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Enhancement of noradrenaline turnover in rat brain by L-dopa

L-3,4-Dihydroxyphenylalanine (L-dopa) has been postulated to enhance the turnover of noradrenaline in the brain. The evidence for this effect is based on two kinds of changes induced by L-dopa, i.e. (i) the decreased accumulation of cerebral [^{14}C]noradrenaline (^{14}C-NA) after intravenous administration of labelled tyrosine (Persson & Waldeck, 1971) and (ii) the accelerated disappearance from the brain of ^{14}C-NA injected into the cerebral ventricles (Chalmers, Baldessarini & Wurtman, 1971; Romero, Chalmers & others, 1972). However, it cannot be excluded that tyrosine and L-dopa compete for penetration through the blood-brain barrier and/or into the neurons and that labelled tyrosine might not mix homogeneously with the endogenous tyrosine. Furthermore, ^{14}C-NA injected intraventricularly possibly accumulates not only in noradrenergic neurons but also in other structures (e.g. dopaminergic and 5-hydroxytryptaminergic neurons, capillary walls, glial cells). Therefore the disappearance of the labelled amine may not exactly reflect its release from noradrenergic neurons. For these reasons, changes of endogenous cerebral noradrenaline induced by L-dopa have been investigated.

Male Wistar rats (Füllinsdorf) 150 g, were administered various doses of L-dopa, alone or 30 min after injection of either 5 mg kg^{-1} FLA63 (bis(4-methyl-1-homopiperazinyl-thiocarbamyl)disulphide) or 50 mg kg^{-1} benserazid (N^1-DL-seryl-N^2-(2,3,4-trihydroxybenzyl)-hydrazine, RO 4-4602) or their combination. Some animals received FLA63 alone 1½ or 4½ h before death. Untreated animals served as controls. All injections were given intraperitoneally. The FLA63-treated rats were maintained at 30° to prevent hypothermia. After decapitation, the whole brain was homogenized in perchloric acid. Endogenous noradrenaline was isolated by adsorption on alumina (Anton & Sayre, 1962), separated from L-dopa and dopamine by column chromatography on Dowex 50W × 8 (Bertler, Carlsson & Rosengren, 1958) and measured spectrophotofluorimetrically (Laverty & Taylor, 1968). In addition, determinations of cerebral 3-methoxy-4-hydroxyphenylethyleneglycol-sulphate (MOPEG) in the whole brain 2 h after administration of L-dopa were made (Meek & Neff, 1972).

In agreement with previous results (Constantinidis, Bartholini & others, 1968), L-dopa alone or in combination with benserazid, an inhibitor of extracerebral decarboxylase (Bartholini & Pletscher, 1968), did not change the levels of cerebral noradrenaline compared to controls. However, 1 and 4 h after FLA63, an inhibitor of dopamine-β-hydroxylase (Corrodi, Fuxe & others, 1970), the amine content decreased significantly ($P<0.001$). The FLA63-induced diminution of cerebral noradrenaline was markedly enhanced by L-dopa alone or in combination with benserazid (Table 1). This enhancement depended on the dose of L-dopa, and in the range of 20–100 mg kg^{-1} L-dopa was more marked in the presence than in the absence of benserazid (Fig. 1).

Table 1. *Effect of* L-*dopa alone or in combination with benserazid on the FLA63-induced decrease of endogenous noradrenaline in the rat brain.*

Treatment* (mg kg^{-1}, i.p.)	Noradrenaline‡ hours after L-dopa 1	4
L-Dopa (200)	104·6 ± 3·5	105·5 ± 2·6
Benserazid (50) +L-dopa (200)	99·4 ± 3·2	94·0 ± 5·6
FLA63 (5)†	75·9 ± 1·9[a]	64·1 ± 3·2[b]
FLA63 (5) + L-dopa (200)	40·6 ± 2·2[c]	39·7 ± 2·7[d]
FLA63 (5) + benserazid (50) + L-dopa (200)	38·8 ± 1·7[e]	29·2 ± 2·1[f]

* FLA63 and/or benserazid were administered 30 min before L-dopa.
† Administered 1½ or 4½ h before death.
‡ Values represent means with s.e. (12 determinations per group) and are expressed in % of controls (0·415 ± 0·014 μg g^{-1} = 100 ± 3·4%).
Significance (Student's *t*-test): **a**, b versus corresponding controls: $P<0.001$; **c**,e versus **a**: $P<0.001$; d, f versus b: $P<0.001$; f versus e, d: $P<0.01$.

The L-dopa-induced noradrenaline decrease after inhibition of dopamine-β-hydroxylase indicates that L-dopa caused a release of noradrenaline as suggested by findings with the labelled amine (Chalmers & others, 1971). In the present experiments with FLA63 the noradrenaline must have been released mainly from noradrenergic neurons (probably by dopamine formed from L-dopa) which synthesize and store the bulk of endogenous cerebral noradrenaline. Since in the absence of FLA63 L-dopa did not change the cerebral noradrenaline content, the release was obviously compensated by the synthesis of the amine. Therefore, L-dopa is likely to cause an increase in the cerebral noradrenaline turnover, the exogenous amino-acid being the source of the newly synthesized amine. An enhancement of the noradrenaline turnover is also indicated by the elevation of the cerebral content of MOPEG (the main metabolite of brain noradrenaline) after 50 mg kg^{-1} L-dopa (i.p.) (0·165 ± 0·005 μg g^{-1}; controls: 0·126 ± 0·003 μg g^{-1}; $P<0.001$; n = 12 per group). Higher doses (200 mg kg^{-1}) of the amino-acid caused a diminution of the MOPEG level (0·090 ± 0·007 μg g^{-1}; $P<0.01$; n = 12), possibly owing to competitive inhibition of catechol-*O*-methyl-transferase by L-dopa (Thoa, Weise & Kopin, 1972).

The lack of increase of the cerebral noradrenaline levels after administration of L-dopa with or without benserazid cannot be explained by the present experiments. It might be due to a small capacity of the noradrenergic neurons to store additional noradrenaline or to a limited hydroxylation of dopamine, the rate-limiting step in the biosynthesis of noradrenaline from L-dopa (Bartholini, Keller & Pletscher, 1973).

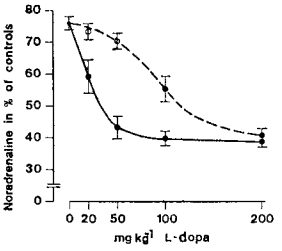

FIG. 1. Effect of various doses of L-dopa alone (– – –) or in combination with benserazid (——) on the cerebral content of noradrenaline in rats treated with FLA63. FLA63 (5 mg kg^{-1} i.p.) was administered either alone or simultaneously with benserazid (50 mg kg^{-1}, i.p.) 30 min before i.p. injection of L-dopa. The rats were killed 90 min after FLA63. The values are expressed in % of those found in untreated controls (0·462 ± 0·011 μg g^{-1} = 100 ± 2·4%). They represent means with s.e. of 10–12 determinations, each performed on a whole brain. The 0 value on the abscissa corresponds to experiments carried out with FLA63 only. Significance versus 0 value (Student's *t*-test): Open circles $P>0.05$; filled circles $P<0.01$. L-Dopa versus L-dopa + benserazid $P<0.01$ for 20–100 mg kg^{-1} L-dopa.

The enhancement by benserazid of the L-dopa-induced decrease of noradrenaline in FLA63-treated animals was probably connected with the inhibition of the extracerebral decarboxylation of L-dopa. As a consequence, larger amounts of the amino-acid penetrated into the brain, leading to an enhanced formation of cerebral dopamine (Bartholini & Pletscher, 1968).

In conclusion, the present experiments indicate that L-dopa accelerates the turnover of noradrenaline *in vivo*: the endogenous amine is probably displaced by the dopamine newly formed and its loss is compensated by synthesis from the amino-acid. The displacement of endogenous noradrenaline may be of importance in enhancing central noradrenergic mechanisms, leading, for instance, to a decrease of blood pressure (Rubenson, 1971; Andén, Engel & Rubenson, 1972). In addition, the enhanced turnover of noradrenaline is possibly involved in the genesis of certain side effects of L-dopa (e.g. mental disturbances, involuntary movements) observed during the treatment of Parkinson's syndrome.

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The involvement of noradrenergic systems in the locomotor activity stimulation in mice produced by β-phenethylamine

β-Phenethylamine (PE) on injection into mice produces an increase in locomotor activity (Mantegazza & Riva, 1963; Jackson, 1972). This response was shown to be biphasic (Jackson, 1972) with a first phase of increased activity occurring between 5–15 min after injection of PE 50 mg kg^{-1} (i.p.) and a second phase between 20–50 min after 100 mg kg^{-1}. The first phase was shown to be dependent on an intact dopamine and noradrenaline synthetic pathway, with the second phase apparently being produced by some metabolite of PE acting directly on dopamine receptors (Jackson, 1974). An involvement with a central cholinergic system has also been postulated, because centrally acting antimuscarinic agents potentiated the locomotor activity