BEHAVIOURAL AND BIOCHEMICAL EFFECTS OF L-DOPA IN PSYCHIATRIC PATIENTS*

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PRIOR studies in our laboratories have suggested that dopamine may play an important role in the etiology of amphetamine psychoses (ANGRIST *et al.*, 1971): this was consistent with an increasing body of evidence linking central dopaminergic hyperactivity with animal stereotypy and some forms of human psychosis. This evidence is derived from several sources. The extensive data indicating that animal stereotyped behaviour is dopaminergically mediated has been reviewed by RANDRUP and MUNKVAD (1970). Many of the drugs that induce this behaviour have been shown to be capable of causing psychotic states (GRIFFITH *et al.*, 1970; RYLANDER, 1969; SPENSLEY and ROCKWELL, 1972) which bear a striking resemblance to some forms of schizophrenia (CONNELL, 1958; ANGRIST and GERSHON, 1970). On the other hand, drugs which block central dopamine receptors both block stereotyped behaviour and frequently prove to be clinically effective as neuroleptics (ANDEN *et al.*, 1970; JANSSEN *et al.*, 1965; VAN ROSSUM, 1966; SNYDER, 1973).

Administration of the dopamine precursor, L-dopa to Parkinsonian patients has frequently precipitated psychotic reactions of various types (BROGDEN *et al.*, 1972; GOODWIN, 1972), a finding consistent with this hypothesis. Accordingly, it was felt desirable to attempt a controlled assessment of the behavioural effects of L-dopa in psychiatric patients whose pre-drug behavioural status was well documented and who were free of neurologic disease.

METHODS

The methodology for this study is reported in detail elsewhere (ANGRIST *et al.*, 1973). Briefly, patients who consented to participate were maintained on matched placebo for 5–10 days before L-dopa was administered. During this time no other drugs were given with the exception of chloral hydrate or sodium amytal as required for agitation or insomnia. L-Dopa was initiated at a dosage of 750 mg/day and then gradually increased to the maximum daily dosage that was tolerated. A clinical laboratory work-up and EKG were done at baseline and weekly. Behaviour was assessed both by daily clinical notes and by a weekly BPRS and CGI. In those patients who consented to lumbar puncture, this was done at baseline and at the maximum dose. Cerebrospinal fluid was analysed for MHPG (WILK *et al.*, 1971) and HVA (GERBODE and BOWERS, 1968). Results were as follows.

RESULTS

Schizophrenic patients

Several patients showed deterioration during the placebo period and were dropped from the study and treated with standard neuroleptics. Ten patients received L-dopa

* This work was supported by USPHS Grant MH 04669.

for a mean of 21·2 days (range 11–29 days). The mean maximum daily dose attained was 5·050 g (range 3–6 g). This resulted in significant deterioration on the BPRS with respect to conceptual disorganization, emotional withdrawal and agitation-excitement (analyses of variance repeated measures model for both raters).

While all patients showed behavioural deterioration, a qualitative distinction into two response patterns could be made. Three patients showed stimulant effects with psychomotor activation, loquaciousness leading to freer expression of pathology, intrusiveness and irritability. No changes, however, were noted in their original psychotic symptomatology.

A second response pattern was shown by 7 of 10 patients. This consisted of both the stimulant effects noted in the first group and a dose-related increase in the original symptom pattern present at baseline. Deterioration was particularly prominent with regard to thought disorder, emotional lability, bizarre behaviour, agitation and hallucinations. Two patients showed the emergence of *de novo* symptoms while on L-dopa, auditory hallucinations in one case and mannerisms in the second.

Non-schizophrenic patients

These patients tolerated larger doses of L-dopa. The mean maximum daily dose was 8·830 g (range 6–10 g). The mean duration of administration was 22 days (range 19–28 days). The responses of this group (6 patients) were variable. The first patient showed hypersexuality and compulsive masturbation without other signs suggestive of hypomania such as euphoria or hyperactivity. The second showed no objective behavioural effects and tolerated dosages of 10 g L-dopa/day. A third patient abruptly developed a toxic confusional state at 9 g L-dopa/day. Two other patients showed a combination of nausea, diaphoresis, a sense of dysphoric stimulation and anxiety. One of these developed ideas of reference. The remaining patient, who had no history of psychosis or psychiatric signs suggestive of schizophrenia developed a paranoid schizophreniform psychosis. This 39-year-old male had been a successful stock broker but had been drinking heavily for 2 years. At a dose of 9 g L-dopa/day, he became intrusive and would not permit conversations to be terminated. He compulsively dwelt on past injustices done to him by a brother-in-law who, he claimed, had unjustly accused him of "interstate narcotics sales" and had dealings with "the mafia". He claimed his own lawyer had joined the conspiracy and tried to have him sent to jail because of vaguely described "big business interests". The connection between the lawyer and brother-in-law could not be clearly explained but he alleged that both were part of a "web" created to ruin him. Changes in formal aspects of speech were striking. He was compulsively circumstantial, unable to give a focused account and constantly introduced irrelevant details so that his line of thought became so rambling that it could not be followed. His speech showed occasional blocking and his affect appeared incongruously blunted when compared to the content of his speech. These signs resolved completely within 16 hr after L-dopa was discontinued and 5 mg haloperidol was administered intramuscularly. Thus, 1 of these 6 showed a clear psychotic reaction to L-dopa administration.

Biochemical data

CSF levels of MHPG and HVA before and after L-dopa administration are given in Table 1.

TABLE 1. CEREBROSPINAL FLUID LEVELS OF MHPG AND HVA (ng/ml) BEFORE AND AFTER L-dopa ADMINISTRATION

Patient No.	MKPG Pre/Post	HVA Pre/Post	L-dopa dosage (mg/day)
1	17/7	0/110	4·000
2	11/12	0/123	3·000
3	9/13	55/78	6·000
4	7/15	19/202	3·000
5	15/8	0/26	3·000
6	14/12	0/82	3·000
7	5/10	0/271	9·000
8	5/11	0/574	9·000
9	7/9	17/235	10·000
10	6/8	30/129	6·000

DISCUSSION

Since L-dopa induces CNS stimulation one might question whether the behavioural deterioration of the schizophrenic patients was due to increased dopaminergic activity or represents an inability of this group to tolerate non-specific CNS stimulation of any sort. We attempted to clarify this by administering caffeine, which does not induce stereotypy in animals (WILLNER *et al.*, 1970), to these subjects. All showed tremor, anxiety and increased heart rate but none showed exacerbation of psychotic symptoms. This suggests that if the two can be separated, the behavioural worsening observed was more likely secondary to dopaminergic events than to non-specific stimulation.

The precipitation of a schizophreniform psychosis by administration of L-dopa in a patient documented to be non-schizophrenic prior to receiving the drug also supports the hypothesised relationship between psychosis and central dopaminergic activity that has been proposed by several investigators. However, the variability of response in the non-schizophrenics, the differing response patterns in the schizophrenics, and the differences in sensitivity of the two patient groups to the drug all suggest the concept of an individually variable threshold of dopaminergic activity that can be tolerated without psychosis. Such a concept would be consistent with recently reported observations by JANOWSKI *et al.* (1973) of striking variation in response to intravenous methylphenidate in psychiatric patients both across diagnostic categories and in the same patient in differing phases of his disease. This concept would also be consistent with the marked variability in sensitivity to the psychotogenic effects of amphetamine that have been noted when this drug has been given in large doses (GRIFFITH *et al.*, 1970; ANGRIST and GERSHON, 1970).

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