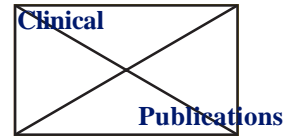


# Research Report



## REDUCTION OF THE EFFECTS OF PROLONGED STRESS DURING A 13 WEEK STUDY USING THE DIETARY SUPPLEMENT beCALM'd™

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### ABSTRACT

beCALM'd™, an amino acid, vitamin, and mineral formulation, was designed to restore catecholaminergic, opioidergic, GABAergic, and serotonergic deficits observed in individuals suffering from long-term, moderate-to-high emotional stressors. The formulation was found to reduce significantly (to very significantly) the variability of blood pressure, skin conductance, and perceived stress of participants during a double-blind, placebo-controlled, cross-over study of public school educators, compared with controls. Each school day, during the 14 weeks of the study, each participant measured his or her Skin Conductance Level (SCL) using an Autogen AT<sub>64</sub>, blood pressure, using a standard digital readout cuff. Each then recorded his or her stress level by responding to the question, "On a scale of 1 to 10, with 1 being no stress and 10 being the most stress you have ever experienced, how would you rate your stress level today?" The factors studied are commonly accepted as stress indicators and are well known to be directly related to harmful continual, low level norepinephrine adrenaline release. During the experimental phase of the study these indicators were very significantly diminished. The results thus suggest that beCALM'd may facilitate the availability of the opioids, GABA, and/or serotonin depleted by long term stress, thereby limiting the tissue and organ degradation associated with prolonged norepinephrine adrenalin release.

## INTRODUCTION

In the 20th century continual, low level stress is a part of everyday life. Traffic jams, job pressures, and difficulty with relationships all have become accepted as normal. [The human body, as it has developed over the millennia, reacts to these stressors in the same way in which men have, for all of recorded history, when preparing to escape from physical danger.] That is, when danger presents itself, the body begins to undergo physiological changes which prepare it for meeting a threat. Heart rate, circulation, oxygen and energy supplies, and metabolism all increase to allow us to defend ourselves or to escape from the threat. Body functions such as digestion, which serve no useful purpose at the time, decrease. All of our resources are marshalled to either “fight or flee” from the enemy or danger.

The stressors, which are a part of life for modern man, are not quickly eliminated. When the body evokes this “stress reaction” for a prolonged period of time in response to long-term stressful situations, the result can be devastating to physical and psychological health. Stress has been implicated in heart disease, hypertension, ulcers, depression and numerous other diseases. Over 30,000 studies have been reported in the last five years relating disease to stress. In fact, it has been estimated that over 75% of all disease prevalent in western society is related to the activation of the stress mechanism, and that more than 66% of all visits to primary-care physicians are for stress-

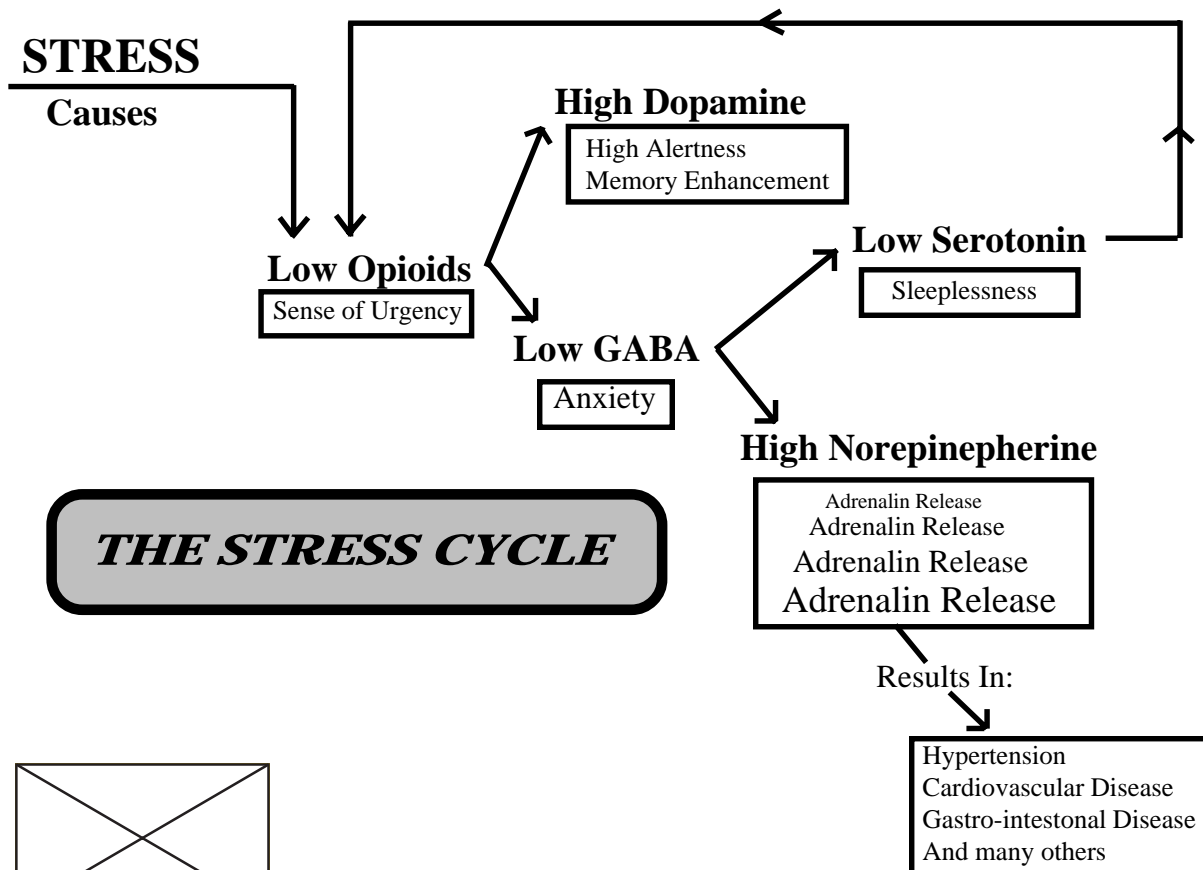


Figure 1

related disorders<sup>14</sup>.

While the cause of stress varies from individual to individual, the changes which, take place in the body when under stress, are similar from person to person. Researchers have found that stress depletes neuroregulators from the endogenous opioid, GABA, and serotonin systems, with a related increase in dopamine and norepinephrine release(1,2,3,5,13). The effects of such neuroregulator changes in causing a variety of diseases have been demonstrated in numerous scientific studies completed and reported during the last fifteen years. A common neurobiological pathway has been suggested to underlie uncontrolled use of psychoactive agents including alcohol by activating the opioid-mediated mesolimbic catecholaminergic receptors to provide pleasure or relief from pain(3).

The Stress Cycle shown in Figure 1 is based upon Blum's "Reward Cascade" Link(2) and is described below. From this is shown the mechanism of continuing stress causing the interrelationship among the reward/punishment systems within the hypothalamus to form an unstable feedback loop which continually releases unneeded adrenalin. The effects of this release are well known:

Stress causes the opioid (endorphin, enkephalin, etc.) levels to diminish. The lower opioid levels create a sense of urgency. The lowering of the opioids causes an increase in dopamine levels and a decrease in GABA levels. This produces a combination of anxiety and alertness.

The lowering of the GABA levels causes the norepinephrine levels to increase and serotonin levels to decrease. The increase in norepinephrine causes adrenalin to be released and the reduction of serotonin makes sleep difficult to impossible. The increased norepinephrine encourages a quick, emotional response and discourages slower, deliberate (logical) thinking.

The adrenalin release causes the heart to beat both faster and harder and causes red corpuscle reserves to be placed in the blood stream. It causes energy sources and nutrients to be diverted from functional organs such as the liver, the digestive tract, etc. for use by the muscles. This results in the person being able to make an almost super-human physical response to the threat.

The serotonin reduction further modulates the opioids downward. Thus, the cycle repeats with increasing intensity.

{An analogy is found when a speaker steps to a microphone and snaps his fingers to test it. This sound is amplified and then reproduced by the loud speakers. The reproduction travels back to the microphone at the speed of sound. There, it is picked up and re-amplified. As this continues, a tone is heard which is so loud that the auditorium is made ineffectual by the very system designed to make it usable. The situation is brought under control by the speaker turning down the amplifier's gain control. When he does so, the system is able to do what it is designed to do.}

This understanding of the neurochemistry(9,10) led us to investigate the effectiveness of restoring brain neuroregulator balance in individuals experiencing stress levels known to cause neuroregulator imbalance.

*Treatment of diseases resulting from the continual release of adrenalin caused by long term stress.*

Traditional treatment for the patient suffering from the effects of long term emotional stress has tended to focus on three steps: 1) recovery from the damage already done (through the use of specific drugs and nutritional supplementation); 2) making the patient more comfortable (through the use of mood elevators such as vitamin B12 and B3, niacin): and 3) preventing further damage (through behavior modification techniques and stressor elimination when possible).

Studies have shown(1,2,3) that human design has the means of automatically “turning down the gain.” However, when stress is long term in nature, the metabolites needed for this action are depleted and ultimately the adjustment can no longer be made. Additional nutrition is required to replace these metabolites. While the quantities vary from one individual to another, getting these additional nutrients from food is difficult. The average person would require several pounds of exotic fish, a quart of milk, and a variety of other high cholesterol and high fat content foods daily. A better alternative is to consume the required additional nutrients as supplements.

A nutritional supplement (beCALM'd) has been formulated, as shown in Table 1. on the following page, to relieve stress by introducing d/l-phenylalanine and l-glutamine which in combination with a formulation of vitamins and minerals has been shown to enhance opioids, GABA, and serotonin availability(1). This study was designed to test the ability of beCALM'd to enable the human to withstand a great deal of constant stress without suffering the effects attributed to continual norepinephrine adrenalin release.

## THE FORMULATION

TABLE 1:  
The ingredients per capsule and their effects are as follows:

Ingredient	Amount	Restorative Action	Mechanism	Expected Behavioral Change
d/l-Phenylalanine	400 mg	Enkephalin (d) Dopamine (l)	Enzyme inhibition Precursor loading	Reduced urgency Alertness
l-Glutamine	50 mg	GABA up which reduces Norepinephrine	Precursor loading	Antianxiety Antistress
Vitamin A	1000 IU	Membrane Maintenance	Supplemental Anti-oxidant	General body repair
Vitamin B6	1 mg	Pyridoxal-5- Phosphate	Promotes absorption of amino acids	Facilitates action of neuroregulators
Calcium Magnesium	50 mg 25 mg	Serotonin	Serotonin production catalysts	Enhanced Sleep
Chromium Picolinate	0.01 mg	l-tryptophan	Accelerate absorption of amino acids by muscles thus reducing l-tryptophan competition at blood-brain barrier	Enhanced Sleep

The LD<sub>50</sub> of d-phenylalanine (DPA) in rodents is 5,452 mg/kg. For a standard human male this toxicity level translates, on a weight basis, to an LD<sub>50</sub> of 436,160 mg. Allowing for a six fold difference in metabolically active body mass between mouse and human(4), this equates to a projected LD<sub>50</sub> in humans of 908.5 mg/kg or 72,693 mg. No toxic effects were seen following acute administration of DPA to monkeys of 3000 mg/kg or chronic administration of 1000 mg/kg/day for 30 days(6). Heller(8) has reported no toxic effects in rodents after two continuous years of dosages equating to 1000 mg/kg/day. The LD<sub>50</sub> of l-phenylalanine in rodents is 5,287 mg/kg, and the LD<sub>50</sub> of l-glutamine in rodents is 1,600 mg/kg.

These ingredients comprise a nutritional supplement known as beCALM'd (patent pending), manufactured by Natural Neuro Nutrition, Inc., Seabrook, Texas. (1-800-232-7563)

To test the formula a double-blind, placebo-controlled, crossover study was conducted in a suburban middle school in Houston, Texas. Educators were selected because they are representative of a large number of U.S. citizens in that they experience nearly continual moderate stressors and occasional moments of high level stress(14).

## SUBJECTS AND METHOD

### *Group Selection and Dosage Regimen*

Forty-seven public middle school educators consisting of teachers, administrators, and support personnel volunteered for the study. Each participant was randomly assigned an identification number and assigned to Group I (placebo-experimental) or to Group II (experimental-placebo). The participants had no knowledge of their group assignments.

After one week of baseline measurements, participants on Group I received a numbered bottle containing capsules of the placebo, vitamin A with inert fillers, while participants in Group II received capsules of the experimental beCALM'd. The participants were instructed to take two capsules before breakfast and two capsules before bedtime for 42 days. After a seven day cross-over period during which no capsules were taken (Spring Break for the educators), Group I was given a 42 day supply of the experimental and Group II of the control. There were 14 subjects who withdrew within the first two weeks of the test. Group I then contained 18 and Group II, 15. As the study was full cross-over in design this gave a resultant "n" of 33, more than sufficient for this type of test(15).

### *Test Measurements*

The time of day for taking measurements was left to the individual educator with the requirement that it was to be the same time each day. Most chose their conference period. One selected immediately after school.

*Cardiovascular Measurements:* Standard systolic and diastolic blood pressure measurements were taken by the participants, using a BMS model 11-780 Oscillometric Unit, and recorded daily throughout the study.

*Skin Conductance Level (SCL):* The electrical properties of the skin have been widely utilized as an indirect measure of an individual's stress level. Early lie detectors used only this measurement. A correlation exists between increased skin conductance and sympathetic activation of anxiety and orienting responses to stress. Therefore, a decrease in conductance is associated with a decrease in an individual's autonomic response to stress (5,11,12). To obtain these measurements, an Autogen, Inc., model AT<sub>64</sub>, was attached to the middle two fingers of the dominant hand of each participant, and a daily skin conductance reading was displayed and recorded by the participant.

*Perceived Stress Level:* Participants were asked to record their perceived stress level by responding to the question "On a scale of 1 to 10, with 1 being no stress and 10 being the most stress you have ever experienced, how would you rate your stress level today?", and to circle their response on a 1 to 10 scale on that day's data sheet.

*Method of Statistical Analysis:*

TABLE 2.  
Means and standard deviations of baseline period:

Test (Group)	Mean	Standard Deviation
Diastolic (I)	75.00	5.20
Diastolic (II)	72.29	5.46
Systolic (I)	117.57	6.04
Systolic (II)	116.86	7.92
SCL (I)	2.20	0.77
SCL (II)	2.03	0.47
Perc'd (I)	5.50	1.52
Perc'd (II)	4.91	1.35

Examination of the baseline data (Table 1) revealed that the two groups did not differ in mean score or variability on any of the measures.

Neuroregulator imbalance may allow wide variability in blood pressure, skin conductance, and perception of stress. The prolonged variability of these factors by continual norepinephrine/adrenalin release may account for the organ and tissue damage associated with long-term stress (15). Therefore the data were analyzed to test the hypothesis that subjects would have less variation in blood pressure, skin conductance and perceived stress level when taking beCALM'd than when taking placebo.

In this case a variance for each test half, placebo and experimental, was derived for each subject. The combination of each half was then evaluated on an "F33/30" distribution basis. The individual means, S<sup>2</sup>'s, group "F" scores, and final "F" score (Table 3) for each test are shown in Tables 4 & 5, ("F" Score Calculations). The group scores are only relatively significant. Each of the final scores indicate significance (probability of error less than .05) with values of 1.84 or higher, and are deemed to be very significant (probability of error less than .01) with values of 2.39 or higher.

TABLE 3  
The final "F" scores for each test:

Diastolic	2.20
Systolic	2.92
Skin Conductance Level	2.58
Perceived Stress Level	3.50

## RESULTS

### *General*

The environmental stress level in the school was typical during the week of the baseline measurements. It went up highly during the first six weeks portion of the test. During this time a property tax roll-back election was passed, which effectively eliminated 18% of the school district's budget for the next three years. In addition the district received notice of a 6.5 million dollar reduction in state funding due to court mandated equalization of state funding of public schools. Each educator was very concerned that he or she might experience severe program cuts, salary reduction, or even loss of employment. By the time the final six weeks portion of the study began, most of the study's participants had regained

their confidence in future job security. However, this period coincided with the ending of the school year causing the stress level to be moderately higher than the baseline period.

This extreme variation in the ambient stress may have increased the variance in the Group I placebo period and the variance in the Group II experimental period. This tends to be supported by comparison of the baseline and placebo results, and the statistical findings for each group. In the first case the results tend to indicate a greater population difference and in the second a lesser difference. However, the demonstrated baseline singularity of population of the two groups and the full cross-over nature of the study gives an overall effect of a more conservative test.

### *Blood Pressure*

As demonstrated above, some of the most damaging effects of continued stressful events are the rapid swings in blood pressure that accompany continuing moderate to high levels of emotional stress. These effects are usually observable by monitoring blood pressure. The "F" Score Calculations sheet shows each subject's diastolic and systolic blood pressure 30 day mean and 30 day "S<sup>2</sup>" (sum or the square of variances from subject's mean for each period.) The 33 S<sup>2</sup>'s for the combined placebo and experimental groups were then evaluated using the F Score ANOVA technic. Interestingly, while the diastolic test showed the results to be significant (probability of error less than 5%), the systolic test showed the results to be highly significant (probability of error less than 1%).

Examples of diastolic data for typical subjects from both group are shown in Figures 2 through 5. Subject No. 10's results for Systolic (blood pressure), Skin Conductance Level, and Perceived Stress are shown for comparative purposes in Figures 6 through 9.

### *Skin Conductance Level*

As stress levels go up, blood vessels in the extremities (e.g. finger tips) are constricted. This causes two well known effects: a) skin temperature of extremities goes down and b) skin conductance from one extremity to another (even between adjacent finger tips) goes down. The later effect is often offset by the presence of sweat on the skin. To counter this effect, electrolytic gel is often used on the probes.

In this test the gel was not used as the tests were taken inside an air conditioned building, and stress significant enough to cause the subjects to break out into a cold sweat was not expected. Comments from the experimenters and subjects during the test indicated this was probably the correct decision.

### *Perceived Stress*

The perception of being under emotional stress is usually not felt in time of fight or flee situations. It is felt heavily afterwards. In continuing stress, however, it is felt continually. The usual symptoms are frustration, fatigue, short temper and in extreme cases, periodic short sighs. These are often accompanied by the desire to eat and/or to drink alcohol excessively.

Thus, in the case of long term stress the perception of stress is usually a good gauge of environmental stress levels.

### **CONCLUSION**

The results of the study show a very significant reduction in four of the most common stress effect indicators. Based upon Blum's well established "Reward Cascade," these results suggest that beCALM'd facilitates the availability of the opioids, GABA, and/or serotonin depleted by long-term stress, thereby limiting or eliminating norepinephrine/adrenalin release except in *fight or flee* incidents. Such a result is expected to significantly diminish the tissue and organ degradation and other related diseases associated with long-term stress (see National Library of Medicine for over 20,000 recent references.)

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