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Actions of levodopa on the blood pressure of conscious rabbits

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Summary

1. In conscious rabbits, the rapid intravenous injection of levodopa alone does not have any significant effects on the blood pressure in doses up to 10 mg/kg.

2. After inhibition of monoamine oxidase, levodopa induces a sustained pressor response.

3. This response can be blocked by inhibition of extracerebral decarboxylase.

4. Possible mechanisms for these interactions are discussed, together with their therapeutic implications in Parkinsonism.

Introduction

We have investigated the pressor responses of conscious rabbits to levodopa alone and in combination with inhibitors of both monoamine oxidase (MAOI) and extracerebral dopa decarboxylase. Our interest in the actions of these enzyme inhibitors stems from the possible therapeutic advantages of augmenting the striatal concentrations of dopamine in Parkinsonian patients receiving levodopa, by administration of MAOI. This combined therapy would only be possible if the dangerous cardiovascular consequences of increased peripheral catecholamine concentrations could be precluded, by concomitant administration of an extracerebral dopa decarboxylase inhibitor.

Methods

Polypropylene catheters were inserted into the central artery and vein of the ear of male New Zealand white rabbits (2·5 kg) under local anaesthetic (lignocaine 1%). The animals were left undisturbed for 2 h before cardiovascular observations were made. The arterial pressure was measured with a Statham P23D6 strain gauge transducer on a Devices M2 recorder. Levodopa was injected intravenously in doses of up to 10 mg/kg given at hourly intervals. The injections were completed over 10–20 seconds.

In subsequent experiments, animals were given iproniazid (25 mg/kg i.p.) 2 h before investigating the pressor response to levodopa.

In a further group of experiments the procedure was repeated after pretreatment with an aqueous suspension of L-2-hydrazino-2-methyl-3-(3,4-dihydroxyphenyl)-propionic acid (L-alpha methyldopahydrazine) (25 mg/kg i.p.), an inhibitor of extracerebral dopa decarboxylase. The injections of L-alpha methyldopahydrazine were started 2 h before the first injection of levodopa and they were repeated at hourly intervals.

Mean bood pressures were estimated by adding one-third of the pulse pressure to the diastolic pressure. Groups of 4 rabbits were employed in each experiment (12 animals altogether).

Results

Levodopa alone. No consistent cardiovascular response was recorded following intravenous injections of levodopa in doses up to 10 mg/kg.

Levodopa following pretreatment with iproniazid. After inhibition of monoamine

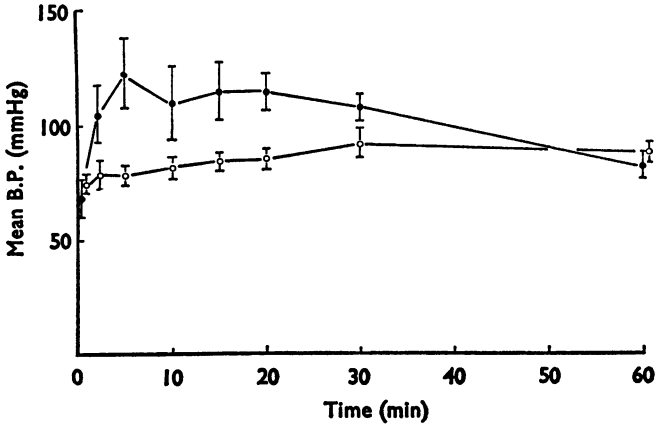

FIG. 1. The mean arterial pressure following 10 mg/kg levodopa intravenously. Results obtained after pretreatment with iproniazid, 25 mg/kg i.p. (4 rabbits) shown in closed circles, and with additional L-alpha methyldopahydrazine, 25 mg/kg i.p., every hour (4 rabbits) shown in open circles. The bars represent ±S.E.M.

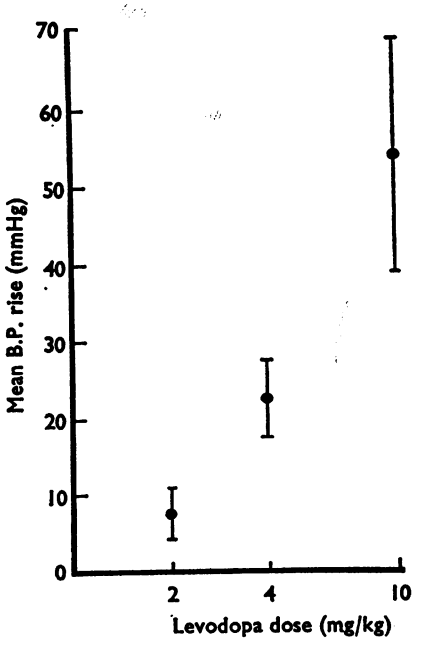

FIG. 2. The action of intravenous levodopa on the mean arterial pressure after pretreatment with iproniazid (25 mg/kg i.p.) two hours before. Results from a group of 4 rabbits. The bars represent ±S.E.M.

oxidase, levodopa (10 mg/kg) produced a sustained rise in arterial blood pressure, starting after about 1 min, reaching a peak of 55 mmHg at 10 minutes. The response is shown in Figure 1. The relation of log-dose of levodopa (2–10 mg/kg i.v.) to the maximal arterial pressure rise is shown in Figure 2.

Levodopa following pretreatment with iproniazid and L-*alpha methyldopahydrazine.* Blockade of extracerebral decarboxylase reduced the pressor response to levodopa. This is illustrated in Figures 1 and 3.

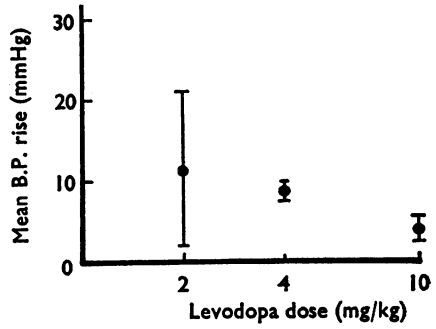

FIG. 3. The action of intravenous levodopa on the mean arterial pressure after pretreatment with iproniazid and L-alpha methyldopahydrazine. The iproniazid (25 mg/kg i.p.) was given 2 h before levodopa. The L-alpha methyldopahydrazine (25 mg/kg i.p.) was started 2 h before levodopa, and repeated every hour. Results from a group of 4 rabbits. The bars represent ±S.E.M.

Discussion

The actions of levodopa and dopamine on the blood pressure depend upon dose, route of administration, species, and interaction with anaesthetic agents where these are employed in the experimental preparation (Goldberg, 1972; Hamilton, 1972; Schmitt, Schmitt & Fénard, 1972). In addition, inhibition of monoamine oxidase and extracerebral dopa decarboxylase can produce substantial modification of the cardiovascular effects of levodopa (Roberts & Street, 1970; Henning & Rubenson, 1970; Robson, 1971; Osborne, Wenger & Willems, 1971).

Our results indicate that in conscious rabbits, intravenous injection of levodopa alone does not produce any significant change in blood pressure in doses up to 10 mg/kg. However, after inhibition of monoamine oxidase, substantial pressor responses are obtained, with a long time-course. This pressor response probably arises from dopamine formation outside the central nervous system, as it is blocked by inhibition of peripheral decarboxylase. Possible mechanisms responsible for this rise in blood pressure include: (1) Displacement and consequent release of noradrenaline by dopamine, at sympathetic nerve endings. (2) Conversion of dopamine to noradrenaline and adrenaline with consequent excitation of adrenoceptors in the heart and peripheral vascular smooth muscle. (3) Direct stimulation of adrenoceptors by dopamine.

One further explanation must be considered. Blockade of extracerebral decarboxylase leads to a higher plasma concentration and hence higher brain concentration of levodopa after each dose. It is possible that the augmented brain concentrations of catecholamines activates a central hypotensive mechanism involving noradrenergic neurones, similar to that reported by Henning & Rubenson (1971) in the rat, which could neutralize the pressor effects. It might be argued that

the inverse dose-response relation in Fig. 3 supports this view. Antagonism between pressor and depressor responses with different sensitivity and time-courses might also explain the late rise in blood pressure after decarboxylase blockade (Fig. 1).

Finally, our results suggest that further experiments would be justified to establish the possible safety of a more powerful antiparkinsonian drug regimen comprising levodopa, iproniazid and L-alpha methyldopahydrazine. The ultimate value of such combined therapy would also depend upon unknown factors, in particular whether central adverse reactions of levodopa such as dyskinesia, are mediated by monoamines. If they are, the potential advantages of augmenting striatal dopamine would be countered by the increased severity of centrally induced side effects.

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