infusion was repeated in the same dog. During the first and repeated infusion of DIT, both labelled iodotyrosines appeared in the thyroid venous plasma (Figure 1B and 1D). After DIT infusion had been stopped, both labelled iodotyrosines disappeared (1C). Similar results were obtained when MIT was infused (Figures 2 and 3). The release of labelled iodotyrosines varied in individual experiments so that in 10 dogs labelled tyrosines amounted to 22.2% (ranging from 14.6–29) of the total labelled iodine of the thyroid venous plasma.

Comments. The results of this experiment brought additional evidence that free iodotyrosines are existing in the thyroid gland[6], and in these conditions can be exchanged by the exogenous blood-born iodotyrosines. The deiodination of iodotyrosines within the gland is a very efficient process, suggested by the findings that TSH acceleration of iodotyrosine-generating hydrolysis of thyroglobulin, and simultaneous exogenous overloading with iodotyrosines are only capable of exceeding the capacity of this process. TSH alone in the conditions of this experiment has released iodide but not iodotyrosines; therefore the enzyme of dehalogenation possesses a higher capacity than the system responsible for further recycling of iodide so generated.

The infusion of only one iodotyrosine released both labelled iodotyrosines, indicating that the 2 are deiodinated by the same enzyme of the gland[7]. This 'interdischarge' between MIT and DIT shows that in these conditions, besides the isotope dilution of the free iodotyrosine pool in the gland, a substrate oversaturation of the dehalogenating system takes place and consequent release of labelled iodotyrosines[8].

Résumé. L'injection de thyréostimuline (20–30 U) suivie d'une infusion de monoidotyrosine (MIT) ou bien de diiodotyrosine (DIT) stables dans l'artère thyroïdienne provoque la libération de MIT et DIT ^{131}I-marquées dans la veine thyroïdienne chez les chiens auxquels on a injecté du ^{131}I. La TSH seule élimine la thyroxine, la triiodothyronine et l'iodure marqués, mais non la iodotyrosine. L'injection d'une seule des 2 iodotyrosines élimine les 2 iodotyrosines marquées.

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On the Norepinephrine Replacement by α-Methyl-Norepinephrine in the Rat Heart after Treatment with α-Methyl-DOPA

α-Methyl-DOPA (α-M-DOPA) depletes norepinephrine (NE) stores of the heart and of other tissues, whereby it is generally accepted that the released NE is replaced by equimolecular amounts of α-methyl-norepinephrine (α-M-NE), the decarboxylation and β-hydroxylation product of α-M-DOPA[1–6]. It has been shown recently, however, that a prolonged treatment with α-M-DOPA or with its metabolite α-M-NE is able to produce besides NE depletion such an accumulation of α-M-NE in adrenergic innervated tissues that the total catecholamine content of these tissues can exceed significantly their normal NE content[7,8].

The presence of α-M-NE in excessive amounts is not in agreement with the replacement phenomenon which was observed in relatively short-term experiments. Because of the importance of this metabolite (for references see MUSCHOLL[9]), it was of interest to study its action on the NE stores as well as the rate of disappearance of α-M-NE after repeated administration of α-M-DOPA or of α-M-NE itself.

Methods. Male guinea-pigs, 250–400 g body-weight, or male rats, 180–240 g body-weight, were treated with D,L-α-M-DOPA (300 mg/kg; p.o.) or with L-α-M-NE·.HCl (0.1–1 mg/kg; s.c.), once or daily for 11 days. Control animals received the same volume of saline. The cardiac catecholamines were extracted twice with 10% trichloracetic acid, adsorbed onto alumina at pH 8.4 and eluted with 0.25 *N* HCl. NE and α-M-NE were estimated differentially by using both biological and fluorometric assay procedures[10,11].

Results. In a preliminary experiment, it was shown that a single injection of α-M-NE depletes markedly myocardial NE stores in rats and guinea-pigs (Table).

In another experiment, rats were pretreated daily for 11 days with D,L-α-M-DOPA or with α-M-NE. Cardiac NE was estimated 24 h after the 1st, 2nd, 4th, and 11th (last) administration, as well as 2, 4, 7, and 10 days after the last administration. Cardiac α-M-NE was estimated concomitantly with NE after the end of the treatment period. The results are shown in the Figure. They clearly demonstrate that the hearts of treated rats regained a normal NE content after 8–10 days. At this time, however, they contained still α-M-NE in amounts which were of the same order of magnitude as those of NE. The rate of disappearance of NE from the heart was faster during

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treatment with α-M-NE than with α-M-DOPA. This difference could be due to a different resorption mechanism of orally administered α-M-DOPA and s.c. injected α-M-NE. The rate of NE recovery after the treatment period as well as the rate of disappearance of α-M-NE was similar with both drugs.

Discussion. α-M-NE – like α-M-DOPA – is able to deplete the peripheral NE stores. These stores then accumulate α-M-NE. Thus the peripheral effects of α-M-DOPA can be explained in terms of the in vivo synthesis of α-M-NE by considering either a replacement mechanism or an inhibition of NE synthesis.

The total amount of α-M-NE found in the heart cannot be the result only of a NE replacement phenomenon since the amount of α-M-NE taken up exceeds the amount of NE which disappeared. This finding is in agreement with the results of PHILIPPU and SCHÜMANN[12] who found after perfusion of isolated guinea-pig hearts with α-M-NE an uptake of this amine which was not accompanied by a corresponding loss of NE. In a more recent study[13] they found also that the guinea-pig heart was able to accumulate large quantities of α-M-NE after repeated treatment with α-M-DOPA.

The amounts of α-M-NE lost during the recovery period approximated the regained NE. This seems to indicate that during the prolonged treatment with α-M-DOPA or with α-M-NE a rather inert store has accumulated which would be released only very slowly.

In addition to this fraction of α-M-NE which is stored apparently independently of NE, there seems to be another fraction which behaves as if it were directly correlated with the NE content since its loss during the 7 days after the withdrawal of the α-M-DOPA treatment paralleled well the reappearance of NE.

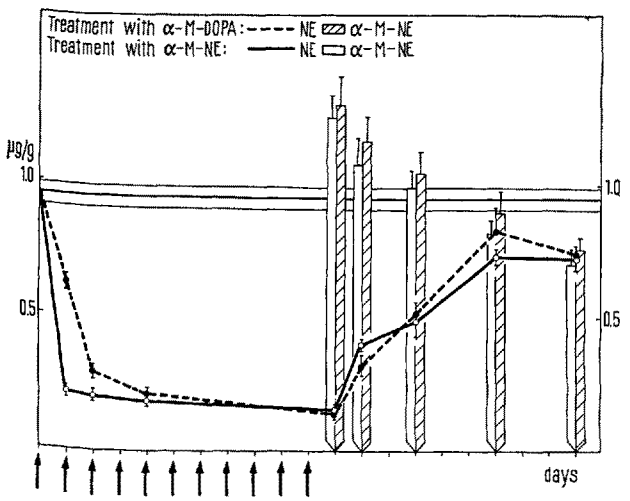
α-M-NE is a potent sympathomimetic agent. It is usually less effective as a vasoconstrictor than NE[14–16]. However, its pressor activity on the blood pressure of the pithed rat[4,5] or the spinal cat[17] is similar to that of NE. Also the cardiac stimulating properties of α-M-NE and NE do not differ markedly[8,15,18]. The question arises now as to whether only one or both fractions of the α-M-NE found in the heart may have functional significance. Stored α-M-NE can act on effector organs only after being released from its storage sites. On the other hand, it can be reasonably expected that only the α-M-NE fraction which is stored in the adrenergic nerve terminals can be released by sympathetic nerve stimulation. Thus it is tempting to speculate that only the fast disappearing α-M-NE fraction is involved in the NE replacement and can act as a false transmitter.

The role of α-M-NE formed from α-M-DOPA in the anti-hypertensive activity of the latter is difficult to assess, since α-M-NE, administered as such, lacks any anti-hypertensive property in the renal hypertensive rat[8]. Thus, the similarity of the biochemical effects seen after treatment with α-M-DOPA and with α-M-NE contrasts with the differences in the anti-hypertensive activities of the 2 drugs.

Effect of L-α-methyl-norepinephrine on the myocardial norepinephrine content in guinea-pigs and rats

Species	L-α-M-NE · HCl mg/kg	Norepinephrine μg/g wet weight (± S.E.M.)	n
Guinea-pig	–	2.65 ± 0.12	6
	1.0	0.96 ± 0.04	3
Rat	–	0.95 ± 0.04	13
	0.1	0.89 ± 0.03	3
	0.3	0.48 ± 0.03	4
	1.0	0.25 ± 0.04	4

L-α-M-NE was administered s.c. The hearts were removed 24–25 h later. Two hearts were pooled for each determination. *n*, number of determinations.



Norepinephrine and/or α-methyl-norepinephrine concentrations in the rat heart during and after 11 days' treatment with α-methyl-DOPA (300 mg/kg, orally), or with α-methyl-norepinephrine (1 mg/kg, s.c.). Arrows indicate the days of treatment. Circles or columns are the mean value of 3–5 extracts from 2 animals each. The cross bars represent standard errors.

Résumé. Des rats ont été traités une fois par jour pendant 11 jours avec de l'α-méthyl-DOPA ou de l'α-méthyl-noradrénaline. Le 12e jour, le taux de la noradrénaline cardiaque était de 15% par rapport aux contrôles. Les cœurs avaient en outre fixé une quantité d'α-méthyl-noradrénaline nettement supérieure au déficit en noradrénaline. Après arrêt du traitement, la remontée du taux de la noradrénaline s'est accompagnée d'une perte correspondante d'α-méthyl-noradrénaline. Après normalisation complète du taux de la noradrénaline, l'α-méthyl-noradrénaline était encore présente dans le cœur en quantité à peu près égale à celle de la noradrénaline, et fixée apparemment dans un dépôt relativement inerte.

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