

NEURONUTRIENT EFFECTS ON WEIGHT LOSS IN CARBOHYDRATE BINGERS: AN OPEN CLINICAL TRIAL

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ABSTRACT

In as much as neurotransmitters and neuromodulators are known to stimulate or inhibit eating behavior, we elected to examine the effects of precursor amino acid loading and enkephalinase inhibition on compulsive eating and weight loss in a controlled-diet clinical setting. In the present 90-day open trial, we investigated the effect of the experimental neuronutrient PCAL-103 on weight loss, uncontrollable carbohydrate binging, and relapse rates in 27 outpatients attending a supervised diet-controlled treatment program. The patients were assigned, retrospectively, to two matched treatment groups: those receiving the neuronutrient (experimental group [E]; $n = 16$) and those not receiving the neuronutrient (control group [C]; $n = 11$). E patients exhibited facilitated withdrawal from carbohydrates compared with the C patients. The E group lost an average of 26.96 ± 2.7 pounds; the C group only 10.0 ± 2.1 pounds. Only 18.2% of the E group relapsed in contrast to 81.8% of the C group. Use of the amino acid supplement PCAL-103 by chronic carbohydrate bingers allowed overweight individuals to lose 2.7 times as much weight as patients without benefit of this product.

INTRODUCTION

The specific causes of uncontrollable ingestive behavior for alcohol, drugs, and food (in particular, carbohydrates) are incompletely understood. Nevertheless, it is clear that these compulsive behaviors are a product of genetic predisposition and environmental insult factors. Both the genetic and environmental factors may be understood as operating through particular alterations in brain neurochemical balance. These alterations appear to induce compulsive-seeking behavior.

Previously, we proposed that a multi-neuronal cascade of events in the reward system may play a role in the neuropharmacology of compulsive-seeking behavior.^{1,2} Others have hypothesized that multiple brain neuro-

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transmitters play a significant role in the control of food intake, appetite for specific macronutrients, and patterns of meal-taking behavior. Leibowitz³ summarized extensive evidence to support the role of a number of brain monoamines and neuropeptides in the control of normal eating behavior. These neurotransmitters operate at neuronal centers, which are part of a complex integrative network known as the mesolimbic reward system.⁴ The medial and lateral portions of the hypothalamus, working in conjunction with forebrain and hindbrain sites and with the peripheral autonomic endocrine pathways, together carry and integrate signals for hunger and satiety. Analyses of cerebrospinal fluid in both humans and animals indicate specific disturbances in brain neurochemical function in association with abnormal eating patterns.^{5,6} In animals these abnormalities have been further localized to the hypothalamus.

The primary neurotransmitters involved in eating behavior include the monoamines dopamine (DA), norepinephrine (NE), epinephrine (EPI), and serotonin (5-HT); the amino acid gamma-aminobutyric acid (GABA); and a variety of neuropeptides such as the pancreatic polypeptides, opioid peptides, hormone-releasing factors, and various gut-brain peptides.

Substantial evidence based on direct application of these neurotransmitters on neurons reveals four classes of eating-stimulatory neurotransmitters, whereas a considerably larger number of substances are shown to inhibit eating.

The literature on eating is very complex. The same drug or neurotransmitter commonly will have different effects when administered in low doses versus high doses, centrally versus peripherally, in short-term versus long-term experiments, in genetically predisposed versus nonpredisposed, in obese versus normal weight versus anorectic animals, as a function of paradigm, and so on. The following statements are not meant to be a critical review but a consensus of the central effects of chronic administration of neurotransmitters/neuromodulators on feeding behavior. Detailed reviews have been published.⁷⁻⁹

Eating-Stimulatory Neurotransmitters

The eating-stimulatory neurotransmitters include the catecholamine NE, acting through noradrenergic receptors, GABA, and three classes of neuropeptides: the opioids (endorphins, enkephalins, and dynorphins); the pancreatic polypeptides (neuropeptide Y and peptide YY), and galanin. These substances, when administered directly into the rat hypothalamus, potentiate eating in satiated animals.^{3,10}

Furthermore, chronic administration of certain monoamines (NE) and neuropeptides significantly alter daily food intake and weight gain.^{11,12}

Eating-Inhibitory Neurotransmitters

The eating-inhibitory neurotransmitters in the brain include the

monoamines DA, NE, 5-HT, and gut-brain peptides cholecystokinin-8 (CCK-8), neurotensin, calcitonin, glucagon, and corticotropin-releasing factor.¹³⁻²¹

The effects of these neurotransmitters on eating are characterized primarily by a specific change in macronutrient selection, rather than an increase or decrease in total food intake. Many peptides, including CCK-8, bombesin, calcitonin, corticotropin-releasing factor, neurotensin, somatostatin, glucagon, and methionine-enkephalin have selective inhibitory actions on macronutrients.^{3,22,23} Leibowitz and associates^{24,25} reported that medial paraventricular nucleus (PVN) injections of NE in the rat induce a selective increase in carbohydrate ingestion with little or no change in fat and suppression of protein intake. Carbohydrate-craving behavior is consistently observed with chronic stimulation of NE and neuropeptide Y.^{26,27} Certain brain monoamines also have selective actions on macronutrient intake. DA-receptor blockade preferentially stimulates protein consumption, whereas catecholamine-releasing drugs such as amphetamine decrease protein ingestion.^{28,29} In contrast, 5-HT, in the medial hypothalamus, may selectively suppress carbohydrate intake, while sparing protein intake.^{30,31}

Direct serotonergic agonists (eg, quipazine), indirect serotonergic agonists (eg, (+)-fenfluramine), or selective inhibitors of 5-HT uptake into serotonergic neurons (eg, fluoxetine) decrease food ingestion in laboratory experiments.³²⁻³⁴ Borsini et al³⁵ reported that (+)-fenfluramine strongly reduced the consumption of a sucrose solution in nondeprived rats.

Leander³⁶ demonstrated that fluoxetine suppresses the ingestion of saccharin solutions in normal rats. A similar finding was true for alcohol intake in preferring rat lines (animals genetically bred to prefer alcohol over water).³⁷ However, the motive to drink saccharin solutions depends only upon its sweet taste, since it provides no calories. Both (+)-fenfluramine and quipazine, a direct serotonergic agonist, produce similar dose-dependent suppression of cumulative consumption of a 5% sucrose solution by rats with gastric fistulas. This indicates that direct and indirect serotonergic agonists can strongly depress a feeding response activated by sweet taste.

Opioid Peptides and Macronutrient Selection

Current evidence suggests that the pharmacology of the opioidergic system on eating behaviors is very complex and it would therefore be difficult to ascribe a generalized role, particularly in view of different effects observed with specific opioid peptides or macronutrient selection.

In support of the above observation, both increases in food intake³⁸⁻⁴⁴ as well as decreases in food intake⁴⁵⁻⁴⁷ have been observed under a variety of experimental conditions.

Differences have also been observed with both opiate/opioid agonists and opiate antagonists dependent on duration or administration. In short-term experiments, administration of agonists, centrally or peripherally, results in feeding increases. In contrast, peripheral administration of opiate antagonists diminishes intake of sweet foods. The inference from these studies is that long-term use of opioid/opiate antagonists would result in a decrease in food intake.

The results have been far more complicated than expected. In general, chronic administration of antagonists has been disappointing.³⁸ Naltrexone caused some reduction in binge-eating in bulimics.⁴⁸ However, it also produced weight gain in anorectic patients.⁴⁹ Shimomura et al⁵⁰ observed increased food intake with chronic naloxone treatment and decreased food intake with chronic morphine. Dhatt et al²² had similar observations with chronic morphine administration.

These observations suggest that while in acute situations opioid agonists increase and antagonists decrease food intake, in chronic situations opposite effects prevail.

One important problem in attempting to discuss and assign a specific pharmacological action of opiates/opioids appears to reside in obtaining exact information on the types of foods (macronutrient selection—lipids, proteins, and carbohydrates) consumed. In this regard, it is noteworthy that the opioid peptides, as well as opiates acting through μ , δ , and κ receptors, augment ingestion of fat and protein, while actually suppressing the relative proportion of carbohydrates ingested.^{23,51,52} The effects of opioid peptides on carbohydrate intake were investigated in animals made obese by neonatal monosodium glutamate (MSG) administration. This procedure results in reduced levels of brain endorphin.⁵³ These obese rats, compared with control animals, choose a greater percentage of their daily calories as carbohydrates and lower percentages as fat and protein.⁵¹

Furthermore, research on the importance of endogenous opioid peptides in feeding behavior primarily focused on their stimulatory effects, especially their role in genetic predisposition to impulsive food intake. In comparison to lean littermates, increased levels of pituitary endorphin were observed in genetically obese mice (Ob/Ob) and rats (Fa/Fa).⁵⁴ However, it has been known for some time that diet choices made by genetically obese mice are similar to the changed choice behavior after morphine administration. Namely, that obese mice select lower proportions of their diets as protein and carbohydrate, and higher proportions as fat.⁵⁵ Work by Gosnell and associates⁵⁶ has concentrated primarily on the feeding effects of central injections of opioid agonists. This resulted in an increased consumption of both saccharin and salt solutions. Similarly a low dose of the selective κ -agonist U-50,488H was found to facilitate the acquisition of a preference for a 20% sucrose solution.⁵⁷

Based on these and other studies, it appears that opioid agonists and

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antagonists, respectively, increase and decrease preferences for palatable tastes. We argue that palatability is a different measure than macronutrient selection (eg, carbohydrates) thus preventing any definitive conclusions with regard to feeding behavior.

The opioid peptides are not only involved in macronutrient intake, but have been implicated in compulsive alcohol and drug-seeking,⁵⁸⁻⁶⁰ as well as brain self-stimulation behavior.^{61,62}

In fact, Blum et al⁵⁹ reversed alcohol-seeking behavior in genetically preferring C57/6J mice with the chronic administration of an enkephalinase inhibitor.⁵⁹ Heibredet et al⁶¹ showed that intracranial self-stimulation by rats was reduced by nucleus accumbens microinjections of kelatorphan, a potent enkephalinase inhibitor. In terms of food intake, Riviere and Bueno⁶³ reported that central injections of the enkephalinase inhibitor, thiorphan, also reduced daily food intake in sheep. Since deficits have been found in neurotransmitter functions underlying craving behavior, and since these deficits may be alleviated by facilitated neurotransmitter release, consequent to use of drugs, alcohol, and food, the studies mentioned above indicate enkephalinase inhibition may similarly compensate for neurotransmitter imbalance (ie, opioids, thereby attenuating craving behavior). These results suggest that human carbohydrate binging might be critically mediated by differences in patterns of endogenous peptides.

We believe that compulsive-seeking behavior is the response to one or more neurotransmitter deficits. Attempts to alleviate this neurotransmitter imbalance through drug-receptor activation (alcohol, heroin, cocaine, and glucose) will only substitute for the lack of reward, and will yield a temporary sense of well-being.

We have shown that recovery from certain forms of uncontrollable ingestive behavior (ie, alcohol, polydrugs, and cocaine) is significantly facilitated by the use of neuronutrients designed to restore brain chemical deficits through the administration of both precursor amino acids and enkephalinase inhibitors.⁶⁴⁻⁶⁶ Thus we elected to evaluate the efficacy of a neuronutrient approach to weight loss in carbohydrate bingers.

PATIENTS AND METHODS

In a 90-day open-trial retrospective study, we investigated the effect of the neuronutrient PCAL-103 on weight loss and carbohydrate binging in outpatients attending a supervised diet-controlled program at the Bariatric Medical Clinic, West Monroe, Louisiana. PCAL-103 is an amino acid and vitamin supplement consisting of DL-phenylalanine, L-tryptophan, L-glutamine, and pyridoxal-5'-phosphate.

Patients were selected if they: (1) remained in the prescribed weight reduction program for at least 90 days; (2) were over 21 years of age; (3)

had a history of sugar binging; and (4) were overweight by standard height-weight tables. All patients selected for the study agreed to participate under standard informed consent procedures. Twenty-seven persons were selected, only one of which was male. In this study, there were 16 experimental subjects (E) and 11 controls (C). Overweight populations are typically 80% to 95% female. Demographic data are shown in Table I.

Composition of PCAL-103 and Dosage

Each patient in the E group took six capsules of PCAL-103 daily. This product is an experimental variant of SAAVE™ (Matrix Technologies, Inc., Houston, Texas), a product used to reduce craving in alcoholics and heroin abusers. The ingredients, DL-phenylalanine, L-tryptophan, L-glutamine, and pyridoxal-5'-phosphate have been described in detail elsewhere.⁶⁷

Diet Regimens

Randomly, all patients were placed on one of three dietary regimens: (1) a low-fat and sugar-free diet; (2) six protein-fiber complex-carbohydrate appetite suppressant cookies daily augmented with one low-fat sugar-free meal; or (3) four or five protein-sparing, modified-fat liquid drink shakes plus one small low-fat, sugar-free meal.

Females were assigned 800 calories total intake per day and males 1,000 to 1,200 calories. All were advised to discontinue the use of sugar immediately upon entry into the program and were given full explanation of sugar addiction and the withdrawal process. The subject of sugar addiction was approached with these patients as a chemical dependency. All were assessed with the same questionnaire to explore the types of binge-eating patterns prior to entry into the program. Patients were followed

Table I. Demographic and other physiologic measures of outpatient carbohydrate bingers treated with and without PCAL 103.

Treatment	No. of Patients	Age (yr)	Weight (lb)	Hypoglycemic Score	Family History Positive*	Sex	
						M†	F
PCAL 103	16	41.8 ± 2.7	205.0 ± 12.0	1.5 ± 0.3	15/15 (94%)	0 (0%)	16 (100%)
No PCAL 103	11	37.3 ± 2.5	217.2 ± 17.4	1.6 ± 0.6	8/8 (100%)	1 (9%)	10 (91%)

* In the no PCAL103 group, only eight subjects knew their family history as it related to eating disorders and/or chemical dependence.

† Randomized selection resulted in a higher proportion of female subjects. This is consistent for this bariatric clinic whereby the total male population over a two-year period was only <10% of the overall patient population.

weekly throughout a 90-day course of their weight reduction and occasional missed visits were recorded.

Measurements

Prior binge Index: A prior binge index was calculated based on answers to the questionnaire. A normal binge index was rated as 0, a mild sugar binge was rated +1, a moderate sugar binge rated +2, and a high sugar binge rated +3. An average index was calculated for each group.

Glucose Tolerance Test: Almost every patient was given a three-hour glucose tolerance test (GTT) upon entry into the program. Exceptions were those who refused the test or those already known to be diabetic. The GTT consisted of a fasting blood sugar followed by an oral 75-gm load of glucose with subsequent blood sugar drawn at the one-, two-, and three-hour time intervals. Normal blood sugar response was grade 0, slightly hypoglycemic 1+, moderately hypoglycemic 2+, and highly hypoglycemic 3+. The average hypoglycemic score was calculated for each group.

Family History: Family histories were obtained on each patient specifically asking if eating disorders, alcoholism, or other chemical dependencies existed in close genetic relatives. Percentages were calculated in each group for those who responded positively or negatively to this question. Three patients did not respond at all because of the lack of knowledge concerning their blood relatives.

Initial Compliance

Each patient was seen approximately one week following entry into the program for an evaluation. Weight reduction was recorded at that time, and an initial compliance score was calculated based on apparent positive withdrawal (ie, lack of binge eating), as evidenced by successful weight reduction.

A score of 3+ was assigned to those who lost the most weight and had apparently had the least difficulty with continued binge eating behavior (four to five pounds), 2+ to those with moderate weight loss and moderate resolution of binge eating (two to three pounds), and 1+ to those experiencing the most difficulty in reducing weight and greatest difficulty in refraining from binge eating behavior (zero to one pound). An average withdrawal score (initial compliance index) for each group was calculated.

Weight Measurements and Calculations

Weight lost during the 90-day trial was measured for each patient. These data were assessed in three ways: (1) total weight lost; (2) loss of

excess weight (defined by standard height-weight tables); (3) percent excess weight lost.

Program Compliance

Weight loss of 25 pounds or more at 90 days was assigned a program compliance score of ten, representing successful abstinence from binge eating; a 12.5-pound loss was given a score of five, representing moderate abstinence from binge eating; and a loss of six pounds or less was given a score of zero, demonstrating poor abstinence from binge eating behavior. Using these assigned values, a compliance index was calculated and averaged for each group.

Relapse

Patients losing less than 15 pounds over 90 days were considered to have relapsed (noncompliant). The percentage of patients who did not participate during the trial period was calculated for each group.

Statistical Methods

The E and C groups were tested for statistically significant differences in each of the above measures using parametric *t* tests and nonparametric Mann-Whitney U tests. The nonparametric test was used to compensate for possible problems caused by small sample sizes and non-normal distributions of the measures.

RESULTS

No statistically significant group differences were found for measures of age, weight, pounds overweight, hypoglycemia, or binge index using both parametric and nonparametric tests. For family history of eating disorders, the two groups were not significantly different, as tested by chi-square test.

Initial Compliance

Initial compliance for the E and C groups differed significantly ($P < 0.026$, Mann-Whitney U test, Figure 1). Thus the E group lost more weight in the first week than did the C group. Similarly, long-term compliance differed significantly ($P < 0.001$) for these two groups (Table II).

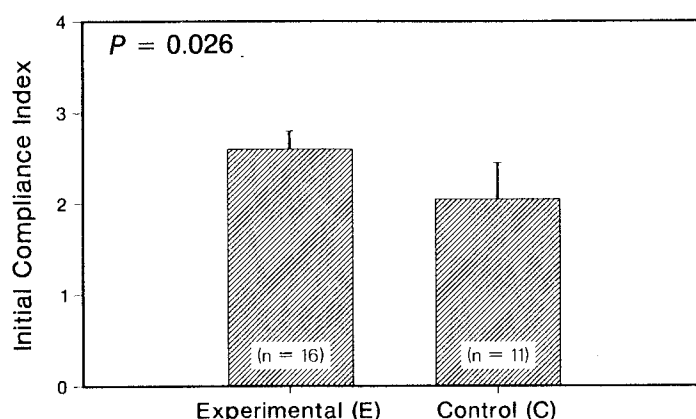


Figure 1. Comparison of the initial compliance index between carbohydrate bingers in the experimental group (E) and the control group (C). The number of subjects is indicated in the brackets. Score ranged from 3+ for most weight lost to 1+ for least weight lost. The vertical bars represent the standard error of the mean. P equals significance as analyzed by one-tailed Mann-Whitney U test.

Weight Loss

The average weight loss in the E group was 26.96 ± 2.7 (SEM) pounds, while the C patients lost an average of 10.0 ± 2.1 pounds. Results were statistically highly significant ($P < 0.001$) (Figure 2 and Table II).

Excess Weight Loss

Examination of percent target excess weight lost reveals a 2.7-fold difference between the E and C groups. This means that the E group lost approximately 2.7-fold more actual pounds over the 90-day test period than the C group (Table II).

Table II. Comparison of the efficacy of treatment with and without PCAL 103 in outpatient carbohydrate bingers.*

Treatment	No. of Patients	Initial Compliance Index*	Weight Lost (lb)	Percent Weight Lost	Program Compliance Index§	Relapse
PCAL 103	16	$2.6 \pm 0.13^\dagger$	$27.0 \pm 2.7^\ddagger$	$48.9 \pm 5.0^\dagger$	$9.0 \pm 0.4^\ddagger$	12.5%
No PCAL 103	11	2.0 ± 0.28	10.0 ± 2.1	18.0 ± 5.8	4.2 ± 0.9	81.8%

* Score ranged from 3+ for most weight lost to 1+ for least weight lost.

† $P < 0.02$ vs r.o PCAL; one-tailed Mann-Whitney U test.

‡ $P < 0.001$ vs no PCAL; student's t test.

§ Score ranged from 10 for weight loss of ≥ 25 pounds to 0 for ≤ 6 pounds lost.

|| $P < 0.001$ vs no PCAL; Pearson's chi-square test.

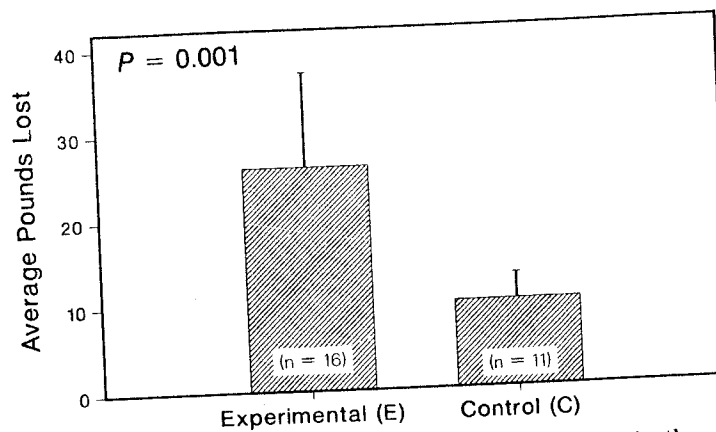


Figure 2. Comparison of pounds lost between carbohydrate bingers in the experimental group (E) and the control group (C). The number of subjects is indicated in the brackets. The vertical bars represent the standard error of the mean. The data were analyzed by the Student's *t* test, and revealed that a significant difference ($P < 0.001$) was observed between groups.

Initial Weight Loss

The E patients lost an average of $48.93 \pm 5.0\%$ of their excess weight, while the C patients lost an average of only $18.0 \pm 5.78\%$. These differences were highly significant ($P < 0.002$) (Figure 3 and Table II).

Program Compliance

The E patients had an average score of 8.96 ± 0.421 , while the C patients had an average score of 4.19 ± 0.901 . This represents almost a 2.0-fold overall improvement in the E group compared with the C group (Figure 3 and Table II).

Relapse

The E and C groups were compared for frequency of noncompliance using Pearson's chi-square test. They differed significantly ($P < 0.00032$). Only 18.2% of patients who did not effectively participate (lost less than six pounds) were in the E group. In contrast, 81.8% of the patients who failed to participate were in the C group. The E group was almost 4.5 times more likely to participate fully in the program and experience significantly greater weight loss (Figure 3).

DISCUSSION

The data presented in this open retrospective investigation suggest that

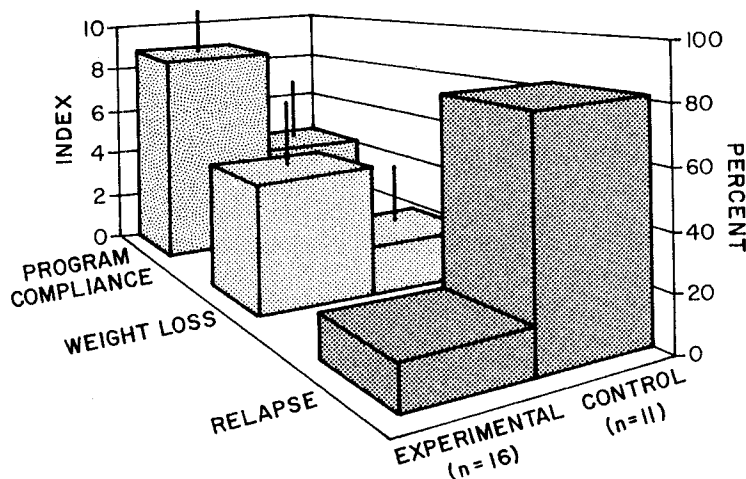


Figure 3. Comparison of relapse, percent weight lost, and program compliance index between carbohydrate bingers in the experimental group (E) and the control group (C). The number of subjects is indicated in the brackets. The vertical bars represent the standard error of the mean. Both the program compliance index and percentage of weight lost were analyzed by parametric and nonparametric tests for significance, and Pearson's chi-square test was used to test for significance for relapse rates. Significant differences were observed between groups.

the neuronutrient PCAL-103 suppresses eating behavior in known carbohydrate bingers participating in a 90-day controlled program in a medical bariatric setting.

Numerous studies have implicated the interaction of opiates, opioid peptides, CCK-8, glucagon, DA, and insulin in glucose utilization and selective intake of carbohydrates.⁶⁸⁻⁷²

We believe that the apparent beneficial effects of PCAL-103 may be explained by the action of both the precursor amino acids and enkephalinase inhibition operating on mesolimbic reward circuitry. We cannot at this time provide an exact mechanism of action for this neuronutrient mixture, nor can we pinpoint which ingredient or combination of ingredients best suppresses carbohydrate binging in our study.

However, an underlying presumption in the field is that a derangement or imbalance of the actions of some or all of this neurochemistry is responsible for eating disorders. Further, the principal candidate region for such imbalance is in the mesolimbic area. Similar data and logic underlies thinking about drug-dependent disorders. Thus alcohol, opiates, cocaine, and glucose induce reward by activating the mesolimbic reward multineuronal circuitry.

Blum and associates^{1,2} have developed a neurotransmitter reward-cascade model that may play a role in the neuropharmacology of compulsive

sive-seeking behavior. In this cascade, the hypothalamic serotonergic neurons innervate met-enkephalinergic neurons that, in turn, inhibit GABA neurons, which then activate DA neurons of the ventral tegmentum. These DA neurons then project to the nucleus accumbens and to CA1 cluster cells in the hippocampus, where the neurotransmitter DA acts as the primary reward substrate.⁷³

The importance of both the nucleus accumbens and enkephalins in this complex circuit is attested to by the report of Heidbreder et al⁶¹ as noted above.

Additionally, using a push-pull cannula technique, Chesselet et al⁶² were able to induce DA release in the striatum after local application of enkephalin, which suggests regulation by delta receptor stimulation. Indeed, kelatorphan may also protect against possible CCK-8 degradation by brain peptidases. This important satiety neuropeptide is colocalized with DA in the nucleus accumbens, and there is a close interaction between CCK-8, DA, and endogenous opioid peptides.^{74,75}

The neurotransmitters, 5-HT, DA, NE, and enkephalins have been shown to reduce intake of sweet foods. Thus PCAL-103 was especially designed to enhance these food inhibitory neurotransmitters through precursor amino acid loading, including 1-tryptophan (5-HT-precursor), 1-phenylalanine (DA and NE precursor), as well as the enkephalinase inhibitor d-phenylalanine^{76,77} (to raise enkephalins).

A plausible positive mechanism for the observed effects of PCAL-103 in these studies includes restoration of deficient monoamines such as serotonin, dopamine, and epinephrine, as well as the neuropeptides methionine-enkephalin and CCK-8. All of which are considered to be inhibitory eating (carbohydrate) substances influenced by either glucose or genetics.⁷⁸⁻⁸²

Based on this work, we believe that glucose binging is, as previously proposed, similar to other chemical dependencies (ie, alcohol, cocaine, heroin). Finding that PCAL-103 or other similar neuronutrients, as previously observed⁶⁴⁻⁶⁶ with alcoholics, polydrug abusers, heroin abusers, and cocaine-dependent individuals, facilitates recovery, further supports a common mode of treatment for these diverse substances. This work certainly warrants more extensive research in a double-blind fashion, and should stimulate our colleagues to perform similar trials with their eating-disorder patients. This research should provide both impetus and hope for the future development of novel therapeutic measures.

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