formation of melatonin. Whether the effects of light on these two enzymatic processes are directly related remains to be established. The experiments described here and elsewhere^{7,8} demonstrate that light information reaches the pineal gland and affects both enzymatic activities by the same anatomic pathway: the sympathetic nervous system. Since light also affects pineal weight via the sympathetic nervous system, it is possible that many other biochemical events in the pineal are regulated by light through this anatomic route.

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Mechanism of the Antihypertensive Effect of α -Methyldopa

It has recently been reported that a decarboxylase inhibitor, α -methyl-3,4-dihydroxyphenylalanine (α -methyldopa), lowers the tissue norepinephrine level of various species of animals^{1,2}. Moreover, this decarboxylase inhibitor has been demonstrated to be antihypertensive in man³.

It seemed that these actions of α -methyldopa could be explained by the inhibition of decarboxylation of 3,4-dihydroxyphenylalanine (dopa). However, norepinephrine depletion produced by α -methyldopa continued long after the activity of the decarboxylase had been restored^{1,2}. Thus the persistent effect on tissue norepinephrine appears to be due to another mechanism. Furthermore, as Clark stated previously in his review⁴, substances which strongly inhibit the enzymatic decarboxylation of dopa *in vitro* do not always play parts as blood-pressure reducing agents *in vivo*. Therefore, not only the inhibitory effect of α -methyldopa on dopa decarboxylase as a direct result of tissue norepinephrine depletion should be considered.

Recently, we have become interested in the uptake and storage of catecholamines in various tissues. In the investigation recorded here, we have carried out model

experiments on the uptake of norepinephrine by rabbit blood platelets and examined the effects of α -methyldopa and its decarboxylated metabolite, α -methyldopamine, on these processes. It was demonstrated that α -methyldopa was itself decarboxylated *in vivo*, in animals and in man^{5,6}.

As shown in Table 1, radioactive norepinephrine is taken up and accumulated by the blood platelets by an active transport mechanism. This uptake of norepinephrine was slightly inhibited by α -methyldopa and strongly inhibited by α -methyldopamine. It is of interest that we found α -methyldopamine to be much more potent than its corresponding amino-acid, α -methyldopa, in the inhibition of uptake of norepinephrine by blood platelets. Thus, it appears that the action of α -methyldopa is in large part, if not entirely, due to the amine derived from it metabolically. Reserpine, known as a catecholamine releaser, also strongly inhibited the uptake of norepinephrine by blood platelets, even at as low a concentration as 10^{-7} – 10^{-9} M. It may be suggested that reserpine lowers the content of catecholamine in tissues primarily by blocking the uptake of amines into storage site. Further investigations have shown that the inhibitory effect of reserpine on the norepinephrine uptake has still remained even after reserpine had been removed from the medium. On the contrary, α -methyldopamine has an inhibitory effect when present in sufficient concentration in the medium. It seems that the action of α -methyldopamine might be of a 'reversible' type, rather than 'irreversible' as exemplified by reserpine. However, it is not yet known whether α -methyldopamine inhibits the uptake of norepinephrine into blood platelets by the same mechanism as reserpine does.

Table 1. EFFECT OF α -METHYLDOPA, α -METHYLDOPAMINE AND RESERPINE ON ¹⁴C-NOREPINEPHRINE UPTAKE BY BLOOD PLATELETS

	Norepinephrine uptake (c.p.m./mg of dry weight)	Inhibition %
Control (°C)	80	—
Control (37° C)	3,160	—
α -Methyldopa (10^{-3} M)	2,820	10
" (10^{-4} M)	3,050	3
α -Methyldopamine (10^{-3} M)	630	80
" (10^{-4} M)	1,170	63
" (10^{-5} M)	2,040	36
" (10^{-6} M)	2,750	13
Reserpine (10^{-6} M)	790	75
" (10^{-7} M)	1,170	63
" (10^{-8} M)	1,640	48
" (10^{-9} M)	2,340	26

Rabbit blood platelets were suspended in 3 ml. of phosphate saline containing 12 μ g of ¹⁴C-norepinephrine (0.2 μ c. of radioactivity) and different concentrations of each substance. The mixture was incubated at 37° C for 60 min. Values given represent the mean of six experiments.

Our results suggest that the depletion of tissue catecholamines produced by α -methyldopa is attributable to two factors. First, to the inhibition of an intermediate step in the biosynthesis of catecholamines. Secondly, catecholamines, synthesized from dopa, are prevented from being taken up by its storage sites by α -methyldopamine which is the decarboxylated metabolite of α -methyldopa. Thus there is an increase in the destruction of unbound catecholamines.

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