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Characteristic responses to L-dopa of cerebral blood flow and EEG pattern in stroke-prone spontaneously hypertensive rats[1]

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Summary. L-Dopa given i.p. increased regional cerebral blood flow and influenced EEG patterns in stroke-prone spontaneously hypertensive, but not in normotensive rats. The feasibility of this approach for determining the pathology of the cerebral vessels and the blood-brain barrier warrants further study.

There are little data on the effect of L-dopa on cerebral blood flow in laboratory animals[3], and apparently none regarding the effect of this norepinephrine precursor on the pathophysiological state of cerebral circulation. We examined the effects of L-dopa on cerebral blood flow (CBF) and cortical electrical activity in spontaneously hypertensive stroke-prone and stroke-resistant and normotensive rats.

Male spontaneously hypertensive stroke-prone (SHR-SP), stroke-resistant (SHR-SR) and Wistar-Kyoto (WK) rats, 6 months old, were used. The experimental groups included 8–7 animals. For the regional cerebral blood flow (rCBF) measurements, rats were prepared according to the method described by Yamori and Horie[4]. Under sodium pentobarbital anesthesia (40 mg/kg i.p.) platinum electrodes were bilaterally implanted into the frontal cerebral cortex. rCBF was measured in conscious unrestrained rats by the hydrogen clearance method[5]. In each rat rCBF was first measured 2 weeks after the implantation of electrodes. All rats implanted with hyposensitive electrodes and with outlying values of rCBF were excluded from further analysis. The same set-up as for rCBF measurements was used for cortical EEG registration[6,7]. Blood pressure was measured in conscious rats by the tail plethysmographic method.

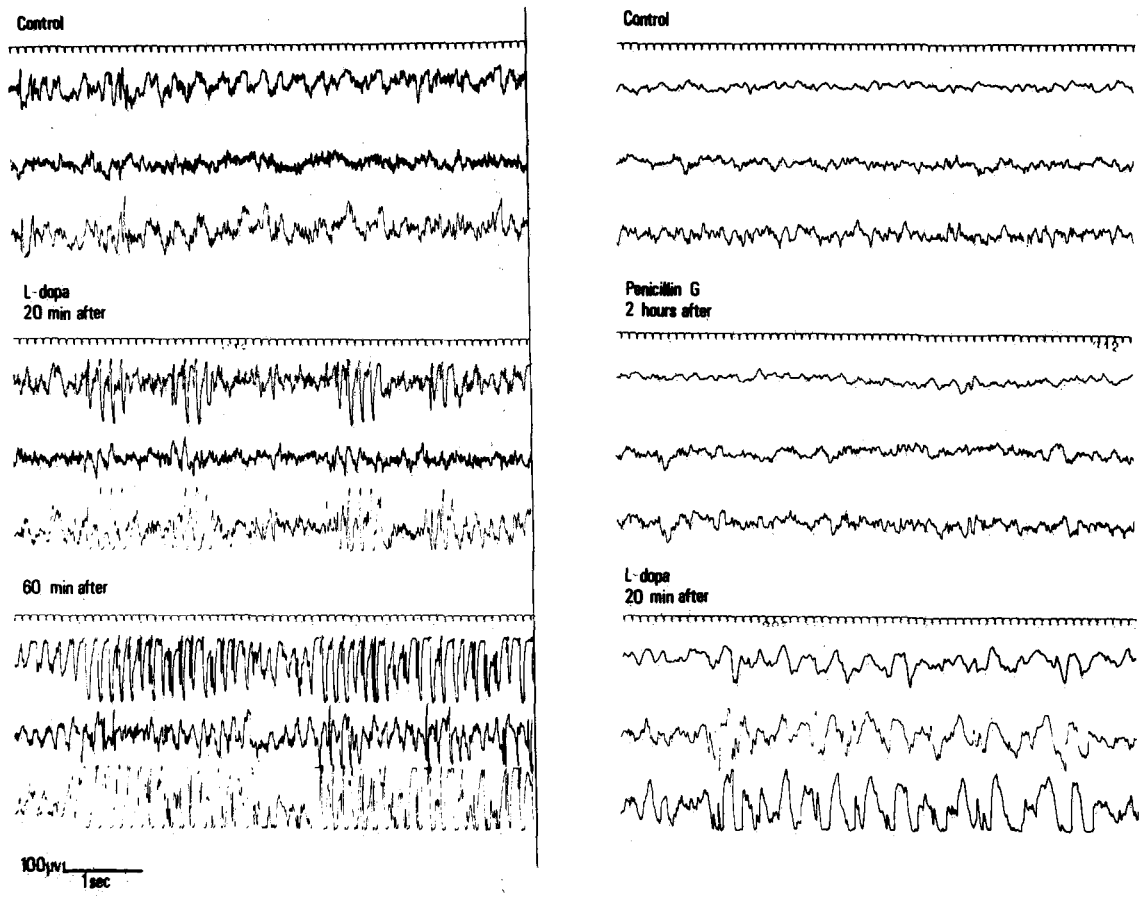
Experimental procedure was as follows: after control rCBF measurements L-dopa ('Nakarai', 100 mg/kg dissolved in physiological saline at a temperature of 45 °C) was given i.p. in the form of a fine-grained suspension. The measurements were performed 0.5, 1, 1.5, 2, 3, 3.5 and 4 h thereafter. Cortical EEG was recorded in the same animals during the intervals of rCBF measurements and the records were analyzed according to the methods of Yamori et al.[6,7]. The cortical EEG was recorded from 20 min up to 4 h after L-dopa injection. Additionally, the state of the blood-brain barrier was assessed in 2 SHR-SP rats by determining the effect of Penicillin G on the EEG[8]. A similar group of animals was used to measure the arterial blood pressure. Student's t-test was used for statistical analysis.

Two different types of rCBF response were observed 0.5 h after i.p. administration of L-dopa (table). In SHR-SP which showed an obvious reduction in rCBF before L-dopa administration, as described previously[4], the significant increase observed in rCBF remained at these elevated levels for over 2.5 h. In contrast, in SHR-SR and WK there was a decrease in rCBF following L-dopa administration and a stepwise recovery occurred within 4 h. The administered dose of L-dopa had no effect on the blood pressure in SHR-SP and SHR-SR. A significant increase in blood pressure was noted only in WK 30 min and 1 h after L-dopa administration.

After the pretreatment with peripheral decarboxylase inhibitor MK-486, L-dopa resulted in a marked rise in rCBF by 39% in SHR-SP and an increase in flow by 11.5% in WK rats.

Differences in the EEG pattern could be observed in SHR-SP depending on whether they were awake or drowsy[6,7]. Control EEG recordings during the waking state in SHR-SP were similar to those observed in the other groups and there was a predominance of 20–50 cps waves (amplitude 10–150 μV). A predominance of θ waves superimposed by β waves was observed in control SHR-SP in a drowsy state. These θ waves were in the form of diffused spindles over 5–15 sec (fig.). After the L-dopa administration the θ waves appeared only in SHR-SP. From 20 min up to about 1 h after L-dopa administration, a further increase of the amplitude (to 600 μV) and the number of θ waves were seen. Also high voltage (400 μV) δ waves often appeared. L-Dopa administration was without apparent effect upon the EEG pattern in both SHR-SR and WK. Administration of Penicillin G to SHR-SP rats did not alter the EEG pattern, indicating that the function of the blood-brain barrier was not extensively impaired[8].

These results were obtained after L-dopa had been given i.p. in a dose which in WK rats only produced an increase in blood pressure due to the convention to L-dopa to norepinephrine in the peripheral vessels. In SHR-SP and SHR-SR such peripheral pressor effects seemed to be cancelled by the central depressor effect[9], resulting in no pressor response after L-dopa administration. In this experiment L-dopa was given i.p in order to examine rCBF, in conscious, unrestricted animals. After this administration there was no enhancement in the respiratory frequency which could, in certain instances, result in hyperventilation. Our observations do not elucidate the mechanism of L-dopa action on CBF; however, the marked effect on both cerebral flow and the electrical activity of the brain mainly observed in the SHR-SP with severe hypertension could be the result of enhancement of the amount of L-dopa available at the blood-brain interface and/or increased penetration of exogenous L-dopa into the central dopaminergic



2 examples of EEG-recording in SHR-SP rats. Increase in high voltage θ waves superimposed by β is seen after L-dopa (100 mg/kg i.p.) (left side). Penicillin G (600.000 IU/kg, i.p.) did not alter the EEG over a 2-h period. L-Dopa administered thereafter resulted in the appearance of δ waves (right side).

system, probably due to a reduced function of the decarboxylase barrier[10] or to an enhanced endothelial permeability[11–13]. The rapid increase in cerebral blood flow in SHR-SP and also the delayed but reversed response in WK to L-dopa after blocking the activity of peripheral decarboxylase, including the decarboxylase barrier at cerebrovascular endothelial cells, can be attributed to the increased quantity of L-dopa available in the brain, which increases centrally the cerebral blood flow. Therefore, observations on rCBF or EEG alterations following L-dopa administration may serve as a non-invasive technique to examine the state of cerebral vessels through which peripherally administered L-dopa is incorporated into the brain. Since an increase in rCBF in response to L-dopa reflects the dysfunction of the endothelial barrier of cerebral vessels and precedes cerebrovascular lesions (arterionecrosis) inducing both hemorrhagic and thrombotic stroke[4,12], detection of such a state may be useful for a clinical prediction of stroke. Moreover, L-dopa, which normalizes CBF reduction in cases of severe hypertension, could theoretically be expected to prevent the development of cerebrovascular lesions caused by chronic CBF reduction[4,12] and, therefore, to contribute to stroke prevention.

Effects of L-dopa (100 mg/kg, i.p.) on blood pressure and rCBF

Group	No of rats	Control BP (mm Hg)	rCBF (ml/min/ min)	L-Dopa BP (mm Hg)	rCBF (ml/min/ 100 g)
SHR-SP	8	248±15	68.3±2.2	242±14	91.0±3.4*
SHR-SR	7	189± 7	98.1±3.0	193± 6	81.1±3.1*
WK	7	121± 3	100.7±2.4	181±17*	83.3±3.9*

* $p < 0.001$.

1 Acknowledgments. This study was supported by Science and Technology Agency of Japanese Government, Japanese Ministry of Education and Ministry of Health and Welfare. We thank M. Ohara for editing the manuscript.
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