in plasma was low; the maximal concentrations reached were between 1 and 4 μg per ml. At this concentration, the Dopa in the total plasma volume accounted for only 0.5 percent of the dose.

In summary, as the dose of L-Dopa was increased HVA in urine accounted for a fairly constant 25 percent of the dose in 13 of 17 patients with Parkinson's disease so treated. In 4 of the 17 patients the fraction of the dose excreted as HVA decreased as the dose of Dopa increased.

There was considerable variation among patients in the amount of the dose of L-Dopa metabolized to VMA but in none did this exceed 0.14 percent of the dose.

5-HIAA concentrations in urine were markedly decreased in most patients receiving L-Dopa.

The concentrations of Dopa in plasma of patients receiving this drug were low. The maximal concentrations, between 1 and 4 μg per ml, were reached two to three hours after the drug was taken.

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AMINO ACIDS AFTER L-DOPA

F. Gerstenbrand and E. Gründig

This paper will present the results of our recent research on the amino acid pattern in cerebrospinal fluid (CSF) and serum in Parkinson's disease before and after L-Dopa administration. There is no brain-CSF barrier for amino acids; therefore, CSF values can be taken to reflect changes in brain metabolism.

Table 1 shows a statistically significant increase in glycine, serine, threonine, cysteine + cystine and methionine in parkinsonism patients as compared to control subjects. Glutamic acid is significantly lower in the parkinsonians than in the controls. However, in serum the amino acids are all within the normal range.

Ten schizophrenic patients with phenothiazine-induced extrapyramidal symptoms were similarly studied and compared to the parkinsonians. In both groups the same pattern was found: glycine, serine, threonine, cysteine + cystine and methionine were increased, and glutamic acid decreased or not detected at all. This alteration is still more striking in phenothiazine-induced parkinsonism.

To investigate a possible metabolic disorder within the brain induced by these phenothiazines, we determined the amino acid level of some brain regions of phenothiazine-treated rats. In these animals, with clinical akinesia, rigidity, and tremor, we found the same change in amino acid content in cortex, striatum, thalamus, and cerebellum. Glycine, serine and threonine content was higher, but glutamic acid content lower than in the control animals; in addition, γ-amino butyric acid was increased two- or threefold.

The CSF was also investigated in brain-injured patients with a midbrain lesion and with distinct parkinsonian symptoms. We know that, in these cases, the histology usually shows a lesion in the substantia nigra on one or both sides. Again in this post-traumatic parkinsonian syndrome, the total amount of amino acids was in the normal range. Glycine was increased (as compared to controls) by about 50 percent, serine 160 percent, threonine 330 percent, cysteine + cystine 80 percent, and methionine 150 percent; glutamic acid was decreased.

From these results, we believe that in the parkinsonism syndrome a disturbance in the metabolism of glycine is highly important, because a change in the turnover of glycine will definitely provoke a change in the turnover of serine, threonine, cysteine and methionine. Thus a disturbance in glycine metabolism may be present with the well-known deficiency in dopamine content of some brain structures, and these disorders may be related to each other.

This hypothesis is supported by the following results: when 100 mg of L-Dopa are injected intravenously to patients with Parkinson's disease, the glycine content of the CSF returns to a normal range while the tyrosine level rises. In normal controls, glycine content increases for 12 hours while tyro-

TABLE 1. CSF Amino Acids in Parkinsonism and Control Subjects (average values in mg percent)

	Control Subjects	*Parkinsonism*
Glycine	0.32	0.62
Serine	0.36	0.76
Threonine	0.21	0.56
Cyteine + cystine	0.19	0.47
Methionine	0.07	0.16
Glutamic acid	0.90	0.10

sine levels remain unchanged. Other amino acids, except lysine, do not show great differences between parkinsonian patients and controls.

In cases of Huntington's chorea, where we found a similar alteration in the amino acid content of CSF, the glycine level is increased fourfold after L-Dopa administration.[1]

We may thus conclude that

1. Every administration of L-Dopa provokes in parkinsonian patients and in normal persons an initial, short-lasting increase in the total amount of amino acids in the CSF and in the serum. This change is accompanied by increases in the blood sugar level.
2. Catecholamine synthesis starts from tyrosine to L-Dopa. After administration of L-Dopa in parkinsonian patients a feedback inhibition of tyrosine hydroxylation can be observed. In our investigation, we could find that a single L-Dopa administration produced a distinct increase in CSF tyrosine as well as in the serum, an effect which we could not observe in normal persons. Thus in Parkinson's disease there exists a disturbance in tyrosine hydroxylation.[2]
3. In parkinsonism the glycine level in CSF is increased. A mechanism probably exists which partly compensates the dopamine deficiency by an increased production of "inhibitor" amino acids such as glycine and gamma-amino butyric acid. After L-Dopa administration, the production of dopamine increases and an enhanced glycine synthesis is no longer necessary. The rise in tyrosine and decrease in glycine after L-Dopa administration confirms the close relationship between these amino acids.

In the CSF of parkinsonian patients, the glutamic acid content is very low. In our experience, this is not characteristic for the Parkinson syndrome. The same deficiency can be found in other neurological diseases, and seems to be a consequence of an insufficient oxygen consumption by brain tissues.[3]

We finally would like to report on our study of the amino acid level in the CSF of parkinsonians with long-term (high-dose) L-Dopa therapy. During this study, six patients were given 1.5 to 4 grams of L-Dopa for several weeks. The high values of glycine and serine were reduced after eight to ten days. In preliminary experiments it would seem that the glycine and serine levels, as well as the content in methionine, threonine and cysteine, remain normal after long-term L-Dopa therapy. The low glutamic acid content was unchanged. The other amino acids have been unchanged as well. An interruption of high-dose L-Dopa caused an increase in glycine and serine.

We think that the finding of typical changes in amino acid content in organic Parkinson syndromes, as well as a similar reversible disturbance of the amino acid pattern in cases of phenothiazine-induced parkinsonism, could improve our knowledge about the biochemistry of Parkinson's disease.

The influence of L-Dopa upon tyrosine and glycine seems to be especially important. It indicates a disturbance in specific enzymatic systems. We actually cannot give an exact explanation. Success of a treatment with L-Dopa could possibly be evaluated through changes in CSF metabolism.

In these investigations amino acids were measured by column chromatography, paper chromatography and paper electrophoresis.

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EFFECT OF DOPA AND JB516 ON GLUCOSE METABOLISM IN BRAIN *

Gertrude M. Tyce

We became interested in the effect of large doses of dihydroxyphenylalanine (Dopa) on glucose metabolism. Since glucose is the chief source of energy in the central nervous system, we were particularly interested in effects of Dopa on glucose metabolism in the brain.

Glucose-U-^{14}C (20 μc, 0.24 mg) was injected intravenously in control rats and in rats which 2¼ hours earlier had been injected with the monoamine oxidase inhibitor β-phenylisopropylhydrazine (JB516) (20 mg per kg) and 15 minutes earlier with Dopa (100 mg per kg). Fifteen minutes after glucose-^{14}C administration the rats were anesthetized with Nembutal (20 mg) and the brains were frozen in situ by immersing the rat in liquid nitrogen. The frozen brains were chiseled out. Concentrations of glucose and lactate were measured in protein-free extracts of plasma and of brain by enzymatic procedures.[1, 2] Concentrations of amino acids in picric acid extracts of brain were measured on ion exchange columns in an amino acid analyzer. Radioactivity in glucose and metabolites in the effluent from the column was measured in a liquid scintillation counter.

At 15 minutes after the administration of glucose-U-^{14}C, the total ^{14}C in brain as unmetabolized glucose was 30 percent in the treated (Dopa and JB516) rats and less than 10 percent in the control rats. There was no difference in the percentages of total ^{14}C in lactate and alanine in the two groups of animals. The proportions of ^{14}C in aspartate, glutamine, glutamate,

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