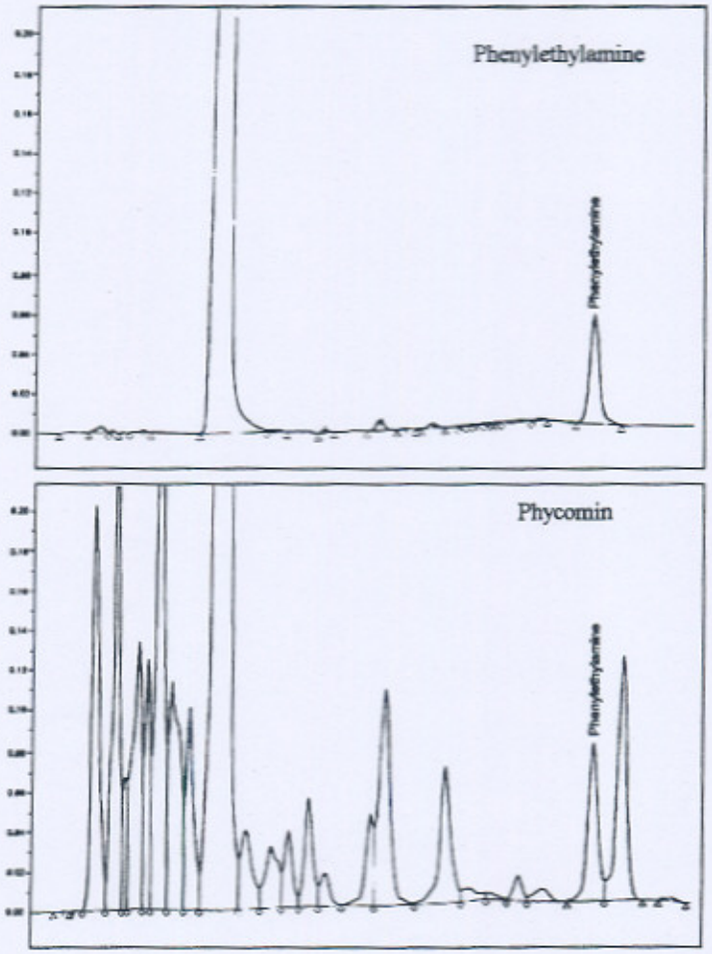
Aphanizomenon flos-aquae And The Nervous System
Attention deficit disorder, Depression and Mood elevation

One of the most commonly reported benefits of eating the blue-green algae *Aphanizomenon flos-aquae* is an increase in concentration and attention and an elevation of mood. In clinical cases, AFA has been reported to alleviate depression and attention deficit disorder.

Recently, it was discovered that AFA contains a significant concentration of phenylethylamine (PEA), an endogenous neuromodulating compound known to increase concentration, elevate mood and alleviate depression. PEA has been coined "the molecule of love." Desert Lake Technologies developed an extract that contains 5-7 mg/gram of PEA.



HPLC chromatogram of PEA standard and PEA in the AFA extract Aphanin™.

The following is a series of abstracts from peer-reviewed scientific papers demonstrating the importance of dopamine transmission in attention and mood, and the role of PEA in enhancing dopamine transmission, thereby increasing attention, elevating mood and alleviating depression.

ROLE OF DOPAMINE TRANSMISSION IN PLEASURE

Dopamine is one of the main transmitters responsible for the sensation of pleasure. Many compounds known to alleviate depression are known to enhance dopamine transmission. Dopamine is also associated with attention and concentration.

- The dopaminergic and opioidergic reward pathways of the brain are critical for survival since they provide the pleasure drives for eating, love and reproduction; these are called 'natural rewards' and involve the release of dopamine in the nucleus accumbens and frontal lobes. However, the same release of dopamine and production of sensations of pleasure can be produced by 'unnatural rewards' such as alcohol, cocaine, methamphetamine, heroin, nicotine, marijuana, and other drugs, and by compulsive activities such as gambling, eating, and sex, and by risk taking behaviors. Since only a minority of individuals become addicted to these compounds or behaviors, it is reasonable to ask what factors distinguish those who do become addicted from those who do not. It has usually been assumed that these behaviors are entirely voluntary and that environmental factors play the major role; however, since all of these behaviors have a significant genetic component, the presence of one or more variant genes presumably act as risk factors for these behaviors. Since the primary neurotransmitter of the reward pathway is dopamine, genes for dopamine synthesis, degradation, receptors, and transporters are reasonable candidates. However, serotonin, norepinephrine, GABA, opioid, and cannabinoid neurons all modify dopamine metabolism and dopamine neurons. We have proposed that defects in various combinations of the genes for these neurotransmitters result in a Reward Deficiency Syndrome (RDS) and that such individuals are at risk for abuse of the unnatural rewards. Because of its importance, the gene for the [figure: see text] dopamine D2 receptor was a major candidate gene. Studies in the past decade have shown that in various subject groups the Taq I A1 allele of the DRD2 gene is associated with alcoholism, drug abuse, smoking, obesity, compulsive gambling, and several personality traits. A range of other dopamine, opioid, cannabinoid, norepinephrine, and related genes have since been added to the list. Like other behavioral disorders, these are polygenically inherited and each gene accounts for only a small per cent of the variance. Techniques such as the Multivariate Analysis of Associations, which simultaneously examine the contribution of multiple genes, hold promise for understanding the genetic make up of polygenic disorders.

  Comings DE, Blum K. (2000) **Reward deficiency syndrome: genetic aspects of behavioral disorders**. Prog Brain Res 126:325-41.

- The goal of this review is to familiarize the reader about the potential involvement of the brain reward system (BRS) in symptoms of Major Depressive Disorder (MDD). The authors introduce a novel approach to study the pathophysiology of MDD that includes pharmacological probing of BRS pathways (e.g. d-amphetamine, hydromorphone) together with an elicited and measurable behavioral component (e.g. pleasant effects, increased energy, altered cognition). To this date, the major focus of MDD pathophysiology studies has been to characterize biological differences between healthy subjects and depressed patients such as alteration in the monoaminergic and endocrine systems. The relative importance of the various biological changes has not been elucidated, that is, linking these with specific behavioral manifestations in MDD have rarely been attempted. One core symptom of MDD is a decreased experience of pleasure or interest in previously enjoyed activities (i.e. anhedonia) such as work or hobbies, and is accompanied by decreased

motivation or drive. The BRS consists of the neural pathways involved in eliciting rewarding experiences in animals and humans. The hypothesis is that altered BRS function may be an underlying brain mechanism of the loss of pleasure/interest experienced in MDD, and will be manifested through an altered response to a BRS probe. The authors have examined BRS function in MDD by introducing a pharmacological probe (i.e. d-amphetamine/d-amph). Amphetamine is defined as a probe due to its ability to release dopamine within major components of the BRS (i.e. the mesocorticolimbic dopamine system.) In addition to the objective pharmacological effects (e.g. altered heart rate), BRS probes like d-amph elicit reliable and measurable behavior, that is, the hedonic effects. A review of the neurobiology of MDD, the BRS, the rationale for implicating the BRS in depressive symptoms, and preliminary data, are presented in this article.

Naranjo et al. (2001) **The role of the brain reward system in depression.** Prog Neuropsychopharmacol Biol Psychiatry (4):781-823.

PEA AND DOPAMINE

PEA enhances dopamine transmission, thereby alleviating symptoms of dopamine deficiency such as depression and attention deficit disorder.

- Experiments with local perfusion of the rat neostriatum and subsequent chromatography of the perfusate have shown that addition of beta-phenylethylamine (beta-PEA) to the perfusion medium in a concentration of 10^{-3} M enhanced spontaneous and inhibited the K+-induced release of 3H-dopamine preliminarily applied to the neostriatum. The stimulating effect of beta-PEA was Ca2+-dependent and was potentiated in sodium-free media. The inhibitory effect of beta-PEA on the K+-induced release of 3H-DA was abolished by haloperidol, a blocker of dopamine receptors. This fact allows one to suggest that this effect of beta-PEA is mediated by presynaptic dopamine autoreceptors. The data obtained indicate that beta-PEA can modulate the dopaminergic synaptic transmission depending on functional activity of dopaminergic neurons.

  Zharikova AD, Godukhin OV. (1984) **Presynaptic regulation of dopamine release by beta-phenylethylamine.** Biull Eksp Biol Med 98(11):574-6

- We quantified the effects amphetamine (AMPH), phenylethylamine (PEA), tyramine (TYR), octopamine (OCT) and DA, on initial rates of DA uptake (striatal minces), binding of [3H]mazindol to the neuronal uptake (NU) site (striatal membranes) and on DA and dihydroxyphenylacetic acid (DOPAC) efflux (striatal slices). In general, the order of potency for the three paradigms was: AMPH less than DA = TYR = PEA less than OCT. The Km values for uptake were positively correlated with the Ki values for inhibition of mazindol binding (r = 0.91; P less than .01) and with the potencies to induce DA efflux (r = 0.96; P less than .005). Potencies for inhibition of mazindol binding and for eliciting DA efflux also were highly correlated (r = 0.92; P less than .01). Correlations were lost if data for nomifensine (NOM), a NU inhibitor, were included in the analysis. Despite the significant correlations, AMPH, TYR, PEA and OCT Despite the significant correlations, AMPH, TYR, PEA, and OCT were 10 to 20 times more potent in inhibiting NU than in eliciting efflux or inhibiting mazindol binding. Conversely, the potency of NOM to inhibit mazindol binding was 10 and 800 times greater than that required to inhibit NU or to elicit DA release, respectively. NOM inhibited competitively AMPH-induced DA release. These results suggest that: 1) AMPH-like drugs bind to and are likely to be transported by the NU carrier, and 2) inward transport of these agents appears to have multiple effects (e.g., an increase in intracellular Na+ and Cl-) that act cooperatively to increase Vmax and reduce

Km for the outward, carrier-mediated DA transport. AMPH, TYR, PEA and OCT had qualitatively similar effects on endogenous DA and [3H]DA release. Monoamine oxidase inhibition potentiated these effects. All these agents released more endogenous DA from control than from reserpine-treated slices. In control slices, TYR and OCT increased DA and DOPAC efflux; whereas AMPH and PEA increased DA and reduced DOPAC efflux, except at high concentrations in which DOPAC efflux also was increased. After reserpine, these agents reduced DOPAC efflux in proportion to the increased DA efflux. In summary, we propose that AMPH-like drugs increase DA efflux from a single cytoplasmic pool maintained by DA synthesis and spontaneous and drug-induced efflux of DA from storage vesicles

Parker EM and Cubeddu LX (1988) **Comparative effects of amphetamine, phenylethylamine and related drugs on dopamine efflux, dopamine uptake and mazindol binding.** J Pharmacol Exp Ther 245(1): 199-210.

PEA AND DEPRESSION

Phenylacetate (PAA), PEA's metabolite, is decreased in the urine of depressive patients, suggesting that depression is related to a deficiency of PEA in the brain.

- The compound 2-phenylethylamine is an "endogenous amphetamine" which may modulate central adrenergic functions. 2-Phenylethylamine is mainly metabolized by monoamine oxidase to form phenyl acetate (PAA). The 24-hour urinary excretion of PAA was measured in normal healthy volunteers and depressed patients. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, edition 3. In 70 percent of healthy volunteers of both sexes, the excretion of PAA ranged between 70 and 175 milligrams per 24 hours (mean = 141.1 +/- 10.2). Inpatients with major depressive disorder (unipolar type) (N = 31) excreted less PAA (68.7 +/- 7.0 milligrams per 24 hours) and 55 percent of them excreted less than 70 milligrams per 24 hours; there were no significant differences in the PAA excretion between untreated patients (N = 13) and those treated with antidepressants that were not effective (N = 18). The PAA excretion was reduced to a lesser extent in 35 less severely depressed unipolar outpatients (drug-free for 1 week) (86.3 +/- 11.8 milligrams per 24 hours). These results suggest that low PAA urinary excretion may be a reliable state marker for the diagnosis of some forms of unipolar major depressive disorders.

  Sabelli HC, Fawcett J, Gusovsky F, Javaid J, Edwards J, Jeffriess H. (1983) **Urinary phenyl acetate: a diagnostic test for depression?** Science 220(4602):1187-8

- Cerebrospinal fluid free phenylacetic acid concentration in a series of depressive patients was significantly lower than values in control subjects. This acid derives from phenylethylamine and the findings may reflect a decrease in its brain formation. Such a deficit may be related to other recent observations of a decrease in urinary output of the major metabolites of the "trace amines", octopamine and tyramine: phenylethylamine is thought to be the precursor of these "trace amines".

  Sandler M, Ruthven CR, Goodwin BL, Coppen A. (1979) **Decreased cerebrospinal fluid concentration of free phenylacetic acid in depressive illness.** Clin Chim Acta 93(1):169-71

Oral intake of PEA alleviates depression in 60% of depressed people -which is similar to the results obtained with all major antidepressants such as Prozac- with no side effects.

- 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.

  Sabelli H, Fink P, Fawcett J and Tom C (1996) **Sustained antidepressant effect of PEA replacement**. J Neuropsychiatry Clin Neurosci 8(2): 168-71

- A review of the literature indicates that brain phenylethylamine (PEA) may be a neuromodulator of aminergic synapses and that it promotes energy, elevates mood, and favors aggression. Phenylacetic acid, the main metabolite of PEA, is decreased in the biological fluids of depressed subjects and schizophrenic subjects and is increased in schizoaffective subjects. The administration of PEA or of its precursor L-phenylalanine improves mood in depressed patients treated with a selective monoamine oxidase B inhibitor. The authors speculate that studies of PEA metabolism may have diagnostic value and that PEA administration may be therapeutic in selected depressed patients.

  Sabelli HC and Javaid JI (1995) **Phenylethylamine modulation of affect: therapeutic and diagnostic implications**. J Neuropsychiatry Clin Neurosci 7(1): 6-14.

- To test the hypothesis that 2-phenylethylamine (PEA) modulates affect, plasma levels and urinary excretion of its main metabolite, phenylacetic acid (PAA), were studied in depressed and manic subjects, and the mood-elevating effects of its precursor, L-phenylalanine, were studied in depressed subjects. Mean total plasma PAA concentrations were 491.83 +/- 232.84 ng/ml in 12 healthy volunteers and 300.33 +/- 197.44 ng/ml in 23 drug-free patients with major depression. The 24-hour urinary PAA excretion was also measured in 48 healthy volunteers (141.1 +/- 10.2 mg PAA/24 hr) and in 144 patients with major depression (78.2 +/- 41.0 mg PAA/24 hr). The results suggest that low plasma and urinary PAA may be state markers for depression and are compatible with the PEA hypothesis. In further support, phenylalanine elevated mood in 31 of 40 depressives.

  Sabelli et al. (1986) **Clinical studies on the phenylethylamine hypothesis of affective disorder: urine and blood phenylacetic acid and phenylalanine dietary supplements.** J Clin Psychiatry 1986 Feb;47(2):66-70

PEA AND ATTENTION

Decrease in the concentration of PAA in urine has also been associated with attention deficit disorder (ADD), and oral intake of PEA was shown to alleviate ADD.

- Urinary excretion (24-hr) of beta-phenylethylamine (PEA), phenylacetic acid (PAA), phenylalanine (Phe), and p-tyrosine (Tyr), and plasma levels of PAA, Phe, and Tyr were examined in 18 normal children and 26 children diagnosed as having attention-deficit hyperactivity disorder (ADHD). The results indicated that urinary excretion (expressed per

g of creatinine) of free and total PEA was significantly lower in the ADHD patients, and plasma levels of Phe and Tyr were also decreased in the ADHD subjects compared with the normal controls.

Baker et al. (1991) **Phenylethylaminergic mechanisms in attention-deficit disorder**. Biol Psychiatry 1991 Jan 1;29(1):15-22

- To clarify the pathophysiology of learning disability (LD), we measured the urinary levels of 3-methoxy-4-hydroxyphenyl glycol (MHPG), and phenylethylamine (PEA) in urine samples collected in a 24 hour period. Findings were compared with those obtained in age-matched controls and diseased controls including patients with attention deficit-hyperactivity disorder (ADHD), infantile autism, and mental retardation. The mean urinary level of MHPG in LD (n = 6) were not significantly different from those in ADHD (n = 16), mental retardation (n = 4), infantile autism (n = 5), and the controls (n = 6), while the mean urinary levels of PEA were significantly lower in LD (n = 6, 91 +/- 17.3 micrograms/mg) and in ADHD (n = 5, 65 +/- 53.6 micrograms/mg) as compared to age-matched controls (n = 3, 340 +/- 264.5 micrograms/mg) ANOVA, ($p < 0.05$). PEA is considered to play an important role for the pathogenesis of LD and ADHD.

  Matsuishi T, Yamashita Y (1999) **Neurochemical and neurotransmitter studies in patients with learning disabilities**. No To Hattatsu 31 (3):245-8

PEA AND MOOD

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