Cardiototoxicity of Catecholamines after Application of L-DOPA in Wistar-Kyoto (WKY) and Spontaneously Hypertensive Rats (SHR)

Manfred Kammermeier, and Horst F. Grobecker

In order to estimate the role of the sympatho-adrenal system as a trigger in cardiovascular mortality risk after L-DOPA administration in patients with Parkinson's disease we performed the following experiments in normotensive Wistar-Kyoto-rats (WKY) and spontaneously hypertensive rats (SHR). L-DOPA was given orally in increasing doses (30, 100, 300 mg/kg b.w.). Haemodynamic parameters (BP, HR) were measured by tail cuff plethysmography and catecholamine concentrations in tissues assayed by high pressure liquid chromatography. Stressful situations were induced by experimental myocardial infarction. After administration of L-DOPA a dose-dependent increase in blood pressure in both WKY and SHR was observed with a prolongation in SHR. Significantly increased concentrations of dopamine in the hearts were measured in both strains. Noradrenaline stores in the heart of WKY were more filled than in the heart of SHR. Only in SHR high adrenaline concentration in the adrenal medulla were measured after L-DOPA administration. Circulating adrenaline concentrations were significantly enhanced after myocardial infarction in WKY and could be further elevated by pretreatment with L-DOPA. From the results obtained it is concluded that L-DOPA administration in WKY and SHR leads to an enhanced synthesis and release of catecholamines and in consequence to an enhanced cardiovascular mortality risk due to cardiotoxicity of catecholamines. It can be extrapolated that increased cardiovascular mortality risk seen in Parkinson patients treated with L-DOPA and benzerazide is probably associated with increased synthesis and release of catecholamines during stressful situations. (Hypertens Res 1995; 18 Suppl. I: S165-S168)

Key Words: L-DOPA, catecholamines, WKY, SHR, cardiotoxicity

During stressful situations large amounts of catecholamines are released from the sympathetic nerve endings and the adrenal medulla. Prolonged exposure of the heart to such high levels of catecholamines results in coronary spasm, arrhythmias, contractile dysfunction, cell damage and myocardial necrosis (1). L-DOPA administration in Parkinson's disease probably leads to exaggerated biosynthesis and release of catecholamines and in consequence to an enhanced cardiovascular mortality risk (2). Therefore the aim of our study was to investigate catecholamine content and release in target organs like the heart after L-DOPA administration in spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto rats (WKY) under various conditions e.g. induction of experimental myocardial infarction.

Methods
Male normotensive Wistar Kyoto (WKY) and spontaneously hypertensive rats (SHR) were used. Their mean body weight was 200 g, mean age 10 weeks. L-DOPA was received by Merck, Darmstadt, Germany. To investigate its reaction on systolic blood pressure after single term administration dosages of 30, 100 and 300 mg/kg L-DOPA were given orally with a stomach tube. The application was carried out in the morning after a 12 h fasting period. Haemodynamic parameters were measured by tail cuff plethysmography.

Groups of 6 WKY and SHR each were administered a single dose of 30 mg/kg L-DOPA p.o. in accordance with the median daily dose in man. Controls were treated with water. 30 minutes after L-DOPA administration rats were killed by decapitation. Hearts and adrenal medullas were removed immediately, frozen in liquid nitrogen and stored in cold (−70°C). Assays of catecholamines in tissues and plasma were made by HPLC and electrochemical detection, evaluation was done with the internal standard method (3,4-dihydroxybenzylamine). Stressful situations were induced by experimental myocardial infarction. Groups of 6-8 normotensive WKY rats were used. The animals were administered 300 mg/kg L-DOPA p.o. two times daily over a period of 4 days. Myocardial infarction was achieved by ligature of the vena cardiaca magna af-
ter anaesthetizing the animals with 80 mg/kg thiopental, which was obtained by Byk Gulden, Konstanz, Germany. Haemodynamic parameters were measured directly in the arteria carotis communis in 15 min intervals after occlusion of the vena cardiaca magna. To quantify infarction size enzyme diagnostic was carried out by measuring CK- and GOT-activity in the heart. Statistical comparison was performed by Student’s t test and Wilcoxon-test respectively. Data are shown as X±SEM.

All experiments on animals were in accordance with guidelines of the German law for animal protection and they were carried out after permission of the authorities.

Results

After administration of a single dose of L-DOPA (30, 100 and 300 mg/kg p.o.) to groups of 6-8 rats systolic blood pressure rises dose dependently. Both WKY and SHR show an increase of approximately 32 mm Hg 60 min after application of 300 mg/kg L-DOPA (Fig. 1). A plateau phase over 2 h was observed only in SHR, where as the normotensive rats reach their control values within this period. The dose of 30 mg/kg significantly decreased blood pressure in WKY but not in SHR.

Involvement of the sympathoadrenal system in the origin of L-DOPA associated cardiac side effects was investigated by assay of catecholamines in the heart and the adrenal medulla. Groups of 6 WKY and SHR each were administered a single dose of 30 mg/kg L-DOPA p.o. comparable with the median daily dose in man. Controls were treated with the same volume of tap water. In both breeds dopamine levels in the myocardium increased significantly after L-DOPA (Table 1). Noradrenaline and adrenaline are enhanced in the normotensive rats only, but diminished in the SHR (Fig. 2). Contrary to this result adrenaline content in the adrenal medulla was only increased in SHR. When compared to SHR noradrenaline stores in the heart of WKY were more filled.

In order to investigate the relationship between L-DOPA application and catecholamine metabolism during stressful situations myocardial infarction was induced in groups of 6-8 normotensive WKY rats. Rats with sham operation served as controls. The animals were administered 300 mg/kg L-DOPA p.o. two times daily over a period of 4 days. To quantify infarction size enzyme diagnostic was carried out by measuring CK- and GOT activity in the heart. Figure 3 shows a significant reduction of noradrenaline and adrenaline concentrations in all investigated areas of

<table>
<thead>
<tr>
<th>L-DOPA</th>
<th>Dopamine</th>
<th>Noradrenaline</th>
<th>Adrenalin</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.82±0.55</td>
<td>110.09±8.45</td>
<td>1.26±0.12</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>5.18±0.72</td>
<td>118.01±8</td>
<td>1.31±0.07</td>
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<tr>
<td>10 mg/kg</td>
<td>17.41±2.98</td>
<td>138.76±9.47</td>
<td>1.78±0.25</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>38.94±5.61</td>
<td>131.05±6.23</td>
<td>1.71±0.23</td>
</tr>
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Table 1.
the heart after L-DOPA treatment. Noradrenaline values are considerably decreased in the ventricles when compared with the atriums.

Up to 32-fold enhanced noradrenaline levels in hearts of WKY could be observed in the sham as well as in the infarction group. Dependent on time after myocardial infarction circulating catecholamines in plasma increase considerably. Circulating adrenaline in infarcted rats were significantly increased within a period of 60 min after infarction. Circulating catecholamine levels were further enhanced after administration of L-DOPA (Fig. 4).

**Discussion**

The L-DOPA induced hypertensive reaction is possibly the effect of its first metabolite dopamine, which can act as an indirect sympathomimetic agent thereby releasing catecholamines. Subsequently, after depletion of the storage vesicles, noradrenaline is increasing systolic blood pressure by vasoconstriction stimulating α-adrenoceptors in the vessels. According to this result high levels of dopamine were observed in both WKY and SHR. An inverse
correlation between hypertension and myocardial noradrenaline concentration is demonstrated by lower noradrenaline contents in the hearts of SHR when compared to WKY. Diminished storage of noradrenaline in the vesicles of SHR may also contribute for hypertension, because high circulating noradrenaline levels are stimulating adrenergic $\alpha$- and $\beta$-receptors in the vessels and the heart, respectively. After myocardial infarction a significant reduction of noradrenaline and adrenaline in the myocardium of WKY with simultaneously increasing concentrations in the plasma probably leads to an enhanced cardiac risk (3).

From our results, it can be concluded that stressful situations after L-DOPA application in SHR and WKY leads to massive release of catecholamines and subsequently to cardiotoxicity. Adrenaline plays a key role in these pathophysiological events. It may be extrapolated that high cardiovascular mortality risk in patients with Parkinson’s disease after L-DOPA administration can be attributed to cardiotoxicity of high amounts of dopamine, noradrenaline and especially of adrenaline. With regard to clinical use L-DOPA treatment from the very beginning can not be recommended in patients with hypertension or cardiac complications in their anamnesis.

References