Anti-stress efficacy of **PNT 200®** on stressed women

By Marta Santuré, Ph.D.

Abstract

Stress is defined as a non-specific response of the body to any demand that disrupts the normal body's homeostasis. During exposure to a stress stimulus, the body responds physiologically by increasing the activity of both hypothalamic-pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS). Stress also triggers a number of characteristic behavioural responses. It has been suggested that an individual will respond to a stress stimulus with a constant physiologic response. This phenomenon is called the Individual Response Stereotypy. Thus every person develops self-specific symptoms in response to stress.

This double-blind cross-over study was carried out on 63 female volunteers showing at least one stress symptom. Subjects were divided into two groups. The first group received the placebo for 30 days and that period was followed by a washout period of 3 weeks. Then the same group received **PNT 200®** for another 30 days. The second group received the same treatments but in reverse. Subjects answered a questionnaire on the 1st, 15th and 30th day of each treatment period. The questionnaire covered 3 main areas and 8 sub-areas potentially affected by stress and their respective symptoms. For each subject, the major stress symptom in a particular area was determined by its intensity score.

A significantly greater positive evolution of stress symptoms in 5 different areas was demonstrated in the group taking **PNT 200®** compared to the one taking the placebo: the digestive, cardiovascular, intellectual, emotional and social problem areas. The effect of **PNT 200®** was greater in subjects having a high intensity score for a major symptom at the beginning of the study. Therefore, the study showed that **PNT 200®** was an effective solution for reducing stress symptoms in stressed women.

Introduction

Hans Selye, a pioneer in the exploration of stress, defined stress as "a non-specific response of the body to any demand" (Selye, 1976). He also defined the response to stress as "general adaptation syndrome" consisting of three successive phases: the alarm phase, the stage of resistance and the stage of exhaustion. If not carefully handled, stress can hinder the body's ability to renew its vital energy reserves and eventually lead to pathophysiologies and weakened immunity.

The neuroendocrine response to stress has been well characterized. Activation of the hypothalamic-pituitary-adrenal axis (HPA axis) by the cocorticotropin-releasing factor (CRF) leads to a rapid secretion of adrenocorticotropin hormone (ACTH) in the anterior pituitary gland and to an increase in circulating glucocorticoids (cortisol, corticosterone). In response to a stress stimulus, there is also an activation of the sympatho-adrenal system (SAS) leading to the secretion of catecholamins. The HPA axis and the SAS coordinate the endocrine, autonomic, behavioural and immune responses to stress. Some of the physiological changes associated with the stress response include increase in alertness, arousal and focused attention, mobilization of energy to maintain brain and muscle function, enhanced cardiovascular output and respiration, redistribution of blood flow increasing substrate and energy delivery to the brain and muscles, modulation of immune function and decreased feeding and appetite (Carrasco and Van de Kar, 2003).

While there is clearly a non-specific and general activation process that contributes to the stress response, there is also considerable evidence of a more stimulus-specific response pattern as well as an organism-specific response pattern. (Lacey and Lacey, 1965; Roessler and Engel 1974). Individual Response Stereotypy (Engel, 1960) is the tendency for an individual to respond to a variety of stressors with a similar physiologic response. It has been proposed that the responses to stress differ between individuals, but are constant for any given individual (Rosenzweig et al., 1998). Based on a non-specificity model of stress and disease, any difference in type of disorder that is developed, e.g. headaches, gastrointestinal or hypertension, would depend on the individual's particular genetic-constitutional factors. Thus, every person will respond to stress differently, developing one or more specific symptoms.

PNT 200® is a casein hydrolysate that has been shown to exert anxiolytic effects in animal and clinical studies. A double-blind clinical study

performed on 52 healthy subjects showed that 150 mg/day of **PNT 200®** for 30 consecutive days reduced stress reactivity, as assessed by mean arterial blood pressure response to a mental stress test. The effect of **PNT 200®** on stress reactivity was significant at days 11 and 31 of the treatment.

This study suggests that **PNT 200®** reduces stress reactivity in the general healthy population but could be even more efficient in reducing stress responses in subjects showing symptoms of stress. The aim of the present study was to investigate the effect of **PNT 200®** in women presenting at least one symptom of stress.

Method

The study was carried out by Dr. D. Desor, Laboratory of Behavioural Neuroscience, Faculté des Sciences, Nancy, France. All the data concerning the volunteers was subjected to the rules of the Commision Nationale de l'Informatique et des Libertés (CNIL).

Subjects

The subjects were 63 female volunteers showing at least one symptom of stress. The subjects answered a questionnaire on the 1st, 15th and 30th day of each treatment period. The questionnaire covered 3 main areas (containing 8 sub-areas) potentially affected by stress and their respective symptoms:

- Physical and physiological area (disorders in digestive tract, respiratory system, cardiovascular system, locomotion system, other physical problems)
- Psychological area (disorders in intellectual functions and on an emotional level)
- Social life

Subject evaluated the intensity score of each symptom for each area using a 10-degree scale (0 = not at all, 9 = excessively).

Subjects with body mass index (BMI) over 25, under anti-depressant, anxiolytic, herbal sedative, hypnotic treatment (in progress at the time of the study or 15 days before the beginning of the study), suffering from serious (or evolving) illness, consuming excessive alcohol or tobacco, or with an history of food allergy problems were excluded from the study.

Study design

The study was based on a double-blind, cross-over schedule. The population of subjects was subsequently separated into 2 groups:

Group 1 received 150 mg/day **PNT 200®** for 30 days, had a wash-out period of 3 weeks, then received the Placebo product for a period of 30 days.

Group 2 received the Placebo product for 30 days, had a wash-out period of 3 weeks, then received 150 mg/day **PNT 200®** for a period of 30 days.

Measurement

The major symptom (highest intensity score) for each patient was determined for each area (digestive, respiratory, cardiovascular, locomotion, physical, intellectual, emotional, social symptoms of stress). The study evaluated only the changes relative to the major symptom for each area and for each patient under the effect of **PNT 200®** or under the effect of the Placebo.

Statistics

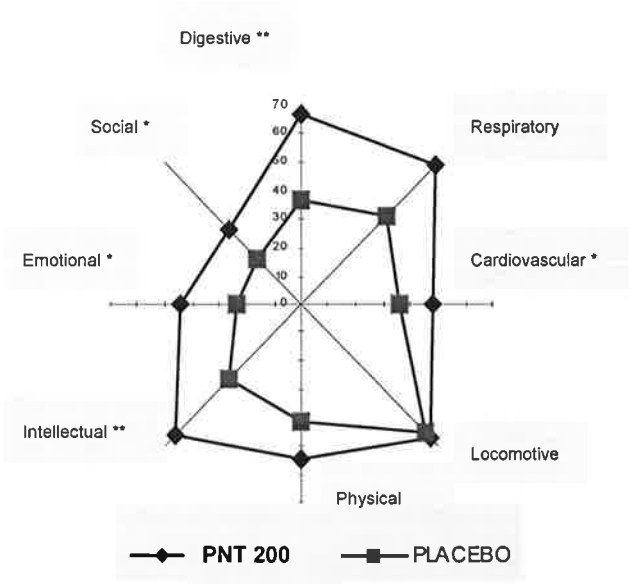
Non parametric statistics (Wilcoxon test) were used (Statistical software: SPSS). Differences were considered significant at the level: $p < .05$.

Results

Time and/or inclusion in a treatment schedule had a considerable effect on the evolution of the symptoms. For 42 symptoms out of 65 evaluated (64.6%), a significant improvement between the first day of the first period and the first day of the second period of the cross-over study could be demonstrated, independently of the treatment by **PNT 200®** or Placebo. Furthermore, the Placebo treatment produced considerable effect. The percentage of improvement of the symptoms during the Placebo treatment ranged from 15% to more than 40%.

The treatment by **PNT 200®** at a dose of 150 mg/day was particularly efficient on the subjects who demonstrated the highest intensities (>4) for their major symptoms. This was true after 15 and 30 days of treatment.

Results
% of Improvement of the Major Stress Symptoms
at day 30 on the subjects with highest initial Intensities (>4 at D0)



Problems	PNT 200	Placebo	Difference	Conclusion
Digestive	66.1	36.6	29.5	p < .01
Respiratory	68.9	43.1	25.8	
Cardiovascular	48	35.5	12.5	p < .04
Locomotive	65.8	63.9	1.9	
Physical	53.8	41	12.8	
Intellectual	64.8	36.7	28.1	p < .01
Emotional	43.8	23.5	20.3	p < .05
Social	36.7	22.5	14.2	p < .05

Some effects of the product **PNT 200®** could be detected on the 15th day of treatment at a dose of 150 mg/day. Significant improvements were demonstrated on digestive system (38.6% for Placebo / 58% for **PNT 200®**) and cardiovascular system (21.8% for Placebo / 53.4% for **PNT 200®**) for the subjects who demonstrated the highest initial intensities for their major symptoms (>4 at day 0). Results not shown.

After 30 days of treatment at a dose of 150 mg/day, **PNT 200®** induced significant improvements in five areas: digestive function (36.6% for Placebo / 66.1% for **PNT 200®**), cardiovascular problems (35.5% for Placebo / 48% for **PNT 200®**), intellectual disorders (36.7% for Placebo / 64.8% for **PNT 200®**), emotional disorders (23.5% for placebo / 43.8% for **PNT 200®**) and social problems (22.5% for Placebo / 36.7% for **PNT 200®**) for the subjects who demonstrated the highest intensities for their major symptoms (>4 at day 0).

Conclusion

A significantly greater positive evolution of stress symptoms was demonstrated in the **PNT 200®** group compared to the placebo group in 5 areas: digestive, cardiovascular, intellectual, emotional and social problems. Those improvements were more significant in subjects presenting a high intensity in their major symptoms at day 0, suggesting that **PNT 200®** has regulating properties in the field of stress-linked troubles.

However, there was also an important Placebo effect. An abundance of evidence from clinical studies and experimental psychology indicates that subjectively assessed disorders such as migraine headache, back pain, postsurgical pain, rheumatoid arthritis, inflammatory bowel syndrome, angina and depression may respond very well to a placebo (Price and Fields, 1997; Kirsch, 1997). Reported placebo response levels in clinical studies of anxiolytics for generalized anxiety disorder and panic disorder vary widely, with a tendency to be rather high (Piercy, 1996). Studies on antidepressants have shown placebo response rates varying from 25 to 60%, levels also observed in this study (Quitkin, 1999). Three major mechanisms have been proposed to explain placebo-evoked improvement: release of endorphins in response to the placebo stimulus (the "opioid model"), a learned response to medical intervention (the "conditioning model") or a more consciously mediated response (the "meaning" or expectancy model) (Hróbjartsson, 1996). High placebo response rates may mask true drug response. In this study for example, the effect of **PNT 200®** on locomotive symptoms could have been blunted by the high placebo response (>60%). Interestingly, thousands of drugs have been tested for use with psychological disorders, but those that have been proved to be more efficient compared to placebo and that have been approved by the FDA are few. In the present study despite a considerable placebo effect, **PNT 200®** was demonstrated to be very

active and effective in reducing several symptoms of stress.

In the light of those results, we can affirm that **PNT 200®** is very effective in reducing stress symptoms in stressed women. The effect of **PNT 200®** is significantly superior compared to the placebo effect. This result is particularly significant considering the difficulty encountered in clinical trials demonstrating a true drug activity because of the high placebo response in the field of anxiety and depression disorders. Interestingly, animal studies have shown that **PNT 200®** does not induce side effects as dependence, loss of memory and tolerance, as shown with the use of pharmaceutical drugs.

Dr. Marta Santuré, Ph.D., *Researcher*

Marta Santuré has a strong background in nutrition. She earned a Ph.D. in physiology-endocrinology from Laval University in 2001 under the supervision of Dr Hélène Bachelard of Hypertension Unit at CHUL Hospital Center. Dr. Santuré has been specializing on antihypertensive properties of peptides. Dr. Santuré is also consultant in sports nutrition (Andorran Mountaineering Federation).

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