
L-DOPA and Psychosis: Evidence for L-DOPA-Induced Increases in Prefrontal Cortex Dopamine and in Serum Corticosterone

Robert J. Carey, Marinete Pinheiro-Carrera, Huiliang Dai, Carlos Tomaz,
and Joseph P. Huston

L-DOPA can often induce psychotic reactions during treatment for Parkinson's disease. This study was undertaken to assess, in an animal model of Parkinson's disease, the impact of L-DOPA treatment on two potential biological risk factors for psychosis, namely, an increase in prefrontal cortex dopamine and an increase in the stress-related hormone corticosterone. Hemiparkinsonian rats with unilateral 6-hydroxydopamine (6-OHDA) lesions which resulted in severe unilateral denervation of dopamine neurons were treated with either saline or 25 mg/kg L-DOPA methyl ester (with 2 mg/kg carbidopa). Serum L-DOPA concentrations were found to be positively and highly correlated with serum corticosterone, with medial prefrontal cortex dopamine and with the dopamine metabolite homovanillic acid. Serum L-DOPA, however, was found not to be correlated with serum or brain concentrations of serotonin, 5-hydroxyindoleacetic acid, or norepinephrine. These findings support the possibility that chronic L-DOPA treatment can expose parkinsonian patients to two significant risk factors for psychosis: 1) increased levels of prefrontal cortex dopamine, and 2) increased levels of serum corticosterone.

Key Words: Psychosis, dopamine, serotonin, prefrontal cortex, Parkinson's disease

BIOL PSYCHIATRY 1995;38:669–676

Introduction

L-DOPA (L-3-4-dihydroxyphenylalanine) is a widely used and often effective treatment for Parkinson's disease (Blair 1989; Calne et al 1984); however, serious iatrogenic effects can develop with chronic L-DOPA therapy (Fahn 1989; Pfeiffer 1982). In particular, L-DOPA-induced dyskinesia

and psychosis represent disabling effects of L-DOPA treatment. While there have been numerous experimental efforts using animal models to identify the biological mechanisms underlying these untoward clinical effects—e.g., altered receptors, neuropathology, and metabolic changes (Dunnett and Bjorklund 1983; Engber et al 1989; Gropetti et al 1986; Melamed and Hefti 1984; Olney et al 1990)—as yet no definitive answers have been obtained. L-DOPA-induced psychosis is undoubtedly the most dysfunctional complication of chronic L-DOPA treatment and, perhaps, the least understood. While it is long known that the biological components of psychosis are complex (Ban 1976; Feldon and Weiner 1992), there does exist a substantial body of evi-

From the State University of New York (SUNY) Health Science Center and VA Medical Center, Syracuse, NY (RJC, HD); University of Sao Paulo, Ribeirao Preto SP, Brazil (MP-C, CT); and University of Duesseldorf, Duesseldorf, Germany (JPH).

Address reprint requests to Dr. Robert J. Carey, Research Service 151, VA Medical Center, 800 Irving Ave., Syracuse, NY 13210.
Received May 13, 1994; revised October 7, 1994.

dence to indicate that disturbances in frontal cortex particularly with regard to dopamine can contribute substantially to the occurrence of psychotic episodes (Goldstein and Deutch 1992; Heritch 1990; Rao et al 1993). Stress is also generally considered to be a risk factor for psychosis (Feldon and Weiner 1992; Sato 1992). The impact of L-DOPA treatment upon these potential biological risk factors, however, has not been investigated in animal models of parkinsonism. Accordingly, the present study examined the effects of L-DOPA treatment in an animal model of hemiparkinsonism in which prefrontal cortex dopamine and serum corticosterone concentrations were assessed. Measurement of serum L-DOPA levels revealed that there was a strong correspondence between L-DOPA levels in serum and dopamine concentrations in the medial prefrontal cortex and serum corticosterone levels. These findings suggest that a chronic L-DOPA activation of these two suspected risk factors for psychosis may contribute to the development of psychotic reactions resulting from chronic L-DOPA therapy for Parkinson's disease.

Methods

Subjects

Adult naive male Sprague-Dawley rats (Taconic Farms, Germantown, NY), ranging from 400–500 g, were housed in individual clear plastic cages (55 × 30 × 20 cm) with continuous access to food and water upon receipt from the supplier. The cages were placed in a climate-controlled (22 ± 1°C) and light-controlled room (12hr light/dark cycles). All treatment and testing were carried out during the light cycle. The animal care and experimental treatment protocols employed were approved by both the VA Medical Center and the SUNY Health Science Center at Syracuse.

Drugs

To prepare L-DOPA for injection, L-DOPA methyl ester (Sigma) was dissolved in deionized sterile H₂O and administered by intraperitoneal (IP) injection. Carbidopa (Sigma) was dissolved in deionized sterile H₂O and also administered IP. The L-DOPA treatments were administered in combination with carbidopa treatments in a 10:1 ratio to attenuate peripheral metabolism of L-DOPA.

Surgery, Histology, and Biochemical Assays

Stereotaxic procedures were carried out as described in a previous report (Carey 1991) following completion of an initial 10-day treatment phase of handling (7 days) and saline injection (3 days). Animals were deeply anesthetized with an injection of (0.1 ml/100 g body weight) of a ketamine HCl (100 mg/ml) and acetopromazine (10 mg/ml) solution. The 6-hydroxydopamine (6-OHDA) injections

were aimed stereotaxically immediately dorsal to the A9 and A10 areas of the midbrain tegmentum. Each animal received 6 µg of 6-OHDA, dissolved in a vehicle solution of sterile 0.15 M NaCl containing 0.2 mg/ml of ascorbic acid. To attenuate norepinephrine neurotoxicity, the animals were pretreated with desipramine HCl (25 mg/kg) 30 min prior to the 6-OHDA injection. Forty-one out of the 55 animals injected unilaterally with 6-OHDA sustained unilateral dopamine losses such that the dopamine concentration was < 10% of the intact striatum. The subsequent data analysis is focused upon this subset of animals with severe unilateral DA denervation in which the serum L-DOPA measurements were available (n = 34). This degree of dopamine deficiency in the denervated striatum is associated with permanent behavioral asymmetries and dopamine receptor supersensitivity (Schwartz et al 1991).

Immediately following completion of the last day of behavioral testing in each experimental group, animals were placed in a plastic restraining cone (Braintree Products, Inc) and sacrificed by decapitation. The brain was rapidly removed and dissected on a chilled glass plate. Under magnification, medial prefrontal cortex samples (2 × 2 mm sections of the medial frontal pole) were dissected as well as neostriatum samples dorsal to the nucleus accumbens. Separate paraffin sections of the ventral tegmentum were prepared for histological evaluation of the injection sites. Following dissection, the samples of brain tissue were immediately weighed, placed in tubes containing 0.5 ml of 0.1 M perchloric acid and 4.5 µl of 10 µg/ml dihydroxybenzylamine (DHBA) as an internal standard, and then homogenized and centrifuged. The resulting supernatant was filtered through 0.2 µm pore filters, and the extracts were stored at –70°C until analysis by high-performance liquid chromatography with electrochemical detection (HPLC-EC), which was completed within 48–72 h. The tissue samples were assayed for dopamine (DA; 3-hydroxytyramine) and the dopamine metabolites DOPAC (3,4-dihydroxyphenyl-acetic acid) and HVA (homovanillic acid), and serotonin (5-HT; 5-hydroxytryptamine), and the serotonin metabolite 5-HIAA (5-hydroxyindole-acetic acid), and also for norepinephrine (NE; arterenol bitartrate). Tissue samples were also analyzed for L-DOPA (L-3,4-dihydroxyphenylalanine) and the L-DOPA metabolite 3-OMD (3-O-methyl DOPA) using HPLC-EC.

Trunk blood at sacrifice was also collected (n = 34; 7 tested with saline, 27 tested with L-DOPA). Half of each sample was diluted 1:1 with 0.4 M perchloric acid in 0.5% NaF for a catecholamine/indoleamine assay; this sample and the remaining portion of the blood were centrifuged for 15 minutes at 14,000 rpm in order to obtain the plasma component. For the neurotransmitter assay, the supernatant was then filtered through 0.2 µm pore filters and injected into the HPLC-EC for catecholamine and indoleamine mea-

surements. For the catecholamine and indoleamine analyses in brain tissue as well as plasma, a biophase C18 reverse-phase column (4.6 × 250 mm, 5 μm) was used (Bioanalytical Systems, West Lafayette, IN). The buffer was 0.15 M monochochloroacetic acid, pH 3.1, 2 mM ethylenediamine-tetraacetic acid (EDTA) 0.86 mM SOS (sodium octyl sulfate). This was added to 35 ml acetonitrile (3.5%) to make 1 L. This solution was then filtered and degassed, and 18 ml (1.8%) tetrahydrofuran (THF) was added. The mobile phase flow rate was 1.2 ml/minute and a BAS 4B EC detector was set at 0.8 V.

To prepare plasma samples for corticosterone, a solid-phase extraction method was used. The extraction column was a C18 3 ml (500 mg) column. Under vacuum, the column was conditioned with 2 × 3 ml methanol followed by 2 × 3 ml HPLC grade H₂O. Before the column could dry, 0.5–2.0 ml of plasma (depending upon availability of samples) was passed through the column and immediately followed with a 2 ml HPLC grade H₂O/acetonitrile wash (80:20). Next, the column was air-dried for 3 minutes. Finally, the sample was eluted with 2 × 0.5 ml methanol for corticosterone. The samples were injected into a BAS phase II C18 reverse-phase column (4.6 × 250 mm, 5 μm) with mobile phase of 60% MeOH, 40% H₂O run at a flow rate of 1.0 ml/min. A BAS variable wavelength ultraviolet (UV) detector was used with the setting at 254 nm.

Behavioral Test Procedures

Postoperatively, the animals received appropriate supportive care, and body weight was monitored daily. Following the acute postoperative phase, the animals had an uneventful recovery, and most animals exhibited the typical ipsilateral response bias characteristic for severe unilateral denervation of dopamine neuron target cells. The animals were handled daily and accustomed to IP saline injections. At 4 weeks postoperative, all animals were injected with saline and then, 30 min later, tested for 10 min in the videochamber. The next day, one set of animals (n = 8) again received a saline injection and were tested 30 min later in the videochamber. The remaining animals (n = 47) were given an injection of L-DOPA (25 mg/kg L-DOPA methyl ester plus 2 mg/kg carbidopa) and tested 30 min later in the videochamber for 10 min. Prior to surgery, all animals had been tested twice without drug treatment in the test compartment to provide nonlesion levels of locomotion as well as ipsilateral and contralateral rotation levels.

Statistical Analysis

Pearson's correlational analysis was applied to determine the relationship between serum L-DOPA concentration and serum/brain neurochemical concentrations. Whenever the correlation reaches the statistically significant level ($p < .05$), a linear regression equation was calculated and presented as $Y = aX + b$.

Results

Figure 1 shows the relationships between serum L-DOPA concentrations and serum 5-HT, 5-HIAA, NE, corticosterone, HVA, and 3-OMD. As expected, there was a high correlation between L-DOPA and its metabolite 3-OMD. Additionally, there were substantial and statistically significant correlations between serum L-DOPA and serum corticosterone and between L-DOPA and the DA metabolite HVA. No other serum correlations were statistically significant.

Figure 2 shows the impact of L-DOPA upon medial prefrontal cortex DA and HVA. There was a high correlation between serum L-DOPA and brain DA and HVA concentrations in the medial prefrontal cortex in both the intact and 6-OHDA hemispheres. In contrast, 5-HT and the serotonin metabolite, 5-HIAA, in medial prefrontal cortex in both hemispheres were not correlated with serum L-DOPA (r from .113–.222, $p > .05$). Similarly, the correlations between serum L-DOPA and cortical NE were not statistically significant, $r = .12$ and $r = -.16$, $p > .05$, for the intact and 6-OHDA hemispheres, respectively.

The relationship between serum L-DOPA and brain DA in the striatum, as shown in Figure 3, was somewhat different. As in the cortex, there was a statistically significant relationship between serum L-DOPA and DA in the intact striatum; but, unlike the cortex, there was no statistically significant relationship between serum L-DOPA and DA in the 6-OHDA hemisphere. In terms of the metabolite HVA, however, serum L-DOPA and striatal HVA were highly correlated for both the intact and 6-OHDA hemispheres. Neither 5-HT nor 5-HIAA in the striatum was significantly correlated with serum L-DOPA (r from .031–.292, $p > .05$). Importantly, correlations between cortical and striatal L-DOPA concentrations and serum L-DOPA were similar and substantial, $r = .65$ –.75, $p < .001$.

The behavioral effects of the L-DOPA treatment are an additional relevant dimension of the present study, which is important for the interpretation of the neurochemical findings. The dose level used in the present study was a threshold dose for drug-naïve animals. Only about 20% of the animals which exhibited > 90% dopamine DA loss in the 6-OHDA hemisphere compared to the intact hemisphere exhibited contralateral rotation behavior (criterion ≥ 20 rotations/10 min), and this effect was not related to the severity of the striatal DA deficit, $r = .06$, $p > .05$. This result suggests that the correlations between L-DOPA with DA and HVA were not closely linked to the L-DOPA-induced behavior, i.e., to the occurrence of contralateral rotation behavior. An additional supportive finding for this conclusion is that the L-DOPA–cortex DA correlation for animals which did not exhibit rotation was $r = .79$, $p < .001$ for the intact hemisphere and $r = .76$, $p < .001$ for the 6-OHDA hemisphere. Furthermore, the relationship between serum L-DOPA and serum corticosterone was essen-

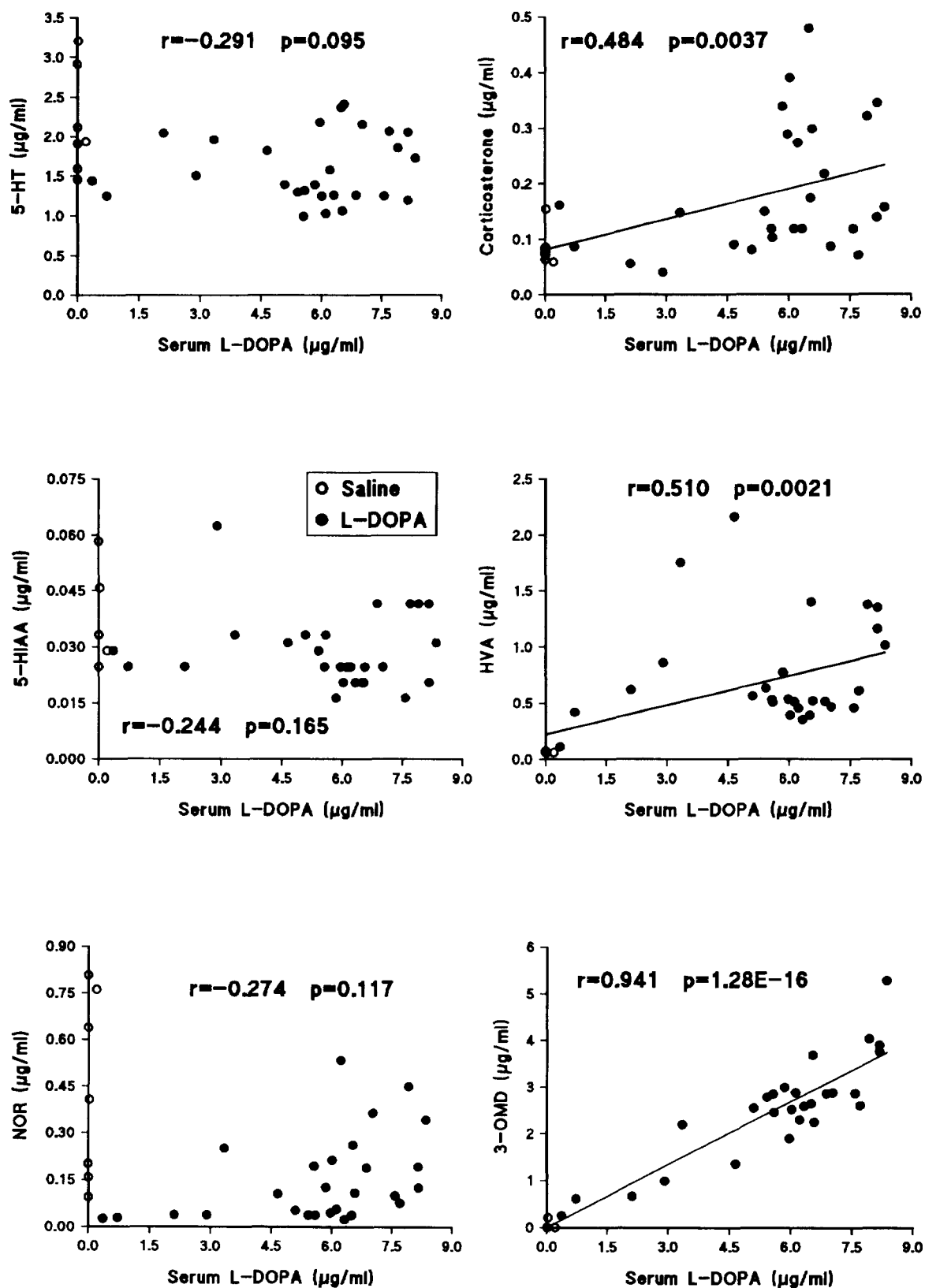


Figure 1. Correlational analyses showing serum L-DOPA concentration levels in $\mu\text{g/ml}$ as related to serum 5-HT, 5-HIAA, and NE concentrations in $\mu\text{g/ml}$ in animals administered L-DOPA or saline (as shown in the left three panels) and for corticosterone, HVA, and 3-OMD in $\mu\text{g/ml}$ (as shown in the right three panels). Only serum corticosterone, HVA, and 3-OMD had significant correlations with serum L-DOPA and their linear regression equations as: Corticosterone $Y = -0.051X + 1.946$; HVA $Y = 0.087X + 0.220$; 3-OMD $Y = 0.448X - 0.001$.

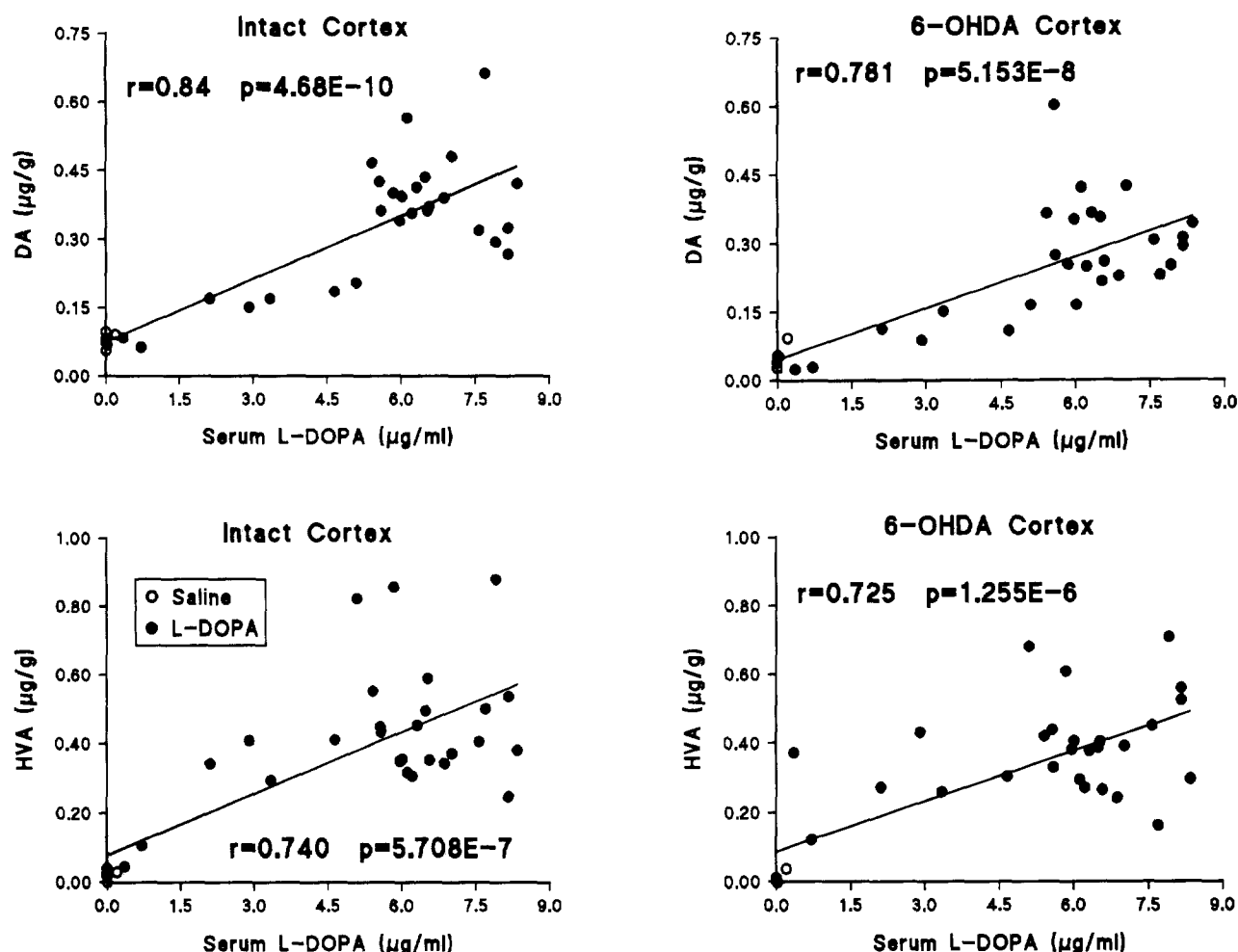


Figure 2. Correlational analyses for the brain tissue concentrations in µg/g of DA and HVA at intact cortex (*left panels*) and 6-OHDA cortex (*right panels*) vs. serum L-DOPA concentration levels in µg/ml. The linear regression equations as: Intact DA $Y = 0.046X + 0.074$; Intact HVA $Y = 0.059X + 0.078$; 6-OHDA DA $Y = 0.037X + 0.046$; 6-OHDA HVA $Y = 0.048X + 0.088$.

tially the same, $r = .51$, $p < .01$. Thus, the impact of L-DOPA on brain dopamine neurochemistry or serum corticosterone is not secondary to L-DOPA-induced rotation behavior.

Discussion

The linkage between dopamine and behavior has been conceptualized as involving two major dopaminergic systems. One is the nigrostriatal dopamine system, which is intimately related to motoric function and is the system most prominently implicated in Parkinson's disease (Carlsson 1993). The other system is the mesocortical-mesolimbic dopamine system, which has been implicated in more subtle behavioral processes related to reward/aversion (Koob 1992) and to adaptive behavior (Swerdlow et al 1986). It is this latter system which provides the underpinning for the dopaminergic involvement in dysfunctional processes such as drug addiction and psychosis. Indeed, it is the mesocortical-mesolim-

bic dopamine system which has been the target site for antidopaminergic treatments for psychosis and is thought to be the brain site at which the newer antipsychotic drug treatments, such as clozapine, exert their therapeutic effects.

In addition to the observed antipsychotic effects of dopaminergic antagonist drugs and, as expected from the dopamine hypothesis of schizophrenia, dopamine agonists can precipitate psychosis (Brady et al 1991; Hurlbut 1991; Nakayama 1993; Satel and Edell 1991). Relative to this direct dopaminergic link to abnormal behavior, stress has long been recognized as a factor which can lead to psychotic reactions in individuals vulnerable and predisposed to psychosis. Significantly, preclinical studies have shown that experimenter-induced stress and stress-related hormones such as corticosterone can impact substantially upon dopamine neurochemistry in the mesocortical dopamine system (Borowski and Kuhn 1991; Heinsbroek et al 1991; Kalivas and Duffy 1989; Keneyuki et al 1991; Moldow and Fisch-

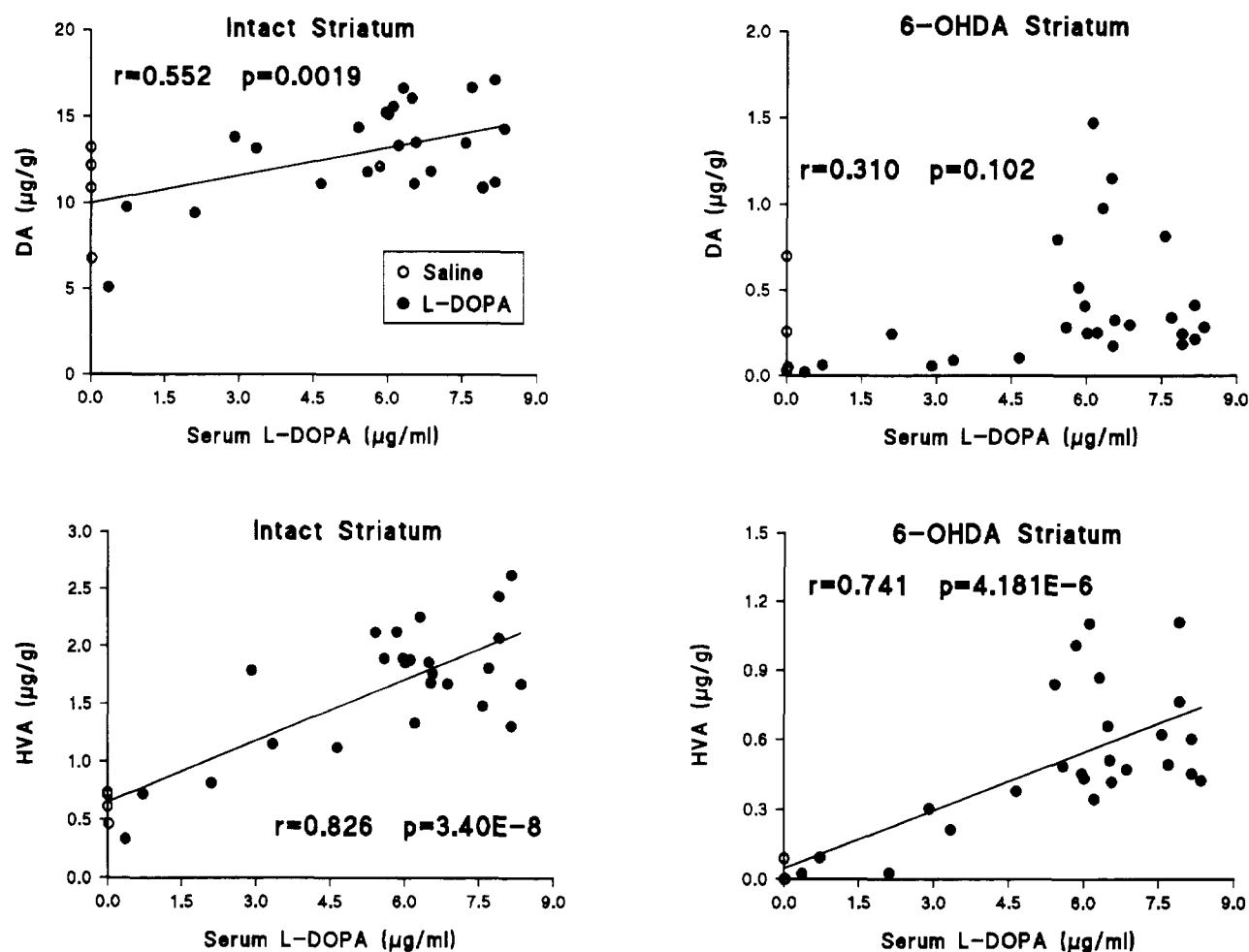


Figure 3. Correlational analyses for the brain tissue concentrations in $\mu\text{g/g}$ of DA and HVA at intact striatum (*left panels*) and 6-OHDA striatum (*right panels*) vs. serum L-DOPA concentration levels in $\mu\text{g/ml}$. HVA in both striata and DA in Intact striatum had significant correlations with serum L-DOPA levels. The linear regression equations as: Intact DA $Y = 0.537X + 9.98$; Intact HVA $Y = 0.176X + 0.65$; 6-OHDA HVA $Y = 0.083X + 0.046$.

man 1987; Sarnyai et al 1992; Thierry et al 1976). The findings of the present study suggest that the efficacy of L-DOPA to induce large increases in medial prefrontal cortex dopamine and to increase levels of the stress-related hormone corticosterone provide a mechanism by which L-DOPA may precipitate a psychotic episode.

There have been a number of reports of the effects of L-DOPA treatment upon striatal dopaminergic metabolism in intact and dopamine deficient animals (Jenner et al 1986; Karoum et al 1988). In studies using ex vivo analyses, L-DOPA has been found to increase dopamine levels in the striatum, in both the intact and the dopamine-denervated striatum, particularly with doses higher than those employed in the present study, e.g., 50 mg/kg (Karoum et al 1988). More recent studies using in vivo microdialysis assessments have also shown that increases in extracellular dopamine can be induced by L-DOPA at doses lower than

those used in the present study, e.g., 5 mg/kg (Sarre et al 1991). Assessments using in vivo microdialysis represent summations of extracellular dopamine over a substantial time interval (e.g., 10 min). In contrast, ex vivo assessments of cellular dopamine concentration represent a momentary summation of extracellular and intracellular concentrations of the transmitter and metabolites. As a consequence, intracellular transmitter levels contribute substantially to the tissue concentrations observed. In the ex vivo technique, dopamine generated from L-DOPA includes dopamine from both neuronal and extraneuronal dopamine decarboxylase (DDC). In the dopamine-denervated striatum, dopamine generated from L-DOPA may be derived largely from extraneuronal DDC and this dopamine subsequently becomes subject to metabolism by catecholomethyltransferase (COMT) and monoamine oxidase (MAO). Given the sparse remaining dopamine terminal networks in the striatum,

reuptake is a less probable source for DA inactivation. Furthermore, the high metabolic level of the remaining nerve terminals renders them a less likely storage site for dopamine. These aspects of the dopamine-denervated striatum may account for the lack of an increase in tissue dopamine in the DA-denervated striatum in response to L-DOPA treatment. In contrast, dopamine metabolism as indexed by HVA concentration is not impacted by DA storage terminals, so that high correlations of HVA concentrations with serum L-DOPA concentrations were found in all tissue samples. While *ex vivo* techniques are not useful to assay short-lived extracellular dopamine, this method can readily detect the byproduct of extracellular dopamine, namely, the dopamine metabolite HVA. The finding in the present study—that L-DOPA substantially increased HVA in the denervated striatum—is therefore in agreement with *in vivo* dialysis measurements of L-DOPA-induced increases of dopamine in the extracellular fluid. *In vivo* microdialysis studies of L-DOPA treatment do not permit an assessment of the L-DOPA treatment upon tissue-bound dopamine. The *ex vivo* measurements therefore provide an important complementary measurement of tissue-bound dopamine. Of critical relevance is the observation that L-DOPA induces substantial increases in tissue levels of frontal cortex dopamine. This aspect of L-DOPA-generated dopamine is of importance in that dopamine accumulation in the neuron terminals can produce feedback inhibition upon tyrosine hydroxylase, the rate-limiting step in the formation of dopamine which is bypassed by L-DOPA. Thus, with chronic treatment, dopamine generated from L-DOPA may lead to long-term changes in the metabolic activity of dopamine terminals in brain areas such as the frontal cortex and thereby contribute to untoward treatment effects.

Since the therapeutic effects of L-DOPA are inextricably connected to its therapeutic efficacy (namely, to the generation of dopamine in the dopamine-deficient striatum), such effects cannot be circumvented by manipulations of LDOPA alone. A further complicating matter is the issue of susceptibility or vulnerability. Even with an acceptance of the dopamine hypothesis of psychosis, dopamine has to be considered but one of several contributing systems to the occurrence of psychotic episodes and psychosis (Snyder 1976). Accordingly, by itself, a rise in dopamine levels does

not necessarily have to lead to psychotic episodes. Besides the contribution of nonbiological factors to psychosis, the biological variability in a drug-induced psychosis related to dopamine includes such factors such as the state of the dopamine receptors, reuptake activity, and metabolic enzymes. With chronic L-DOPA therapy for Parkinson's disease, the persistent elevation and possible fluctuations in dopamine availability in critical brain areas such as the medial prefrontal cortex may precipitate psychosis in vulnerable individuals. Since dopamine deficits in prefrontal cortex have been implicated in the positive and negative signs of psychosis (Deutch 1993), it may be that chronic high levels of dopamine in the prefrontal cortex induced by long-term L-DOPA therapy may induce inactivation effects as a consequence of the development of a depolarization block. Alternatively, long-term stimulation of cortical outflow neurons by excessive prefrontal cortex dopamine may generate excitotoxic effects in subcortical brain areas as a consequence of persistent overstimulation of glutamatergic neurons. While these possibilities are only speculative, they serve to point to possible untoward effects of chronically elevated dopamine levels in a brain region critically involved in the maintenance of behavioral stability. Similarly, stress hormones also impact upon prefrontal cortex dopamine and serotonin activity (Deutch and Roth 1990). Thus, L-DOPA effects upon generation of excess dopamine in the prefrontal cortex and excess stress-related hormones may be important factors in the psychiatric disturbances which can develop with L-DOPA therapy for Parkinson's disease. The present findings point to the importance of clinical studies of L-DOPA treatment which incorporate the use of radioactive isotopes and magnetic imaging techniques to address the issue of L-DOPA and dopamine activity in frontal cortex brain regions. Additionally, the possibility is suggested that the newer antipsychotic drugs such as clozapine which do not have a motoric liability (DeVeau-Geiss 1980) might be useful as adjuvant therapy to prevent L-DOPA-induced psychosis.

This research was supported by a VA Merit Review Grant, a NATO Cooperative Grant, and a Deutsche Forschungsgemeinschaft Grant (Hu 306/6/4-2480; FAPESP 90/3474 and CNPq).

References

- Ban TA (1976): Pharmacotherapy of schizophrenia. *Curr Psychiatr Ther* 16:163-175.
- Blair RDG (1989): *Drugs for the Treatment of Parkinson's Disease*. Berlin: Springer-Verlag.
- Borowsky B, Kuhn CM (1991): Monoamine mediation of cocaine-induced hypothalamo-pituitary-adrenal activation. *J Pharmacol Exp Ther* 256:204-210.
- Brady KT, Lydiard RB, Malcolm R, Bellenger JC (1991): Cocaine-induced psychosis. *J Clin Psychiatry* 52:509-512.
- Calne DB, Burton K, Beckman J, Martin WR (1984): Dopamine agonists in Parkinson's disease. *Can J Neurol Sci* 11:221-224.
- Carey RJ (1991): Chronic L-DOPA treatment in the unilateral 6-OHDA rat: Evidence for behavioral sensitization and biochemical tolerance. *Brain Res* 568:205-214.
- Carlsson A (1993): Thirty years of dopamine research. *Adv Neurol* 60:1-10.
- Deutch AY (1993): Prefrontal cortical dopamine systems and the elaboration of functional corticostriatal circuits: Implications

- for schizophrenia and Parkinson's disease. *J Neural Transm* 91:197-221.
- Deutch AY, Roth RH (1990): The determinants of stress-induced activation of the prefrontal cortical dopamine system. In Uyling HBM, Van Eden CG, De Bruin JPC, et al (eds), *The Prefrontal Cortex: Its Structure, Function, and Pathology*. Amsterdam: Elsevier Science Publishers, pp 367-393.
- DeVeugh-Geiss J (1980): Tardive dyskinesia and related involuntary movement disorders. In DeVeugh-Geiss J (ed), *The Long-Term Effects of Antipsychotic Drugs*. Boston: John Wright.
- Dilsaver SC (1993): Antipsychotic agents: A review. *Am Fam Phys* 47:199-204.
- Dunnett SB, Bjorklund A (1983): Conditioned turning in rats: Dopaminergic involvement in the initiation of movement rather than the movement itself. *Neurosci Lett* 41:173-178.
- Engber TM, Susel Z, Juncos JL, Chase TN (1989): Continuous and intermittent levodopa differentially affect rotation induced by D-1 and D-2 dopamine agonists. *Eur J Pharmacol* 168:291-298.
- Fahn S (1989): Adverse effects of levodopa in Parkinson's disease. In Calne DB (ed), *Handbook of Experimental Pharmacology*, vol 88. Berlin: Springer Verlag, pp 385-414.
- Feldon J, Weiner O (1992): From an animal model of an attentional deficit towards new insights into the pathophysiology of schizophrenia. *J Psychiatr Res* 26:345-366.
- Goldstein M, Deutch AY (1992): Dopaminergic mechanisms in the pathogenesis of schizophrenia. *FASEB J* 6:2413-2421.
- Gropetti A, Flauto C, Parati E, Vescovi A, Rusconi L, Parenti M (1986): Dopamine receptor changes in response to prolonged treatment with L-DOPA. *J Neural Transm Suppl* 22:33-45.
- Heinsbroek RP, van Haaren F, Feenstra MG, Boon P, van den Poll NE (1991): Controllable and uncontrollable footshock and monoaminergic activity in the frontal cortex of male and female rats. *Brain Res* 551:247-255.
- Heritch AJ (1990): Evidence for reduced and dysregulated turnover of dopamine in schizophrenia. *Schizophr Bull* 16:605-615.
- Hurlbut KM (1991): Drug-induced psychoses. *Energ Med Clin North Am* 9:31-52.
- Jenner P, Boyce S, Marsden CD (1986): Effect of repeated L-DOPA administration on striatal dopamine receptor function in the rat. In Fahn S (ed), *Recent Developments in Parkinson's Disease*. London: Raven Press, pp 189-203.
- Kalivas PW, Duffy P (1989): Similar effects of daily cocaine and stress on mesocorticolimbic dopamine neurotransmission in the rat. *Biol Psychiatry* 25:913-928.
- Karoum F, Freed WJ, Chuang LW, Cannon-Spoor E, Wyatt RJ, Costa E (1988): D-DOPA and L-DOPA similarly elevate brain dopamine and produce turning behavior in rats. *Brain Res* 440:190-194.
- Keneyuki H, Yokoo H, Tsuda A, Yoshida M, Mizuki Y, Yamada M, Tanaka M (1991): Psychological stress increases dopamine turnover selectively in mesoprefrontal dopamine neurons of rats: Reversal by diazepam. *Brain Res* 557:154-161.
- Koob GF (1992): Drugs of abuse: Anatomy, pharmacology and function of reward pathways. *Eur J Pharmacol* 13:177-184.
- Melamed E, Hefti F (1984): Mechanism of action of short and long-term L-DOPA treatment in parkinsonism: Role of the surviving nigrostriatal dopaminergic neurons. *Adv Neurol* 40:149-157.
- Moldow RL, Fischman AJ (1987): Cocaine induced secretion of ACTH, beta-endorphin, and corticosterone. *Peptides* 8:819-822.
- Nakayama M (1993): Changes of the dopamine uptake sites in the rat striatum induced by repeated methamphetamine administration: A neurochemical approach to a mechanism of relapse. *Hokkaido J Med Sci* 68:507-519.
- Olney JW, Zorumski CF, Stewart GR, Price MT, Wang GJ, Labruyere J (1990): Excitotoxicity of L-DOPA and 6-OHDA: Implications for Parkinson's and Huntington's diseases. *Exp Neurol* 108:269-272.
- Pfeiffer R (1992): Optimization of levodopa therapy. *Neurology* 42 (suppl 1):39-43.
- Rao ML, Gross G, Halaris A, Huber G, Marler M, Strebel B, Braunig P (1993): Hyperdopaminergia in schizophreniform psychosis: A chronological study. *Psychiatr Res* 47:187-203.
- Sarre S, Herregodts P, Devrieze A, et al (1991): L-DOPA in striatum and substantia nigra of hemi-Parkinson rats: bioavailability and biotransformation studied by microdialysis. In Rolfe H, Westerink B, Drijfhout WJ (eds), *Monitoring Molecules in Neuroscience: Proceedings of the 5th International Conference on In Vivo Methods*. Groningen: University Center for Pharmacy, pp 407-412.
- Sarnayai Z, Biro E, Penke B, Telegdy G (1992): The cocaine-induced elevation of plasma corticosterone is mediated by endogenous corticotropin-releasing factor (CRF) in rats. *Brain Res* 589:154-156.
- Satel SL, Edell WB (1991): Cocaine-induced paranoia and psychosis proneness. *Am J Psychiatry* 148:1708-1711.
- Sato M (1992): A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis. *Ann NY Acad Sci* 654:160-170.
- Schwartz R, Bonatz AE, Carey RJ, Huston JP (1991): Relationship between indices of behavioral asymmetries and neurochemical changes following mesencephalic 6-hydroxydopamine injections. *Brain Res* 554:46-55.
- Snyder S (1976): The dopamine hypothesis of schizophrenia; focus on the dopamine receptor. *Am J Psychiatry* 133:197-201.
- Swardlow NR, Vaccarino FJ, Amalric M, Koob GR (1986): The neural substrates for the motoractivating properties of psychostimulants: A review of recent findings. *Pharm Biochem Behav* 25:233-248.
- Thierry AM, Tassin JP, Blanc G, Glowinski J (1976): Selective activation of mesocortical DA system by stress. *Nature* 263:242-244.