Diminished Serotonin-Mediated Prolactin Responses in Nondepressed Stroke Patients Compared With Healthy Normal Subjects

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Background and Purpose—The purpose of this study was to use hormonal responsiveness to $d$-fenfluramine ($d$-FEN) challenge as a measure of central serotonin (5-HT) function in a comparative evaluation of serotonergic abnormalities between stroke patients and healthy elderly normal subjects to test the hypothesis that stroke may be associated with diminished serotonergic functioning.

Methods—Eight nondepressed medically stable stroke patients and 12 healthy volunteers completed a single-blind, placebo-controlled, fixed-order, crossover design challenge test with 30 mg of oral $d$-FEN. Baseline prolactin (PRL) and cortisol (CORT) and hormonal responses to $d$-FEN and placebo were measured at hourly intervals over a 4-hour period. Cardiovascular responses (pulse and blood pressure) and behavioral responses were also recorded at the same time points.

Results—The 2 groups were comparable in demographics, body weight, plasma drug concentration, and behavioral and CORT responses. A 3-way ANOVA for repeated measures showed group differences for baseline adjusted PRL responses (change of scores from baseline). Peak PRL responses (maximal PRL change from baseline scores after treatment with $d$-FEN) in nondepressed stroke patients were attenuated compared with healthy elderly subjects, suggesting diminished serotonergic responsiveness in stroke patients.

Conclusions—The demonstrated serotonergic hypofunctioning poststroke may contribute to the high incidence of depressive disorders in stroke patients. Serotonergic agents may have a role in augmentation of stroke recovery. (Stroke. 1998;29:1293-1298.)

Key Words: hormones ■ serotonin ■ stroke

There is evidence from preclinical and clinical studies that brain vascular lesions induce abnormalities in serotonergic functioning.1–5 Excessive release of 5-HT from ischemic neurons during the acute phase of infarction and the diminished monoamine synthesis due to enzyme inhibition of enzymes during ischemia have been postulated to account for depletion of 5-HT after cerebral infarction.1 5-HT has been implicated in the regulation of mood,6 sleep, and appetite,7 as well as in the expression of brain-derived neurotrophic factor.8 Therefore, diminished serotonergic functioning associated with vascular brain lesions may contribute to emotional and physical consequences of stroke.

Most of our knowledge concerning serotonergic abnormalities associated with vascular lesions is derived from animal experiments1–3 and CSF studies involving stroke patients.4,5 These studies could be criticized on a number of methodological grounds. Animal models of stroke involved very young animals without any chronic diseases such as hypertension or genetic predisposition to such diseases.9 Furthermore, there is considerable variation among species in neuronal and biochemical responses to cerebral ischemia. Hence, animal models of stroke may have limited relevance to humans. CSF studies are limited by the fact that metabolite concentration ratios in CSF obtained from lumbar puncture may not be representative of central 5-HT activity.10

The neuroendocrine challenge paradigm provides a better measure of net physiological responsiveness of the central 5-HT system in comparison to platelet and early positron emission tomography studies that are used to study specific 5-HT receptors. Neuroendocrine challenge tests have been designed on the basis of abundant evidence substantiating the stimulatory role of 5-HT in the release of PRL, adrenocorticotropic hormone, and CORT in animals and humans.11,12 FEN is an anorectic drug that enhances 5-HT function by both increasing release and inhibiting reuptake. A direct action on 5-HT receptors has also been reported.13,14 The
racemic compound of FEN (d,l-FEN) is a mixture of d and l isomers. Because the l isomer has dopamine-antagonist properties,15 the d isomer has been reported to be more specific to the 5-HT system than d,l-FEN. Hence, PRL and CORT responses induced by d-FEN might be assumed to be mediated solely by specific activation of the 5-HT system. d-FEN induces a dose-dependent increase in plasma PRL levels that has been shown to be attenuated by pretreatment with the 5-HT2A/2C receptor antagonist ritanserin16 or the 5-HT1A receptor antagonist pindolol,17 suggesting that this response is mediated by a serotonergic mechanism.

Another advantage of using oral d-FEN as a 5-HT probe is that 30 mg of oral d-FEN is well tolerated in healthy normal subjects without any spontaneously reported adverse effects.18 Furthermore, d-FEN is considered to be an appropriate probe to study net presynaptic and postsynaptic serotonergic activity because serotonergic agents that act primarily on receptors indicate receptor responsiveness and may not necessarily reflect the net functional activity of the system.19 5-HT precursors such as tryptophan and 5-hydroxytryptophan (5-HTPP) are not specific to 5-HT neurons,20 and side effects of intravenous clomipramine, such as nausea and vomiting,21 and the development of early tolerance to the PRL-releasing effect of fluvoxamine22 reduce their practical utility as 5-HT probes.

The purpose of this study was to examine net central serotonergic function in stroke patients by comparing PRL and CORT responses to oral d-FEN in nondepressed stroke patients and healthy normal subjects to test the hypothesis that stroke may be associated with diminished serotonergic functioning.

Subjects and Methods
This study represents part of a larger investigation examining serotonergic function in stroke patients with and without depression and in healthy elderly subjects. Eight nondepressed stroke patients (4 women, 4 men) with a mean age of 73 ± 7.56 years and 12 healthy volunteers (9 women, 3 men) with a mean age of 71.08 ± 6.78 years participated in a single-blind, fixed-order, placebo-controlled d-FEN challenge test.

Subject Selection
Stroke patients were recruited from the stroke rehabilitation unit of the Queen Elizabeth Hospital, Toronto, and from the community through local distribution of posters and media advertisements. The diagnosis of stroke was confirmed by clinical examination by a qualified neurologist and by CT scan findings. A minimum of 1 month had elapsed since onset of the stroke and inclusion of subjects into the study. Stroke includes thrombotic or embolic infarct or cerebral hemorrhage. These patients were screened for the presence of a depressive disorder by using the Center for Epidemiological Studies of Depression Scale, a self-report instrument.23 Stroke subjects who scored 15 or less on the Center for Epidemiological Studies of Depression Scale were considered to be nondepressed and were included in this analysis. The Barthel Index was used to assess functional abilities of stroke patients,24 and cognitive deficits were evaluated using the Mini-Mental State Examination.25 CT scan findings pertaining to laterality and location of lesions were obtained from the radiologist’s report. Physical examination and laboratory tests were performed to rule out any other major neurological and medical diseases.

Exclusion criteria were as follows: (1) inability to speak or understand English, (2) severe cognitive deficits as determined by the Mini-Mental State Examination (scores < 15), (3) severe impairment in comprehension and expressive language, (4) severe essential hypertension (diastolic blood pressure ≥ 120 mm Hg),26 (5) uncontrolled diabetes mellitus, (6) myocardial infarction within the past 2 months, (7) hypothyroidism, (8) other neurological illnesses, (9) a history of alcohol or drug abuse, (10) schizophrenia or other psychoses, (11) a lifetime history of depressive disorder, or (12) the use of medications known to produce changes in the 5-HT system or PRL concentrations, including ketanserin, methyldopa, estrogen, glucocorticoids, thyroid supplementation, metoclopramide, cimetidine, antipsychotic, and antidepressive medications.

Healthy normal subjects were recruited by media advertisements and word of mouth. An honorarium was provided for participating in the study. Normal control subjects were screened for severe mental disorders, substance abuse, and also for a family history of mental disorders, using a semistructured interview. Appropriate laboratory tests and a physical examination were performed to rule out any severe medical illnesses. These subjects were not receiving any medications that could alter 5-HT function or PRL secretion as mentioned above. Signed informed consent as approved by the local ethics committee was obtained from all subjects who participated in the study.

Challenge Tests
Identical challenges with single-dose placebo and d-FEN were carried out under single-blind conditions separated by a consistent interval of 24 hours. In all cases d-FEN, which has a long carryover effect, was administered second, although both rater and patient were kept blind to the order. Challenge tests were conducted at the Clinical Investigation Unit of The Toronto Hospital. Participants remained fasting from midnight on the night before testing. They attended the test center at 8 AM. A breakfast low in tryptophan (apple sauce, jello, orange juice) was served to prevent hormonal changes due to hypoglycemia. They were not allowed to take caffeine or nicotine, and they remained awake during the test sessions. A cannula was inserted into the anterior cubital vein, and a physiological saline drip was begun. Blood samples were taken 30 minutes after drug administration (zero time) before the oral or placebo and at hourly intervals for 4 hours postchallenge. A fixed dose of 30 mg of oral d-FEN was used because it is considered to be equivalent to the dose of l isomer in 60 mg oral d,l-FEN.27 The sampling period was limited to 4 hours postchallenge on the basis of the fact that peak PRL response occurs at 4 hours after oral administration of d-FEN.28 The blood sample drawn at 3 hours after administration of d-FEN was selected for determination of d-FEN and d-nor-FEN levels because the pharmacokinetics of oral d-FEN show a maximal plasma level of its active metabolites d-FEN and d-nor-FEN 2 to 4 hours after treatment with d-FEN.29 Vital signs (blood pressure and pulse) and self-rated behavioral responses (drowsy, anxious, sad, or high) were also recorded at these time points using a visual analogue scale.

Assays
Each blood sample was centrifuged, and plasma was stored at −25°C before assays. Each sample was assayed for PRL and CORT by quantitative enzyme immunoassay using transferable solid-phase technology. The kits were supplied by Sychron Enzyme Linked Immunosorbent Assay (SYNELISA-USA). The mean intra- and interassay coefficients of variation for plasma PRL were 5.0% and 7.8%, respectively, and sensitivity was 2 mg/mL. The intra-assay
and interassay coefficients of variation for plasma CORT were 5.2% and 7.1%, respectively, and sensitivity was 0.5 mg/mL. Levels of d-FEN and d-nor-FEN were determined by gas liquid chromatography using a nitrogen selective detector according to the methods of Kerbs et al (1984) with minor modifications. The intra- and interassay coefficients of variation for FEN at 15 mg/mL were 2.7% and 2.7%, respectively, and for nor-FEN at 15 mg/mL were 3.7% and 5.4%, respectively. The lower detection limit was 2 mg/mL.

Data Analysis
PRL and CORT responses were calculated for 2 outcome measures: (1) mean baseline-adjusted net changes (change scores from baseline) and (2) peak hormonal responses (baseline values subtracted from the maximum increase in after treatment with d-FEN). Baseline-adjusted net changes in PRL and CORT concentrations in placebo and drug conditions were compared between 2 groups using 3-way ANOVA for repeated measures. -AUC for hormonal responses to d-FEN was calculated using the trapezoid rule. Intergroup differences in AUC values between each of the time point were compared using the Student t test. Peak hormonal concentrations between groups were compared using Student t tests. Comparisons of continuous and categorical variables were performed using Student’s t tests and χ² tests, respectively. Statistical significance of all tests was set at P<0.05 (2-tailed). Data were analyzed using Statistical Program for the Social Sciences (SPSS, Inc).

Results
Sample characteristics of 8 nondepressed stroke patients are summarized in Table 1. As shown in Table 2, stroke patients did not significantly differ from healthy normal subjects in age (t=0.59, df=18, P=0.56), sex (χ²=1.31, df=1, P=0.25), body weight (t=1.64, df=18, P=0.12), or plasma concentration of d-FEN or d-nor-FEN (t=0.77, df=15, P=0.45). The mean of baseline PRL concentration in both drug and placebo conditions (t=1.24, df=18, P=0.23) and the mean of baseline CORT in both drug and placebo conditions (t=70, df=18, P=0.49) were comparable between groups.

PRL Responses
Baseline-adjusted net PRL responses to d-FEN and placebo over 240 minutes are shown in Figure 1. A 3-way ANOVA revealed a main effect of drug (F=4.47; df=1,18; P=0.043), time (F=5.65; df=3,54; P=0.002), a drug-time interaction (F=5.36; df=3,54; P=0.003), and group-time interaction (F=8.90; df=3,54; P=0.005), suggesting an increase in PRL concentration in response to d-FEN and also intergroup differences in PRL responses. A 2-way ANOVA was per-

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of 8 Nondepressed Stroke Patients</th>
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<td>Patient/Age/Sex</td>
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<tr>
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MMSE indicates Mini-Mental State Examination.

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<th>TABLE 2. Comparison of Characteristics Between Nondepressed Stroke and Healthy Normal Subjects</th>
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<td>Variable</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>Body weight, kg</td>
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<tr>
<td>d-FEN and d-nor-FEN</td>
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<td>Baseline PRL on placebo/drug</td>
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<td>Baseline CORT on placebo/drug</td>
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Figure 1. Baseline-adjusted net PRL responses to d-FEN and placebo over 240 minutes.
formed to determine whether the observed group-time interaction was caused by different PRL responses to placebo or to d-FEN. Group-time interaction was significant for baseline-adjusted PRL responses to d-FEN ($F=5.49; df=3.54; P=0.002$) but not for baseline-adjusted PRL responses to placebo ($F=1.25; df=3.54; P=0.30$). AUC analysis of PRL responses from time points 180 to 240 minutes after the administration of d-FEN demonstrated significantly higher values in healthy normal subjects than in nondepressed stroke patients ($t=2.43, df=18, P=0.026$). Similarly, peak PRL responses to d-FEN in healthy normal subjects were significantly higher than in nondepressed stroke patients ($t=2.26, df=12.04, P=0.043$), suggesting blunted PRL responses in nondepressed stroke patients.

### CORT Responses

Figure 2 summarizes the CORT responses to d-FEN and placebo. For baseline-adjusted CORT changes, ANOVA showed a main effect of drug ($F=24.29; df=1.18, P=0.00$), but there was no group effect ($F=0.31; df=1.18, P=0.59$), group-time interaction ($F=0.29; df=3.54; P=0.83$), group-drug interaction ($F=0.21; df=1.18, P=0.65$), or group-time-drug interaction ($F=0.96; df=3.54; P=0.42$), indicating an absence of intergroup differences in CORT responses. Furthermore, there were no differences in peak CORT responses between the 2 groups ($t=0.63, df=18, P=0.54$).

### Cardiovascular and Behavioral Responses

None of the stroke patients or the healthy normal subjects experienced unpleasant side effects or reported any change in mood state or alertness after treatment with d-FEN. There were no significant differences in heart rate (group-drug-time interaction: $F=0.62; df=4.56; P=0.65$), systolic blood pressure (group-drug-time interaction: $F=1.36; df=4.56; P=0.26$), or diastolic blood pressure (group-drug-time interaction: $F=0.83; df=4.60; P=0.51$).

### Discussion

This study demonstrates a blunted PRL response to the acute administration of 30 mg of oral d-FEN in medically stable nondepressed chronic stroke patients compared with healthy normal subjects. Since PRL responsiveness to d-FEN reflects brain 5-HT function, the blunted PRL responses observed suggest diminished serotonergic function in stroke patients. However, it could be argued that the blunted PRL responses observed in stroke patients might be mediated by nonserotonergic mechanisms. Ischemic damage to the hypothalamic-pituitary axis resulting in decreased biosynthesis, storage, or release of PRL, poor sensitivity of the pituitary lactotroph to PRL-releasing factor, enhanced dopamine activity, or hypercortisolism could contribute to blunted PRL responses. When one considers the fact that PRL responses with placebo reflect baseline PRL synthesis, storage, and release in the normal resting state, the comparable PRL responses to placebo administration in both groups suggest that the diminished PRL responsiveness in stroke patients is not because of any anatomic or functional deficit in the hypothalamic-pituitary axis. In addition there is no firm evidence in the literature to suggest an alteration in sensitivity of pituitary lactotroph to PRL-releasing factor as a remote effect of brain vascular lesions. Furthermore, 5-HT activation has been reported to be associated with a reduction in dopamine function, and basal PRL concentrations, which may be under tonic control of dopamine system, were comparable between stroke patients and healthy normal subjects. It is also unlikely that PRL responses are blunted due to stroke-related hypercortisolism because there were no intergroup differences in either basal CORT concentrations or CORT responses to placebo or d-FEN. Hence, it is reasonable to think that attenuation of PRL responses to d-FEN challenge in stroke patients might be directly related to diminished serotonergic functioning. Previous CSF studies reported an increased CSF-5H1AA content in the first few days after the onset of stroke. This increased CSF-5H1AA content is considered to be a reflection of increased release of 5-HT in the affected area leading to depletion of 5-HT. When one takes into account these considerations in combination with our findings of serotonergic hypofunction in chronic stroke patients, it might be suggested that the association between diminished serotonergic function and stroke may be independent of time since stroke in at least some stroke patients.

Several mechanisms could be postulated to explain the diminished serotonergic responsiveness in nondepressed stroke patients. Focal vascular lesions may alter the serotonergic functioning of anatomically intact and distant brain structures. In this study, 1 patient had a pontine lesion and 7 patients had frontal lesions. A pontine lesion may have damaged serotonergic projections from the dorsal and median raphe to the hypothalamus, resulting in diminished PRL release to 5-HT activation. Frontal lesions may have caused direct retrograde changes in 5-HT cell bodies of the raphe nuclei, which in turn could alter serotonergic responsiveness.
at the hypothalamus. The other possibility is that frontal lesions may have caused disruption of efferent pathways from the orbitofrontal cortex to serotonergic raphe nuclei or to the hypothalamus. The preponderance of left-sided lesions in our stroke sample, and the observation of diminished serotonergic functioning, is consistent with previous studies reporting right-left asymmetry in serotonergic functioning in healthy normal subjects and stroke patients. There is evidence that the right frontal cortex has a significantly higher number of imipramine-binding sites than the left frontal cortex. Furthermore, patients with right-sided lesions have been found to have greater cortical 5-HT$_2$ receptor binding than patients with left-sided lesions 16 months poststroke. Hence, it is possible that left-sided lesions may cause greater depletion than right-sided lesions, because of failure in upregulation of 5-HT receptors after left-sided lesions and also because of a relative increase in 5-HT binding sites in the right hemisphere compared with the left hemisphere.

The effect of lesions on the 5-HT system may also depend on the volume of the infarcted area. We did not repeat the CT head scans at the time patients entered the study. As a result we could not accurately assess the relationship between lesion volume and serotonergic responsiveness, since lesion volume may have changed between the time of the stroke (when the CT scans were performed) and the time of the study. Another important issue is that, besides stroke lesions, comorbid diseases such as diabetes mellitus and hypertension may influence serotonergic function in stroke patients. Prolonged psychosocial stress associated with physical and cognitive impairment in stroke patients may lead to downregulation of 5-HT$_1$A receptors. We did not quantify cognitive and physical functioning in the healthy control subjects so we are unable to determine whether impairment-related stress may have contributed to PRL differences between the groups. A reduction in precursor supply due to poor intake of tryptophan or inhibition of tryptophan uptake or tryptophan hydroxylase due to brain ischemia may result in decreased 5-HT synthesis. Unfortunately, we did not have measures of these variables to compare between the 2 groups. Hence, factors other than the stroke lesion may also have contributed to diminished serotonergic responsiveness in the group of stroke patients.

In contrast to PRL responses, CORT responses failed to distinguish between the nondepressed stroke group and the healthy control group. This might be explained by the fact that d-FEN–induced PRL and CORT responses might involve different 5-HT receptor subtypes or mechanisms. Some studies suggest that PRL and CORT responses are mediated by 5-HT$_1$A and 5-HT$_2$A/C respectively. Hence, it is possible that blunted PRL response in stroke patients might be caused by selective vulnerability of 5-HT$_1$A receptors to ischemic neuronal damage because the hippocampus, a brain structure that is selectively vulnerable to ischemia, has a high density of 5-HT$_1$A receptors. However, 5-HT$_3$/5-HT$_2$C receptors also have been implicated in PRL secretion, and d-FEN used in this study is not specific to any receptor subtype. It is not possible to determine from this experiment which receptor subtypes are affected in stroke patients. Van de Kar et al (1985) proposed that cortisolemia effect of d,l-FEN might be due to direct stimulation of the adrenal gland or d,l-FEN–induced hypoglycemia in addition to serotonin activation. Precautions were taken to minimize hypoglycemic effects of d-FEN during the challenge test by providing a light breakfast at the beginning of the study. However since corticotropin and corticotropin-releasing factor responses were not examined, it is not possible to rule out peripheral mechanisms involved in the mediation of CORT responses in this study. Hence, normal CORT responses in contrast to diminished PRL responses to d-FEN in stroke patients compared with normal subjects might be due to selective involvement of 5-HT subtypes and or direct stimulation of the adrenal gland.

We recognize that this study has methodological shortcomings that limit the validity of inferences beyond the sample analyzed. First, the stroke patients participating in the study cannot be considered to be a random sample. Second, the sample size is small and heterogeneous in lesion characteristics, with a preponderance of left-sided lesions and also a variation in time since stroke. Third, there are several possible differences between stroke patients and healthy subjects such as comorbid physical illnesses and tryptophan status, which were not measured but which may have affected the results. Hence, the findings of the study should be considered preliminary.

Despite these shortcomings, this study has several implications. To the best of our knowledge, this is the first study to examine central serotonergic responsiveness in stroke patients. The findings of serotonergic hypofunction in stroke patients may explain why a significant proportion of stroke patients develop major depressive illnesses and emotional lability, which are believed to be associated with central 5-HT deficiency. Furthermore, when one takes into account the efficacy of specific 5-HT reuptake inhibitors in the treatment of poststroke depres- sion and the demonstrated mood-independent serotonergic hypofunction in stroke patients, this abnormality may be considered both a trait and state marker of poststroke depression. The observed diminished serotonergic function in stroke patients may have adverse consequences on stroke recovery because recent studies suggest that the 5-HT$_2$A receptors may play a role in the expression of brain-derived neurotrophic factor and neuronal survival and that 5-HT$_1$A receptors may limit neuronal damage after cortical ischemia. Furthermore, fluoxetine, a selective 5-HT reuptake inhibitor, was found to be superior to maprotiline, an α-adrenergic antidepressant, in augmentation of functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy.

Therefore the role of specific 5-HT reuptake inhibitors and 5-HT$_1$A agonists in augmentation of neurological and functional recovery in stroke patients are the potential areas for future investigations.

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