

How Nexalin Therapy Works

Brain Stimulation Using Nexalin Technology: A Non-Invasive Method of Relieving Pain Associated with Osteoarthritis

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Nexalin Advanced Therapy Centers, LLC's

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SYNOPSIS

The human brain is the most complex organ in the body and is constantly changing, making it difficult for science to know exactly how it works. Although we have very strong opinions about it, the exact mechanism by which Nexalin[®] Advanced Therapy produces such positive results is not fully understood. However, laboratory and clinical evidence suggest that Nexalin's patented electrical stimulation¹ affects the hypothalamus and related brain structures to adapt and change the levels of neurochemicals, including neuropeptides, neurotransmitters and neuromodulators and endocrine outputs. The data support that the Nexalin electrical stimulation results in the endocrine outputs moving toward "normalization," specifically those coming from the hypothalamic nuclei and associated brain structures. A key indicator of this is a significant clinical change in levels of enkephalins and beta-endorphins in the cerebral spinal fluid of Nexalin treated subjects. Additionally, in patients with chronic pain, the Nexalin therapy counters the nociceptive response of the body² as evidenced by the clinical responses noted in subjects after they receive Nexalin Advanced Therapy.

The hypothalamus' main function is to maintain homeostasis (state of equilibrium) of the body. In order to perform this function, it is constantly sensing and responding to information received by the brain. So, by nature the hypothalamus is sensitive and responsive to stimuli. Many disorders including pain associated with osteoarthritis are believed to be a result of a decrease in the production of specific neurochemicals via the nociceptive system. Studies have observed one such neurochemical, beta-endorphin, in normal subjects to be 150% higher than in subjects with chronic pain.³ Pharmaceutical therapies act by blocking the nociceptive system signals or by replacing these neurochemicals with a drug; Nexalin therapy works by permitting your body to manage the levels of these neurochemicals on its own. With its regimen of consecutive treatment sessions, Nexalin therapy utilizes the hypothalamus' adaptive ability resulting in changes in the production of these neurochemicals to more normalized levels. The clinical effect is a decrease in the symptoms by 50% or more. Clinical trial results confirm these results as illustrated in Figures 3 - 6, where the clinical effect maintains its statistical significance through the 12-week follow up period. It has been observed that some subjects have sustained their pain relief for more than 3 years.

The Nexalin device has extensive clinical experience; the clinical trials have studies more than 700 subjects and provided more than 10,000 therapies. Nexalin Therapy has been and continues to be used in clinical studies involving a number of additional symptoms that arise from an imbalance in neurochemicals. The symptoms include those in patients with pain from osteoarthritis, Parkinson's disease, anxiety, depression, insomnia, and post surgical pain. Although the numbers of therapy sessions differ, the Nexalin electrical stimulation has consistently shown positive results and statistically significant results in most cases. Furthermore, the improvements are clinically significant and lasting typically for months, with no statistically significant drop off. We believe that this provides strong support for Nexalin Therapy's positive and durable effects.

Attachment A is included to provide more detailed information on the function of key brain structures.

¹ U.S. Patent #6904322B2

² Neuropeptide Organization of the Nociceptive and Antinociceptive Brain Systems in the Cat; V. N. Kazakov¹, T. I. Panova¹ and Yu. E. Panov¹

³ CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA, L. N. Airapetov, A. M. Zaitchik, M. S. Trukhmanov, V. P. Lebedev, V. A. Sorokoumov, Ya.S. Katsnelson, V. G. Abisogomian, and Yu. K. Kodzaev, Pavlov Institute of Physiology of the USSR Academy of Sciences, Pediatric Medical Institute, Leningrad, USSR

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HOW DOES NEXALIN ADVANCED THERAPY WORK?

As stated earlier, the brain is the most complex organ of the human body, thus the exact mechanism by which Nexalin Advanced Therapy produces such dramatic results is not fully understood. However, data suggest that the patented waveform⁴ delivered during the Nexalin Therapy effects the hypothalamus and associated brain structures. A key indicator of this effect is a significant change in levels of enkephalins and beta-endorphins in the cerebral spinal fluid and brain structures⁵, as well as other neurochemicals including serotonin, and substance P. The result produces an antinociceptive response in the brain.

A major function of the hypothalamus is to maintain homeostasis by constantly sensing and responding to information received by the brain. When the body is faced with a degenerative or chronic process, the hypothalamus appears unable to maintain normal levels of serotonin, beta-endorphins and other neuropeptides, neurotransmitters, and neuromodulators.⁶ With modified levels of these important neurochemicals, the nociceptive system result is chronic pain. The pain and degeneration of the joint, for example, can increase in frequency and severity if not treated.

Nexalin Therapy consists of consecutive, daily treatment sessions. Through repetitive stimulation of the hypothalamus and other brain structures, Nexalin Therapy can trigger significant changes in the levels of important neurochemicals within the brain, as well as trigger antinociception. Changes in the normalized levels of neurochemicals, including serotonin, beta-endorphins and substance P, may then be produced within the body to effect a response, i.e., “stop the degenerative or chronic process” – to restore, rebalance, and renew homeostasis. Since the hypothalamus’ primary job is to maintain the body in a stable, constant condition (homeostasis), we believe that Nexalin therapy can re-establish and sustain these neurochemicals at the body’s healthy, normalized levels resulting in long term improvement, as observed in recent clinical studies.

SCIENTIFIC EVIDENCE

Nexalin’s Patented Waveform

The Nexalin device produces a patented waveform that provides transcranial electrical stimulation (TES) delivered at a frequency of 77.5 Hz. This unique frequency results in the greatest increase in beta-endorphins as illustrated in Figures 1 and 2. This study resulted in an average of 580% increase ($p < 0.001$) in beta-endorphins in the cerebral spinal fluid measured in patients with chronic spinal pain and 350% increase ($p < 0.001$) in normal patients with no chronic pain symptoms.⁷

⁴ U.S. Patent #6904322B2

⁵ CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA, L. N. Airapetov, A. M. Zaitchik, M. S. Trukhmanov, V. P. Lebedev, V. A. Sorokoumov, Ya.S. Katsnelson, V. G. Abisogomian, and Yu. K. Kodzaev, Pavlov Institute of Physiology of the USSR Academy of Sciences, Pediatric Medical Institute, Leningrad, USSR

⁶ *The Handbook of Clinical Neurology, Vol 80 (3rd series Vol 2)* The Human Hypothalamus: Basic and Clinical Aspects by Dick Frans Swaab; © 2004

⁷ CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA, L. N. Airapetov, A. M. Zaitchik, M. S. Trukhmanov, V. P. Lebedev, V. A. Sorokoumov, Ya.S. Katsnelson, V. G. Abisogomian, and Yu. K. Kodzaev, Pavlov Institute of Physiology of the USSR Academy of Sciences, Pediatric Medical Institute, Leningrad, USSR

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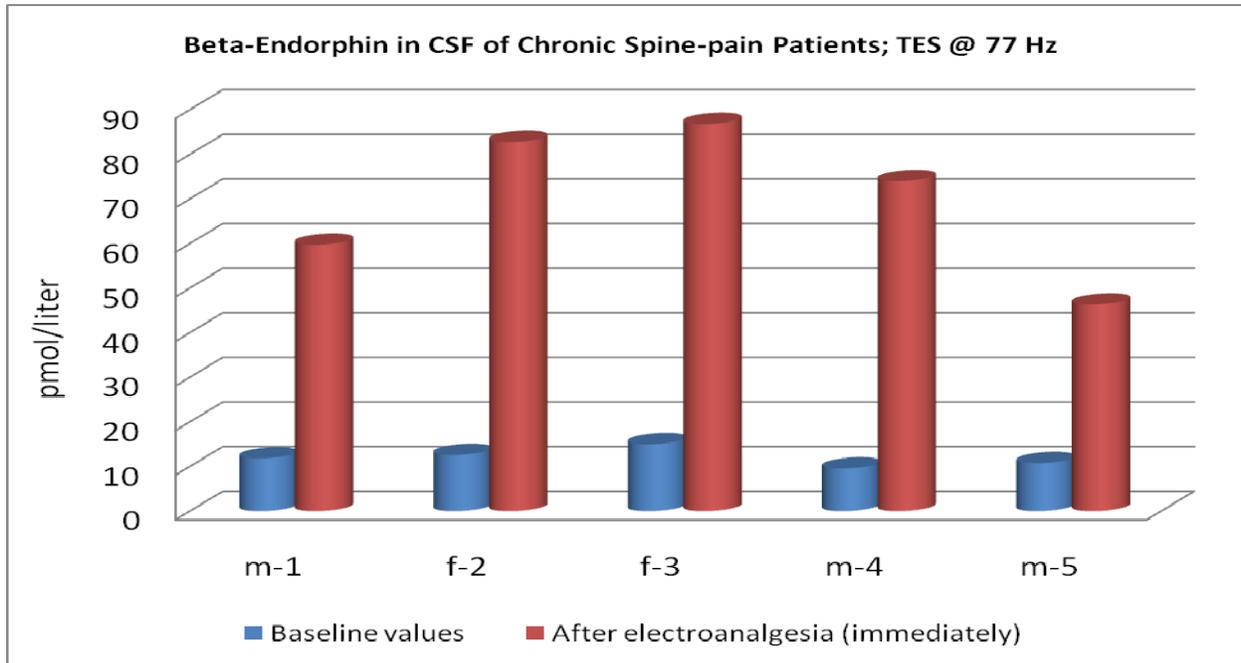


Figure 1 – Amount of Beta-Endorphin in the Cerebral Spinal Fluid (CSF) in Chronic Spine pain patients when stimulated using TES at 77 Hz. In patients with chronic pain, beta-endorphin concentration was 1.5-times lower than that in normal subjects and had an average value of 11.9+0.8-pmole/l. After 30-min. electrostimulation, average CSF beta-endorphin concentrations increase 580% higher to reach the level of 69.9+7.5-pmole/l ($p < 0.001$).

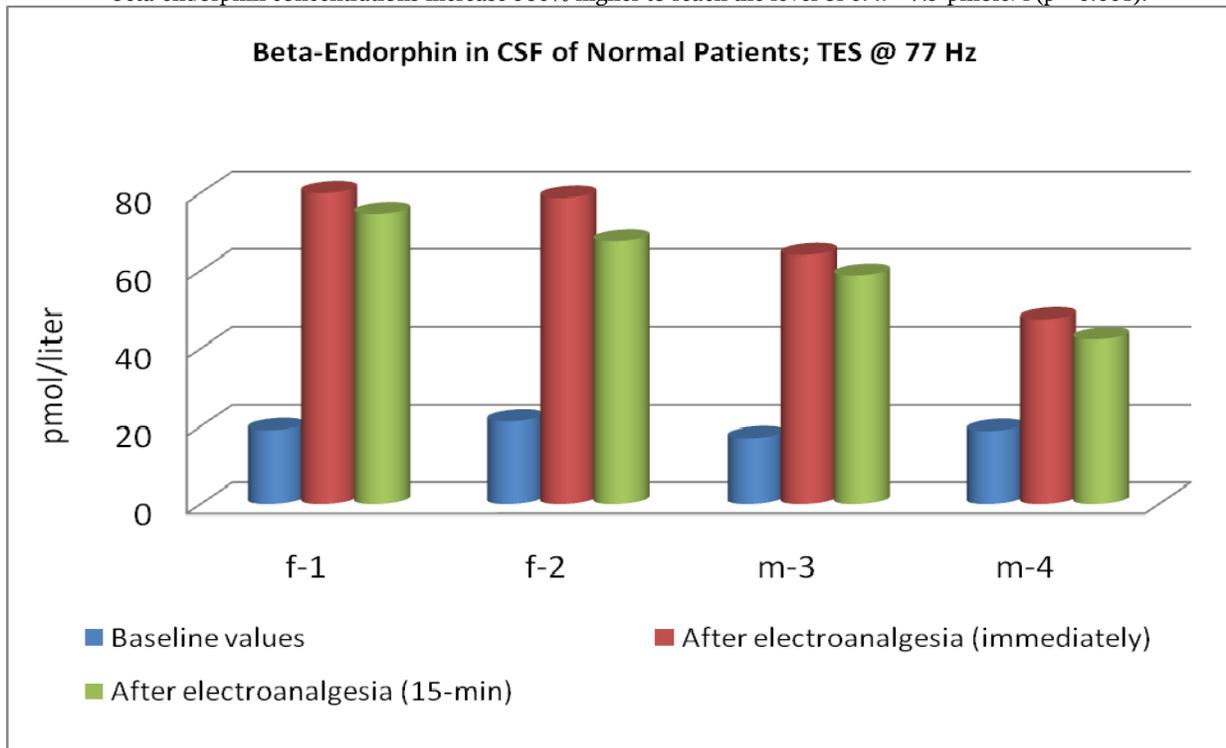


Figure 2 – Amount of Beta-Endorphin in the Cerebral Spinal Fluid (CSF) in normal patients when stimulated using TES at 77 Hz. Average beta-endorphin concentration in CSF of normal individuals was 19.1+0.9- pmole/l. Transcranial electro analgesia caused average beta-endorphin concentrations to increase 350% ($p < 0.001$) and to reach the level of 67.6+7.6-pmole/l. 15 minutes after the end of electrostimulation, no significant increase in the beta-endorphin levels could be observed ($p < 0.05$).

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THE CLINICAL RESULTS

The results of a double-blind-placebo controlled Phase III Pivotal Study, Using Nexalin Advanced Therapy to Treat Pain Associated with Osteoarthritis, showed statistically significant results (Figures 3-6). These results indicate that Nexalin Therapy can be effective at providing long term pain relief for pain associated with osteoarthritis.

Patients treated with Nexalin Therapy reported significant clinical improvement (measured using the Visual Score (VS) Pain Scale) that lasted the entire 12 week follow up period⁸. The encouraging aspect of these results is that they are both statistically and clinically significant.

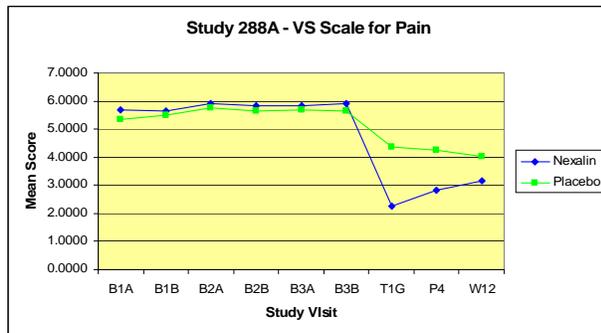


Figure 3 – Plot of the average pain relief using the VS pain scale: Statistically Significant to 12 weeks; T1G* (p =0.0000); W12* (p=0.017).

T1G – Following 7th consecutive day of electrical stimulation
W12 – Week 12 of the follow up period

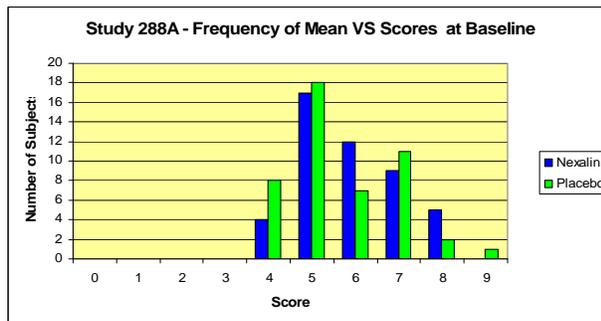


Figure 4 – Plot of the pain levels during baseline.

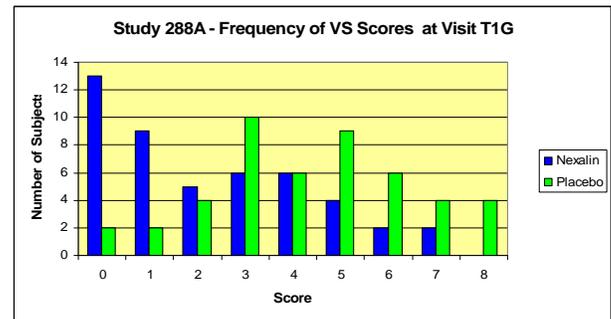


Figure 5 – Plot of the pain levels after Nexalin Therapy; 70% responders (>= 50% reduction).

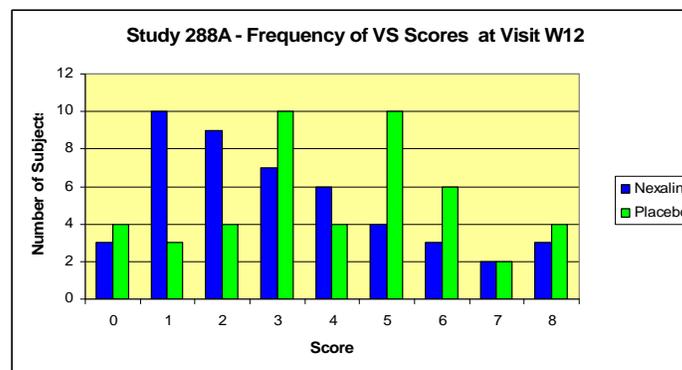


Figure 6 – Plot of the pain levels after 12 weeks; 64% responders.

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⁸ Phase III Pivotal Study, Using Nexalin Advanced Therapy to Treat Pain Associated with Osteoarthritis

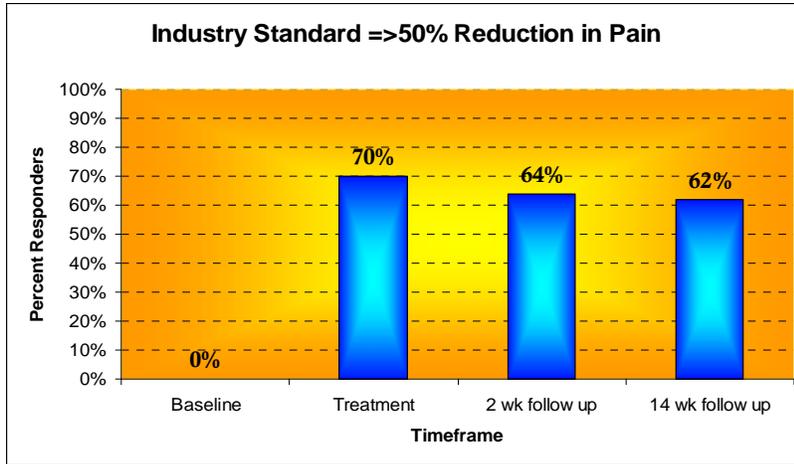


Figure 7

At Baseline, patients in both the *NEXALIN* and *Placebo* groups reported pain levels no less than Moderate (ref. Figure 4).

Clinically significant results are noted at conclusion of the treatment and are maintained through the 2 week follow-up, as well as 14 week follow-up with no significant drop-off in effectiveness through the 14 weeks of follow up.

DEMONSTRATED CLINICAL SAFETY

The Nexalin device has undergone extensive safety analyses with the results clearly indicating that the device is safe for its intended use. Additionally, the classification of the device places it into a non-significant risk (low risk device) category.

A review of multiple Clinical Trials (with a follow up period of one year) involving almost 500 subjects, demonstrates that Nexalin Therapy does not result in any significant

untoward responses. In fact, there was no significant difference between reported events in the placebo controlled group and reported events in the active treatment group (Figure 7).

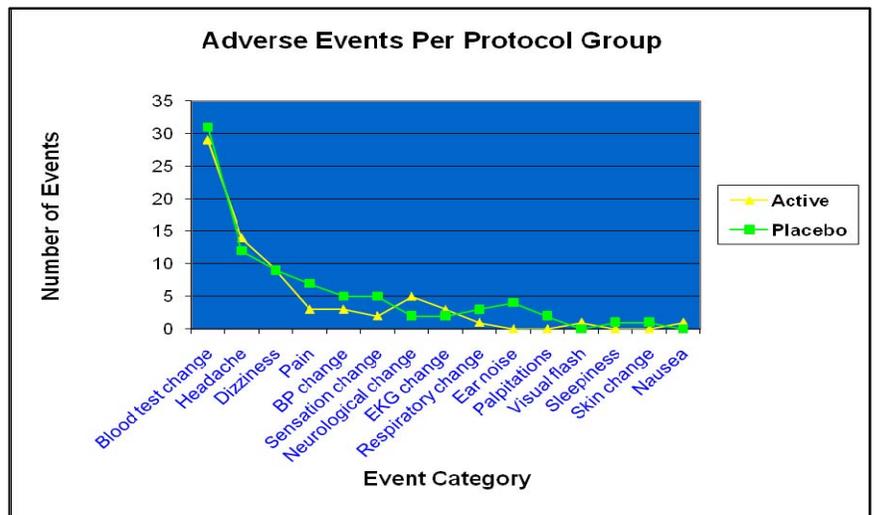


Figure 8

HOW IS THE THERAPY ADMINISTERED?

The patented waveform of Nexalin Advanced Therapy is administered through medical grade conductive pads that are produced specifically for the Nexalin technology. The pads are placed on the forehead and behind each ear, and are connected to the Nexalin device with thin cables.

Nexalin Advanced Therapy is a highly effective, yet soothing treatment. Most patients feel nothing during Nexalin Therapy. At Nexalin Advanced Therapy Centers, patients are treated to a quiet, 45-minute session where many actually relax to the point of sleep during a session. Relief starts as early as the first therapy and for most by the third.



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CONCLUSION

The brain is the most complex and least understood organ of the human body. Nexalin Therapy appears to provide stimulation that affects the hypothalamus and associated brain structures to adapt and alter the levels of neuropeptides, neurotransmitters and neuromodulators critical to maintaining normal antinociception. This effect is long lasting. It is hypothesized that with a maintenance program normalization can be maintained for prolonged periods.

At the completion of the Nexalin Therapy the hypothalamus has either adapted to a new level and stabilized or is in the process of stabilizing, resulting in the long lasting benefit.

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ATTACHMENT A

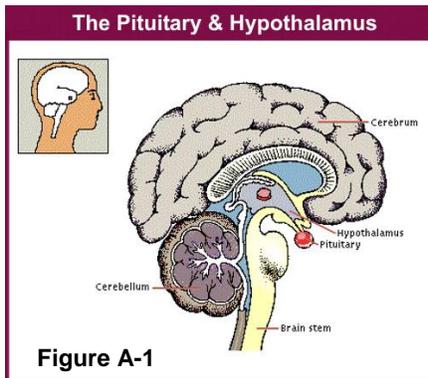
FUNCTION OF KEY BRAIN STRUCTURES

An overview of the endocrine system, and more specifically the hypothalamus, is provided below to help you better understand the impact of Nexalin® Advanced Therapy’s stimulation on these vital areas of the brain.

The Hypothalamus

Within the body’s endocrine system, the hypothalamus is a collection of specialized cells located in the lower central part of the brain. This vital area is the control center of all autonomic regulatory activities of the body. It has been said that the hypothalamus is the “brain of the brain.” It is also:

- An important emotional center, controlling the molecules that make you feel exhilarated, angry, or unhappy.⁹
- The hub for automatic (or subconscious) and endocrine homeostatic systems such as cardiovascular, temperature, and abdominal visceral regulation.
- Management system for all endocrine hormonal levels, sensory processing, and organizing body metabolism, as well as ingestive behaviors.



The hypothalamus is the primary link between the endocrine and nervous systems; it appears that almost everything the hypothalamus does is related in some way to the management of the brain and body connection. Nerve cells in the hypothalamus control the pituitary gland by producing chemicals that either stimulate or suppress hormone secretions from the pituitary.

The hypothalamus is responsible for maintaining **homeostasis**, the body’s regulation of its internal environment so as to maintain a stable, constant condition. To maintain homeostasis, the hypothalamus is constantly adapting to stimuli from the five senses (sight, hearing, touch, taste, smell) as well as feedback from the nervous and endocrine systems.

“Once the hypothalamus is aware of a problem, how does it fix it? Essentially, there are two main outputs: neural signals to the autonomic system and endocrine signals to/through the pituitary.”¹⁰

The hypothalamus controls pituitary output by secreting specific chemicals to the pituitary's front lobe. If the hypothalamus is the “command center,” the pituitary gland is the “first lieutenant.” “The pituitary gland is often portrayed as the ‘master gland’ of the body. Such praise is justified

⁹ *Brain Basics: Know Your Brain*, National Institute of Neurological Disorders and Stroke (part of the National Institutes of Health), NIH Publication No.01-3440a, last updated May 01, 2007

¹⁰ *Neuroscience Tutorial*, created by Diana Weedman Molavi, PhD at the Washington University School of Medicine; Washington University Program in Neuroscience, copyright 1997

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in the sense that the anterior and posterior pituitary secretes a battery of hormones that collectively influence all cells and affect virtually all physiologic processes. *The pituitary gland may be king, but the power behind the throne is clearly the hypothalamus.*¹¹

The paraventricular nucleus (PVN) is an aggregation of neurons in the hypothalamus, which produces many hormones. It is adjacent to the third ventricle (hence the name of the nucleus.) Although it is in the periventricular zone, it is not to be confused with the periventricular nucleus that occupies a more medial, subjacent position to the third ventricle. The PVN is highly vascularised and is within the blood-brain barrier, although the neuroendocrine neurons in this nucleus project to sites (the median eminence and the posterior pituitary) that lack a blood-brain barrier.¹²

Neurochemicals

The brain produces more than 50 identified active drugs. Some of these are associated with memory, others with intelligence, still others are sedating. Some of the neurochemicals believed to be affected by Nexalin Therapy are:

- *Endorphin* – Called the brain's painkiller, it is 3 times more potent than morphine.
- *Serotonin* – An opiate-like chemical that helps maintain a "happy feeling," and seems to help keep moods under control.
- *Melatonin* – Produced by the pineal gland, melatonin regulates behavioral and physiological circadian rhythms. Levels of melatonin in the blood are highest prior to bedtime.
- *Dopamine* – Similar to adrenaline; it affects brain processes that control movement, emotional response, and ability to experience pleasure and pain. The brains of people with Parkinson's disease contain almost no dopamine.
- *Substance P* – In the central nervous system, is associated with the regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, neurotoxicity and pain.
- *Acetylcholine* – The first neurotransmitter ever identified, it is particularly important in the stimulation of muscle tissue. In high doses, it can cause convulsions and tremors. In deficient levels, it can contribute to motor dysfunction.

Neurologists have long been aware of four classical neurotransmitters: *epinephrine*, *norepinephrine*, *serotonin*, and *acetylcholine*; but recently there have emerged a large number of additional neurotransmitters, of which an important group is the *neuropeptides*. While neuropeptides function as neurotransmitters, some of them also perform the role of *neuromodulators*; they do not act directly as neurotransmitters but rather as inhibitors or stimulators of neurotransmission. Opiates are a group of neuropeptides that act as both neurotransmitters and neuromodulators. Opiates' are so named because they are the naturally occurring neuropeptides with a strong affinity for the receptors that bind opiate drugs such as morphine and heroin. In effect, they are the body's opiates.

¹¹ Hypertexts for Biomedical Sciences, *Pathophysiology of the Endocrine System – Functional Anatomy of the Hypothalamus and Pituitary Gland*, Colorado State University; last updated on September 04, 2001; author: R. Bowen

¹² Paraventricular nucleus of hypothalamus - Wikipedia

The Endocrine System

“Although we rarely think about them, the glands of the endocrine system and the hormones they release influence almost every cell, organ, and function of our bodies. The endocrine system is instrumental in regulating mood, growth and development, tissue function, and metabolism, as well as sexual function and reproductive processes. Even though the nervous system and endocrine system are separate systems, they often work together to help the body function properly.

The foundations of the endocrine system are the **hormones and glands**. As the body's chemical messengers, hormones transfer information and instructions from one set of cells to another. Hormone levels can be influenced by factors such as stress, infection, and changes in the balance of fluid and minerals in the blood.

A gland is a group of cells that produces and secretes, or gives off, chemicals. Some types of glands release their secretions in specific areas. Endocrine glands release more than 20 major hormones directly into the bloodstream where they can be transported to cells in other parts of the body.

The major glands that make up the human endocrine system are the **hypothalamus, pituitary**, thyroid, parathyroids, adrenals, **pineal body**, and the reproductive glands.

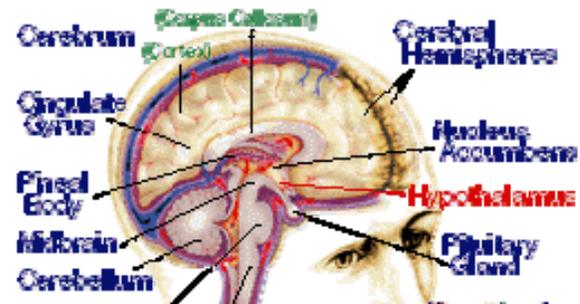


Figure A-2

The Pituitary Gland

The **pituitary gland** is located at the base of the brain just beneath the hypothalamus and is considered the most important gland of the endocrine system. It's often called the "master gland" because it receives instructions from the hypothalamus and then releases hormones that control the thyroid and adrenal glands. The production and secretion of pituitary hormones can be influenced by factors such as emotions and seasonal change. To accomplish this, the hypothalamus relays information sensed by the brain (such as environmental temperature, light exposure patterns, and feelings) to the pituitary. Some of the hormones secreted by the pituitary are **endorphins**, chemicals that act on the nervous system to reduce sensitivity to pain.”¹³

The Pineal Gland

The **pineal body**, also called the pineal gland. The **pineal gland** is a small organ shaped like a pine cone (hence its name) located in the middle of the brain. The pineal gland synthesizes and secretes melatonin, a structurally simple hormone that communicates information about

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¹³ Excerpts from KidsHealth website, created by The Nemours Foundation's Center for Children's Health Media; updated and reviewed by: Steven Dowshen, MD; July 2007

environmental lighting to various parts of the body. The duration of melatonin secretion each day is directly proportional to the length of the night. The light-transducing ability of the pineal gland has led some to call the pineal the "third eye".¹⁴

The Limbic System

The **limbic system** wraps around the brain stem and is beneath the cerebral cortex. It is a major center for emotion formation, behavior, learning, and memory. The limbic structures are also connected with other major structures such as the cortex, hypothalamus, thalamus, and basal ganglia.

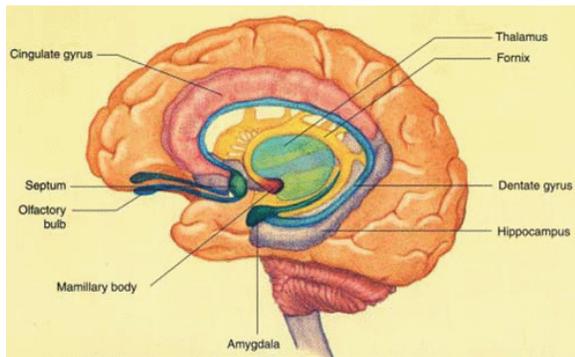


Figure A-3

The structures of the limbic system are highly interconnected with the rest of the brain, and they likely form a gateway for communication between the cerebral cortex and the hypothalamus. This gateway allows for cognitive processes to modify the affect of the limbic system on hypothalamic functions, which provides a more extensive adaptive mechanism in an effort to normalize.

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¹⁴ Hypertexts for Biomedical Sciences, *Pathophysiology of the Endocrine System – The Pineal Gland*, Colorado State University; last updated on March 17, 2003 Author: R. Bowen