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Analysis of the action of *m*-tyrosine on blood pressure in the conscious rat: evidence for a central hypotensive effect

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Mean arterial blood pressure was recorded through indwelling arterial catheters in conscious normotensive rats. DL-*m*-Tyrosine, 400 mg/kg, was given intraperitoneally alone and after pretreatment with two inhibitors of dopa decarboxylase [DL-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl) propionic acid (MK 485) or N^1-(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl)hydrazine (Ro 4-4602)]. DL-*m*-Tyrosine alone produced a hypertensive response, but after MK 485 it caused a significant lowering of blood pressure after 5–7 min and after Ro 4-4602 (400 + 200 mg/kg) it had no significant influence on blood pressure. The hypotensive response to DL-*m*-tyrosine was not influenced by the central dopamine receptor blocking agent spiroperidol (0·1 mg/kg) or by pretreatment with the tyrosine hydroxylase inhibitor H 44/68 (250 mg/kg). However, the depressor action could be completely inhibited after depletion of central catecholamines by α-methyl-*m*-tyrosine, 400 + 400 + 200 mg/kg, in combination with H 44/68, 250 mg/kg. Further, the depressor action was abolished by the dopamine β-hydroxylase inhibitor bis (4-methyl-1-homopiperazinyl-thiocarbonyl) disulphide (FLA-63) 40 mg/kg. In correlative biochemical experiments the concentrations of the decarboxylation products of *m*-tyrosine were measured in brain and heart. DL-*m*-Tyrosine alone produced an accumulation of *m*-tyramine and *m*-octopamine in these tissues. MK 485 + *m*-tyrosine substantially reduced the levels of *m*-tyramine and *m*-octopamine in the heart, but their accumulation in brain was largely unaltered. The results suggest that when decarboxylation of DL-*m*-tyrosine occurs in both the central and peripheral nervous system, there is a pressor action. When decarboxylation occurs mainly in the central nervous system there is a hypotensive response which is associated with accumulation of decarboxylation products of *m*-tyrosine.

We have recently observed that L-dopa may produce a hypotensive response via its metabolites acting in the central nervous system, possibly through activation of sympatho-inhibitory noradrenergic mechanisms (Henning & Rubenson, 1970 a, b). It is evident from the literature that structural analogues of L-dopa, e.g. *m*-tyrosine, have many pharmacological effects in common with the parent compound. Thus, *o*- and *m*-tyrosine produced sympathomimetic signs as well as central nervous excitatory actions in the rat and these effects were augmented by an inhibitor of monoamine oxidase (Mitoma, Posner & others, 1957). Like L-dopa, *m*-tyrosine increased motor activity of normal mice and had an awakening effect in reserpinized mice; inhibitors of monoamine oxidase augmented these actions (Blaschko & Chruschiel, 1960). Similar findings were reported in rats (Ernst, 1965). *m*-Tyrosine pretreatment largely prevented the appearance of the reserpine syndrome in mice and partially

protected the stores of dopamine and noradrenaline in the brain from the action of reserpine (Carlsson & Lindqvist, 1967).

These similarities between some actions of L-dopa and *m*-tyrosine prompted a study of the effects of *m*-tyrosine on blood pressure and tissue monoamines, using essentially the same approach as that previously employed to study L-dopa (Henning & Rubenson, 1970b). The results show that *m*-tyrosine, like L-dopa, has a central hypotensive effect which is probably of noradrenergic nature and which may be indirect, mediated by displacement of endogenous noradrenaline.

METHODS

Male Sprague-Dawley rats, 250–300 g, were used. Mean arterial blood pressure was recorded in conscious unrestrained animals through indwelling arterial catheters connected to Statham P23 Dc pressure transducers writing on a Grass Polygraph (Henning, 1969). The blood pressure values represent averages of recordings for the 10 min periods immediately before the administration of the drugs except those values after *m*-tyrosine which are averages of the pressure for 5–10 min after the injection. For doses and time intervals see results. Tests of significance were conducted by analysis of variance with two independent criteria of classification followed by the *t*-test. For the examination of *m*-tyramine and *m*-octopamine content in heart and brain, organs from 2–4 animals of corresponding body weight were pooled. *m*-Tyramine and *m*-octopamine were purified and separated by cation exchange chromatography and determined spectrophotofluorimetrically after condensation with *o*-phthalaldehyde (Shore & Alpers, 1964). Recovery was checked by adding known amounts of amines to aliquots of the brain extracts. All values in brain were corrected for recovery (see Table 1).

Drugs

The following drugs were used for the purposes stated: DL-α-hydrazino-α-methyl-β-(dihydroxyphenyl)propionic acid (MK 485)—inhibition of peripheral dopa decarboxylase (Porter, Watson & others, 1962); N^1-DL-seryl-N^2-2,3,4-trihydroxybenzylhydrazine hydrochloride (Ro4-4602)—inhibition of both central and peripheral dopa decarboxylase (Burkard, Gey & Pletscher, 1964); bis-(4-methyl-1-homopiperazinylthiocarbonyl)disulphide (FLA-63)—inhibition of dopamine-β-hydroxylase (Florvall & Corrodi, 1970); 8-[3-(4-fluorobenzoyl)-propyl]-4-oxo-1-phenyl-1,3,8-triaza-spiro-[4,5]decane (spiroperidol)—blockade of central dopamine receptors (Andén, Butcher & Engel, 1970); DL-α-methyl-*p*-tyrosine methylester (H 44/68)—inhibition of tyrosine hydroxylase (Corrodi & Hanson, 1966); DL-α-methyl-*m*-tyrosine (α-MMT)—depletion of tissue catecholamines (for review see Muscholl, 1966).

RESULTS

Blood pressure experiments

m-*Tyrosine.* After an injection of DL-*m*-tyrosine (400 mg/kg, i.p.) a rapid increase in mean arterial blood pressure was observed (Fig. 1 a), with a maximal effect after 5–10 min ($P < 0{\cdot}005$). The pressure was still elevated after 20 min ($P < 0{\cdot}01$), but not after 30 min (Fig. 1a).

The animals showed piloerection and exophthalmus during the period of increased blood pressure. In addition, there was an increase in locomotor activity starting

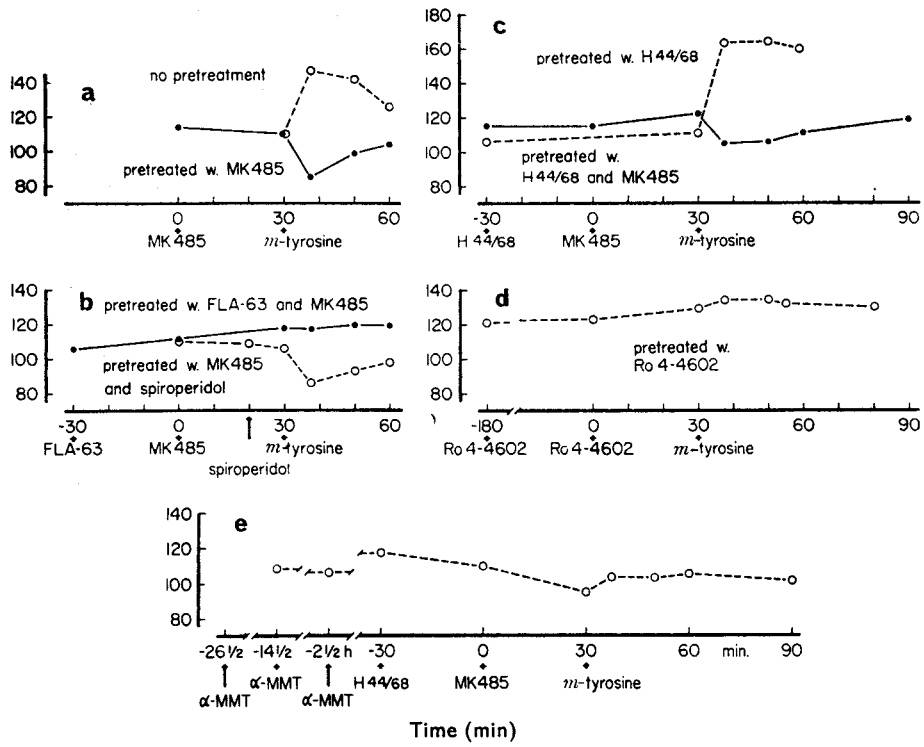

FIG. 1. Changes in mean arterial blood pressure in conscious normotensive rats after i.p. injection of drugs as indicated. The blood pressure values represent averages of recordings during 10 min periods before and after the drugs except the values immediately after *m*-tyrosine which represent the average of the recording 5-7 min after its injection. S.e. were calculated by analysis of variance. a. DL-*m*-Tyrosine, 400 mg/kg (open symbols; s.e. = 7·6; 6 exp.). DL-*m*-Tyrosine, 400 mg/kg, 30 min after MK 485, 100 mg/kg (solid symbols; s.e. = 2·7; 6 exp.). b. DL-*m*-Tyrosine, 400 mg/kg, 30 min after MK 485, 100 mg/kg, and 60 min after FLA-63, 40 mg/kg (solid symbols; s.e. = 2·7; 5 exp.). DL-*m*-Tyrosine, 400 mg/kg, 10 min after spiroperidol, 0.1 mg/kg, and 30 min after MK 485, 100 mg/kg (open symbols; s.e. = 3·4; 5 exp.). c. DL-*m*-Tyrosine, 400 mg/kg, 60 min after α-methyl-*p*-tyrosine methylester (H 44/68) 250 mg/kg (open symbols; s.e. = 2·6; 4 exp.). DL-*m*-Tyrosine, 400 mg/kg, 60 min after H 44/68, 250 mg/kg, and 30 min after MK 485, 100 mg/kg (solid symbols; s.e. = 2·6, n = 7). d. DL-*m*-Tyrosine, 400 mg/kg, 3 h after Ro 4-4602, 400 mg/kg, and 0·5 h after Ro 4-4602, 200 mg/kg (s.e. = 2·5; 5 exp.). e. DL-*m*-Tyrosine, 400 mg/kg, 30 min after MK 485, 100 mg/kg, 60 min after H 44/68, 250 mg/kg, 3 h after α-methyl-*m*-tyrosine (αMMT), 200 mg/kg, 15 h after αMMT, 400 mg/kg, and 27 h after αMMT, 400 mg/kg (s.e. = 5·3, n = 4). Figures on ordinate represent mean arterial blood pressure (mm Hg); figures on abscissa represent time in min.

after 15–20 min. No clear signs of aggressiveness or stereotyped movements were observed.

Dopa decarboxylase inhibition with MK 485 + m-*tyrosine.* Injection of MK 485 (100 mg/kg) did not influence the mean arterial blood pressure in the subsequent 30 min ($P > 0{\cdot}10$). Then *m*-tyrosine (400 mg/kg, i.p.) produced a decrease in blood pressure (Fig. 1 a). The time course of this effect was similar to the hypertensive response to *m*-tyrosine alone, maximum effect being reached after 5–10 min ($P < 0{\cdot}001$). After 20 min there was still a significant lowering of blood pressure ($P < 0{\cdot}001$) when compared to the level before MK 485 ($P < 0{\cdot}01$ when compared to the level before *m*-tyrosine). The values after 30 min were lower than those obtained before MK 485 ($P < 0{\cdot}025$).

In these rats, piloerection and exophthalmus were not apparent but there was an increased spontaneous motility, including "rearing", starting after 15–20 min.

Dopa decarboxylase inhibition with Ro 4-4602 + m-*tyrosine.* After pretreatment with Ro 4-4602, 400 and 200 mg/kg 3 h and 0·5 h before hand respectively, *m*-tyrosine (400 mg/kg) had no significant effect on mean arterial blood pressure (Fig. 1d).

FLA-63 + *MK* 485 + m-*tyrosine.* In this series, rats were pretreated with an inhibitor of dopamine β-hydroxylase, FLA-63 (40 mg/kg), and MK 485 (100 mg/kg) 60 and 30 min, respectively, before injection of *m*-tyrosine (400 mg/kg). The blood pressure level 5–10 min after *m*-tyrosine was not significantly different from the level before *m*-tyrosine ($P > 0{\cdot}1$) or before MK 485 ($P > 0{\cdot}10$) but was significantly higher than the level before FLA 63 ($P < 0{\cdot}01$) (Fig. 1b).

The rats did not differ in gross behaviour from the animals given MK 485 + *m*-tyrosine only.

MK 485 + *spiroperidol* + m-*tyrosine.* Spiroperidol (0·1 mg/kg) was given 20 min after MK 485 (100 mg/kg) and 10 min before *m*-tyrosine (400 mg/kg) (Fig.1 b). *m*-Tyrosine lowered blood pressure to the same extent as in animals pretreated with MK 485 alone. Thus, the level of blood pressure 5–10 min after *m*-tyrosine was significantly lower than the levels before *m*-tyrosine, spiroperidol or MK 485 ($P > 0{\cdot}001$). This was also the case with the level of blood pressure after 20 min ($P < 0{\cdot}025$, $P < 0{\cdot}005$ and $P < 0{\cdot}001$, respectively). With this combination of drugs the increase in locomotor activity was less than in the previous series.

H 44/68 + m-*tyrosine.* Pretreatment with the tyrosine hydroxylase inhibitor, α-methyl-*p*-tyrosine methylester, H 44/68 (250 mg/kg), 60 min before *m*-tyrosine (400 mg/kg), did not influence the hypertensive effect of the latter drug (Fig. 1 c). Thus, there was a highly significant ($P < 0{\cdot}001$) increase in blood pressure at all intervals after *m*-tyrosine. The effects on gross behaviour were the same as rats receiving *m*-tyrosine alone.

H 44/68 + *MK* 485 + *m-tyrosine.* Fig. 1c also shows the effect of tyrosine hydroxylase inhibition on the hypotensive response to *m*-tyrosine after MK 485. H 44/68 (250 mg/kg) was given 30 min before MK 485 (100 mg/kg) and 60 min before *m*-tyrosine (400 mg/kg). In this series, *m*-tyrosine lowered blood pressure significantly after 5–10 min as well as 20 min (*P* values when compared to blood pressure before *m*-tyrosine: $<0{\cdot}001$: before MK 485: $<0{\cdot}025$; before H 44/68: $<0{\cdot}025$).

The behavioural changes were the same as those produced by *m*-tyrosine after MK 485.

α-*MMT* + *H* 44/68 + *MK* 485 + m-*tyrosine.* The effect of *m*-tyrosine was studied in a group of animals pretreated with α-MMT (400, 400 and 200 mg/kg) given 27, 15 and 3 h before *m*-tyrosine, H 44/68 (250 mg/kg) and MK 485 (100 mg/kg) given 60 and 30 min before *m*-tyrosine. There was no significant difference ($P > 0{\cdot}10$) between the initial blood pressure level and the levels after any of the drugs (Fig. 1e).

Heart and brain content of m-*tyramine and* m-*octopamine*

The results of organ analysis are shown in Table 1. All analyses were made at the time of maximal hypotensive effect of *m*-tyrosine after MK 485, i.e. 7 min after the injection of *m*-tyrosine.

Table 1. *Levels of* m-*tyramine and* m-*octopamine in brain and heart of normal rats 7 min after* m-*tyrosine* (400 mg/kg, i.p.) *alone and after pretreatment with MK* 485 (100 mg/kg i.p.) 30 *min previously.* A third group of animals were only given MK 485 (100 mg/kg) 37 min before death. Values of means and s.e. are given.

Treatment: MK 485 100 mg/kg

Brain (μg/g)		Heart (μg/g)	
m-Tyramine	*m*-Octopamine	*m*-Tyramine	*m*-Octopamine
0·19	0·021	0·20	0·029
0·14	0·026	0·15	0·042
—	0·020	0·15	0·033
Mean = 0·17	0·022	0·17	0·035
s.e. = 0·025	0·002	0·017	0·004

Treatment: *m*-tyrosine 400 mg/kg

Brain (μg/g)		Brain recovery (%)		Heart (μg/g)	
m-Tyramine	*m*-Octopamine	*m*-Tyramine	*m*-Octopamine	*m*-Tyramine	*m*-Octopamine
4·00	0·073	129	138	16·25	0·306
6·51	0·060	64	136	17·92	0·247
5·88	0·037	103	107	14·27	0·110
4·90	0·075	71	134	14·42	0·350
Mean = 5·32	0·061			Mean = 15·72	0·253
s.e. = 0·55	0·009			s.e. = 0·86	0·052

Treatment: MK 485 100 mg/kg + *m*-tyrosine 400 mg/kg

Brain (μg/g)		Brain recovery (%)		Heart (μg/g)	
m-Tyramine	*m*-Octopamine	*m*-Tyramine	*m*-Octopamine	*m*-Tyramine	*m*-Octopamine
4·32	0·041	69	136	3·28	0·11
4·22	0·071	73	116	3·01	0·14
5·13	0·049	56	93	3·90	0·078
2·64	0·026	76	113	—	0·042
2·87	0·106	64	91	1·36	0·050
Mean = 3·83	0·059			Mean = 2·88	0·084
s.e. = 0·47	0·014			s.e. = 0·54	0·018

m-Tyrosine alone (400 mg/kg) produced an increase in the *m*-tyramine content of brain and heart. Smaller amounts of *m*-octopamine were also formed. With both amines the concentrations in heart were about three times those in brain.

In animals given MK 485 (100 mg/kg) 30 min before *m*-tyrosine (400 mg/kg) much smaller amounts of *m*-tyramine as well as *m*-octopamine were found in the heart. However, there was also a decreased formation of *m*-tyramine in the brain and the levels of *m*-octopamine were about the same as in the heart. The ratio heart : brain was approximately 1 : 1 for both amines.

In animals treated with MK 485 (100 mg/kg) only and killed after 37 min, the amounts of *m*-tyramine and *m*-octopamine found were always much smaller than after *m*-tyrosine, alone or in combination with MK 485.

DISCUSSION

The results show that injection of *m*-tyrosine, like that of L-dopa, produces sympathomimetic symptoms and an increase in mean arterial blood pressure in conscious rats. The magnitude of the response to *m*-tyrosine was similar to that previously found after a much lower dose of L-dopa (Henning & Rubenson, 1970a,b), except

that the onset was more rapid and duration shorter. Previous work has indicated that *m*-tyrosine may produce sympathomimetic signs in rats (Mitoma & others, 1957).

The pressor effect of *m*-tyrosine was abolished by pretreatment with Ro 4-4602, which inhibits dopa decarboxylase in peripheral tissues and the brain (Pletscher & Gey, 1963; Burkhard, Gey & Pletscher, 1964) and also after inhibition of peripheral dopa decarboxylase alone by MK 485 (Porter, Totaro & Leiby, 1962; Bartholini & Pletscher, 1969). On the other hand, pretreatment with a tyrosine hydroxylase inhibitor, H 44/68, did not influence the increase in blood pressure. Therefore, it may be concluded that the sympathomimetic effects and the hypertensive response to *m*-tyrosine is mediated by its metabolites acting in the periphery. After inhibition of peripheral decarboxylase with MK 485, *m*-tyrosine produced a significant decrease in blood pressure. The time characteristics of this response were similar to those of the hypertensive reaction after *m*-tyrosine alone. A similar effect has been observed with L-dopa after MK 485 (Henning & Rubenson, 1970). Since the hypotensive response to *m*-tyrosine in the present study did not occur after a decarboxylase inhibitor which acts in the central nervous system, Ro 4-4602, the effect may be due to the central actions of *m*-tyrosine metabolites. It is well established that *m*-tyrosine is decarboxylated in the brain to form *m*-tyramine (Mitoma & others, 1957; Carlsson & Lindqvist, 1967; Andén, Butcher & Engel, 1970), and the β-hydroxylated derivative, β-hydroxy-*m*-tyramine has also been demonstrated in brain tissue after treatment with *m*-tyrosine (Carlsson & Lindqvist, 1967).

The response is therefore likely to be mediated via the decarboxylated products of *m*-tyrosine. The amines may exert their effect through different mechanisms: (1) direct stimulation of central nervous receptor mechanisms via (a) *m*-tyramine, (b) *m*-octopamine, or both, or (2) an indirect effect via displacement of endogenous amines by (a) *m*-tyramine, (b) *m*-octopamine, or both.

The present results appear to make a direct stimulation of dopamine and noradrenaline receptors less likely since severe depletion of these amines by pretreatment with α-MMT (Andén, 1964) in combination with the tyrosine hydroxylase inhibitor, H44/68, prevented the hypotensive response to *m*-tyrosine after MK 485.

The hypotensive effect of L-dopa after MK 485 is also prevented following this type of pretreatment (Rubenson, 1971). Since in these experiments the last dose of α-MMT was given only 3 h before *m*-tyrosine or L-dopa, it is possible that the decarboxylation of the latter amino-acids may have been prevented to some extent; α-MMT has a slight inhibitory effect on dopa decarboxylase (Hess, Connamacher & others, 1961; Porter, Watson & others, 1962). However, this appears less likely since identical results were obtained with L-dopa, regardless of whether the last dose of α-MMT was given (Rubenson, 1971).

Study of the flexor reflex activity of spinal rats by Andén & others (1970) has revealed that the metabolites of *m*-tyrosine, in contrast to those of L-dopa, are unable to stimulate central noradrenaline receptors. However, in these experiments the rats were pretreated with reserpine and indirect effects may have been prevented. Pretreatment with an inhibitor of dopamine β-hydroxylase, FLA-63 (Svensson & Waldeck, 1969; Florvall & Corrodi, 1970), blocked the depressor response to *m*-tyrosine after MK 485. Therefore this response may have been produced by the β-hydroxylated product of *m*-tyrosine. Another possibility to be considered is an indirect effect by the *m*-tyramine formed. Recent studies indicate that FLA-63, in

the dose used in the present experiments, may reduce endogenous noradrenaline in the brain (Persson & Waldeck, 1970). The effect of FLA-63 in the present investigation could therefore also be explained by a decreased availability of endogenous noradrenaline for displacement by *m*-tyramine. On the other hand, pretreatment with the tyrosine hydroxylase inhibitor H 44/68, unlike FLA-63, did not influence the hypotensive response to *m*-tyrosine after MK 485. However, the lowering of endogenous noradrenaline after H 44/68 is not as rapid as that after FLA-63 (Persson & Waldeck, 1970).

The *m*-tyrosine injected may be decarboxylated both intra- and extraneuronally in the brain. In this connection, the existence of dopa decarboxylase in the brain capillaries (Bertler, Falck & others, 1966) is of interest. The tendency to a decreased accumulation of *m*-tyramine after MK 485 + *m*-tyrosine compared to that seen after *m*-tyrosine alone might be explained by a decreased extraneuronal accumulation of *m*-tyramine due to inhibition of the capillary decarboxylase by MK 485 (*cf.* Constantinidis, De la Torre & others, 1969). The levels of β-hydroxy-*m*-tyramine (*m*-octopamine) which may be assumed to be formed from *m*-tyramine mainly intraneuronally were not reduced after MK 485 pretreatment and this gives further support for this explanation. In the heart, MK 485 prevented the accumulation of *m*-hydroxylated amines to a large extent.

The biochemical studies thus show a central accumulation of *m*-tyramine and *m*-octopamine at the time of the maximal hypotensive effect.

In conclusion, both the biochemical and functional studies point to a central nervous origin of the hypotensive effect of *m*-tyrosine after peripheral dopa decarboxylase inhibition. The hypotensive effect appears to be elicited by the catabolites of *m*-tyrosine which may act indirectly by displacement of endogenous catecholamines, particularly noradrenaline.

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