Sustained Antidepressant Effect of PEA Replacement

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Phenylethylamine (PEA), an endogenous neuroamine, increases attention and activity in animals and has been shown to relieve depression in 60% of depressed patients. It has been proposed that PEA deficit may be the cause of a common form of depressive illness. Fourteen patients with major depressive episodes that responded to PEA treatment (10–60 mg orally per day, with 10 mg/day selegiline to prevent rapid PEA destruction) were reexamined 20 to 50 weeks later. The antidepressant response had been maintained in 12 patients. Effective dosage did not change with time. There were no apparent side effects. PEA produces sustained relief of depression in a significant number of patients, including some unresponsive to the standard treatments. PEA improves mood as rapidly as amphetamine but does not produce tolerance.

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The administration of phenylethylamine (PEA) rapidly improves mood and relieves depression in 60% of depressed patients, according to recent open studies.[1–3] In these studies, subjects had been pretreated with low doses (10 mg) of selegiline (L-deprenyl) to prevent rapid PEA metabolism. At this dose, selegiline is a selective inhibitor of monoamine oxidase (MAO) type B, has no antidepressant effects, and does not require a low-tyramine diet. The PEA precursor phenylalanine (in combination with selegiline) also has been found useful in the treatment of depression.[4,5] PEA, an endogenous neuroamine, may function as a neurohormone that maintains energy, attention, and mood.[3,6–8] PEA is structurally similar to amphetamine (α-methylphenethylamine), and it produces similar pharmacological effects. PEA is selectively metabolized by MAO-B to phenylacetic acid (PAA). Phenylacetic acid levels are decreased in the cerebrospinal fluid[9] and the plasma[10–12] of depressed subjects; studies of PAA urinary excretion indicate that the phenylalanine-PEA pathway may be hypofunctional in about 60% of depressed patients, whether unipolar or bipolar.[13–17] Fischer, Sabelli, and co-workers thus proposed that a deficiency in PEA production is the cause of a subtype of affective illness responsible for a large proportion of unipolar and bipolar depressive episodes.[3,7,18] On the basis of the greater responsiveness of atypical depressions to MAO

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inhibitors, Klein[19] suggested that these clinical features are associated with a deficiency or dysregulation of PEA. PEA administration may thus represent a physiological treatment of depression, that is, the replacement of the deficient chemical, much as insulin is used to treat diabetes.

A previous study with PEA[1] demonstrated rapid elevation of mood and effective antidepressant response in 6 of 10 patients; PEA was discontinued after remission. In a second study,[2] the administration of PEA relieved depression in 15 of 22 patients with major depression (unipolar or bipolar). Among responders, symptom amelioration occurred within days, and patients no longer met criteria for major depressive episode at 2–3 weeks. Thirteen of these 15 responders had previously failed to respond to a wide variety of antidepressants. Patients who took PEA reported no anticholinergic, sexual-inhibitory, or cardiovascular side effects. Of these 15 subjects, one became manic and 2 relapsed within a month. The issue of tolerance was not addressed by these time-limited studies. Tolerance develops to the mood-elevating effects of the PEA synthetic analogue amphetamine but has not been observed in animals treated with PEA.[3] Here we demonstrate that tolerance does not develop in depressed patients who responded to PEA.

METHODS

Our sample consisted of 14 outpatients (8 women and 6 men, ages 29 to 61 years) with recurrent major depressive episodes meeting DSM-IV criteria for unipolar major depressive disorder (10 subjects) or bipolar disorder I or II (4 subjects). Patients had been successfully treated with PEA plus selegiline, with the depressive episode in full remission for 1 month or more. All patients received selegiline (5 mg bid) plus 10 to 60 mg of PEA per day, according to clinical response, administered in divided doses (2.5–20 mg) before 5:00 P.M. to avoid interfering with sleep. Although these patients were in remission after 4 weeks of PEA treatment, no attempts had been made to suspend the treatment because all of them had chronic and/or recurrent depressions. Efficacy was defined as complete remission from depression, specified as 1) not meeting DSM-IV criteria for major depressive episode; and 2) scoring 10 or lower on the Hamilton Rating Scale for Depression (Ham-D).

Initial diagnosis had been made by clinical interview assisted by ratings on the Ham-D. Subjects with concomitant physical or mental illness were excluded. Before beginning PEA treatment, patients had received a physical examination, electrocardiogram, blood chemistry, complete blood count, and urinalysis, and had washed out current antidepressant medications for at least 10 days (2 weeks for MAO inhibitors, 5 weeks for fluoxetine). Patients had a stimulant challenge test, which consisted of the oral administration of amphetamine (5 to 20 mg twice a day for 2 days) and was considered positive (mood elevation) in all cases; this test had been performed usually weeks prior to PEA treatment. An increase in mood or well-being (but not a simple increase in energy) is considered a predictive response to adrenergic-type antidepressants.[20] The daily urinary excretion of PAA was measured by using gas-liquid chromatography[9] prior to treatment, whenever full collections were available, but a large percentage of samples were discarded because measures of volume and creatinine indicated that the collection was not complete.

This research was conducted under the approval of the Food and Drug Administration. All patients learned about the medication through oral discussions and a written information sheet approved by the Medical Center Human Investigation Committee, and all had signed a written informed consent form. Patients were middle-class subjects with education beyond high school level and understood the experimental nature of the treatment. Patients had received prior treatment for depression with several medications, including tricyclic antidepressants, serotonin reuptake inhibitors, and MAO inhibitors.

RESULTS

Of the 14 subjects who were euthymic or only minimally depressed after 4 weeks of treatment as previously reported,[2] 12 were euthymic when reexamined 20 to 50 weeks later (Table 1). None of the subjects had required an increase in dosage. One subject relapsed while taking PEA and another man, Mr. C., relapsed when he discontinued it, as described below. Patients continued to experience therapeutic effects with PEA administration, including increases in energy, concentration, motivation, sexual drive, and sleep. There was also a clear shift in cognitive functions, and several patients have made substantial changes in their lives.

No patient reported nausea, fatigue, inhibition of sexual function, agitation, excitement, or euphoria. There were no increases or decreases in blood pressure, no significant tachycardia, and no important changes in appetite or weight. Although several subjects lost the weight they had gained with previous antidepressants, one patient gained weight during treatment.

Twenty-four-hour urinary samples were available in

TABLE 1. Sustained antidepressant effect of PEA replacement

Age	Sex	Diagnosis	Months in Remission	Dosage (mg)
61	M	Bipolar II, alcoholism	10	50–60
49	F	Unipolar	19	50
38	M	Bipolar I	17	60
39	M	Major depressive disorder and dysthymic disorder	6	20
38	F	Bipolar II	14	40
29	F	Major depressive disorder and dysthymic disorder	8	60
45	F	Bipolar II	Relapse at 10 weeks	20–60
33	F	Unipolar, panic disorder	17	60
31	M	Unipolar, panic disorder, schizoid	18	60
29	M	Unipolar, narcissistic personality disorder	13	60
37	F	Unipolar	15	40–50
35	F	Atypical unipolar, obsessive-compulsive disorder, autoimmune disease, dissociative disorder not otherwise specified	6	40
34	M	Major depressive disorder	Relapse at 8 weeks	30
44	F	Major depressive disorder	7	10

only 9 of the subjects studied prior to treatment. Of these, PAA excretion was low in only 4 cases.

CASE REPORTS

Case 1. Mr. A. is a 38-year-old man with bipolar disorder, alcoholism (in remission), and a history of serious suicide attempts. Lithium controlled his manias, but he has had numerous episodes of depression requiring multiple hospitalizations. During these episodes, PAA excretion varied within the range of 70 to 200 mg, considered normal in our laboratory. On admission to the PEA trial, he was depressed (Ham-D = 18, Global Assessment of Functioning [GAF] = 61). Treatment with PEA (60 mg/day) rapidly relieved his depression (Ham-D = 10, GAF = 70 after 4 weeks; Ham-D = 2, GAF = 90 after 12 weeks). Response has been maintained 17 months after initiation of treatment.

Case 2. Mrs. B. is a 44-year-old woman with chronic major depressive disorder with atypical features. Her illness began at age 37 and had proven unresponsive to all medical treatments, including nortriptyline, sertraline, fluoxetine, and paroxetine. She had experienced marked side effects with a variety of medications, including but not limited to psychotropic agents. She responded immediately to PEA 2.5 mg bid, but higher doses initially produced agitation. Her depression has been under control with 5 mg bid for 7 months. Prior to treatment, her PAA excretion was found to be normal (167 mg/day).

Case 3. Mr. C. is a 34-year-old man with recurrent major depressive episodes. He had relapsed on fluoxetine but rapidly responded to PEA treatment (30 mg/day). He grew so confident that he took a vacation without carrying his medications. After 4 days of not receiving PEA, he made a suicidal gesture, which led to a discontinuation of this treatment. He has subsequently responded to nortriptyline.

Case 4. Mrs. D. is a 29-year-old woman with recurrent major depressive disorder, a history of attention-deficit disorder in childhood, and a current complaint of marked decrease in concentration. She rapidly responded to PEA treatment (60 mg/day), but after 2 weeks she interrupted treatment and remained euthymic for 6 weeks. After this time she noted a progressive impairment of mood and concentration. Restarted on PEA (60 mg/day), she recovered euthymia.

DISCUSSION

The results obtained in this small group of subjects indicate that PEA administration can control depressive symptomatology in patients with long-lasting or recurrent depressive episodes. Treatment response was rapid, within days of reaching effective doses, and it was sustained in 12 of the 14 subjects who had initially improved.

Some patients reported that mood remained elevated for weeks after they had interrupted PEA intake; others experienced a rapid deterioration of mood in a matter of days. Presumably PEA simply relieves the symptoms of depression, so continuous administration is necessary until the depressive episode terminates.

Like its synthetic analogue amphetamine, and in contrast to synthetic antidepressants, PEA increases energy and produces mood elevation as soon as it is administered. This rapid onset of action could significantly decrease the cost of patient care. PEA also differs from synthetic antidepressants in not producing significant side effects (anticholinergic symptoms, sexual inhibition, gastrointestinal disturbance, blood pressure lowering or elevation) and in requiring no special diet (because at the low doses used selegiline inhibits only MAO-B). PEA differs from amphetamine in that its chronic administration does not produce tolerance. PEA also differs from amphetamine in not inducing insomnia, significant appetite loss, artificial stimulation, or euphoria. As an endogenous neuroamine, PEA may be expected to have low toxicity, particularly if used as a replacement in cases of deficit. However, the existence of PEA deficit as a pathological entity remains a speculative hypothesis, as there is no clinical test to diagnose it.

The observed therapeutic efficacy of PEA supports the view that PEA deficit may play a role in the pathophysiology of depression in a significant number of patients, regardless of clinical presentation. Therapeutic responses to PEA were observed in both bipolar and unipolar subjects, with or without atypical features. We have found no relation, however, between a reduction in the urinary excretion of phenylacetic acid and therapeutic response to PEA. A relative PEA deficit could exist as the result of either reduced synthesis (in which case PAA excretion would be low) or excessive destruction (in which case PAA excretion would be elevated); similarly, insulin plasma levels can be low or high in diabetes.

Regardless of the possible significance of these studies for the role of PEA in the pathogenesis of depression, the rapid onset, sustained response, and paucity of side effects of PEA administration indicate the need for a double-blind, placebo-controlled study of this new treatment. Although PEA interacts with both norepinephrine and serotonin,[3] PEA replacement targets a very different physiological process than synthetic antidepressants. Hence, PEA treatment may provide new avenues in the treatment of affective disorders.

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