PRIMER

ON THE PHYSIOLOGIC EFFECTS OF PAIN ON THE HORMONE SYSTEM

CHAPTER 4
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BRINGING A NEW DIMENSION TO PAIN CARE

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Hormones & Pain Care **Information Network**

INTRODUCTION

Every health professional who deals with pain must know the effects of pain on the hormone (endocrine) system. Some hormone serum levels now allow us to evaluate the complaint of pain in an "objective" rather than merely "subjective" manner. As such, these biomarkers help us separate the pain patient who needs greatly enhanced care from those who only require minimal care. This primer is for the professional who is just getting started in trying to understand pain's effect on the hormone system. Don't be intimidated. A little reading and thinking, and you'll grasp the material presented here in little time. Severe, as opposed to mild, pain has profound physiologic effects on the hormone system.[1-12] Fundamentally, severe pain, acute or chronic, is a severe stressor that activates the major stress control mechanism of the body which is the hypothalamic-pituitary-adrenal-thyroid-gonadal system.[10,13-16] This system is often referred to as an "axis" since it is a closed system with hormonal feedback or controls within the system.[16-18] This paper will refer to the "axis" as the "HPATG", indicating the first letter of the endocrine glands involved in the system. The biologic purpose of this system (See Figure One) is to produce extra hormones in the thyroid, adrenals, and gonads and secrete them into the serum as these compounds are required by the body for many pain control functions including protection and regeneration of injured tissue, immunologic activity, and metabolic controls.[13,16,17] Once these extra hormones, such as thyroid, cortisol, or testosterone, enter the serum, they travel throughout the body to target areas including injured nerves and the central nervous system (CNS).[18,19] Although it is known that pain has an effect on neurohormones produced in the brain, insulin produced in the pancreas, and adrenalin produced in the adrenal medulla, there are few studies or reports on these effects and they will not be covered here.

PERIPHERAL GLANDS FOR PAIN CONTROL

Adrenals
Gonads
Thyroids

Over the past 50 years, there have been numerous reports and studies on pain's physiologic effect on the HPATG, so it is the focus of this primer.[1-12,20-30] Studies clearly point out that severe pain initially stimulates the hormone system to produce extra hormones which raise serum levels and if severe pain goes uncontrolled for too long, the glands can't keep up production and serum hormone levels drop below normal. (Figures One & Two) It is also cogent to note that the accumulated information and understanding about pain's effects on the HPATG is now such that testing and replacement of certain hormones should be a basic foundation of clinical pain treatment.

TABLE ONE

HORMONES FROM PERIPHERAL GLANDS THAT ARE CRITICAL FOR PAIN CONTROL

- CORTISOL
- PREGNENOLONE
- DEHYDROEPIANDROSTERONE (DHEA)
- PROGESTERONE
- TESTOSTERONE
- ESTROGEN
- THYROID

HORMONE FUNCTIONS IN PAIN CONTROL

Adequate pain control may not be achieved without homeostasis of certain hormones.[31-52] Hormonal homeostasis is defined here as the maintenance of a hormone within a normal serum range. The critical pain control hormones that are produced in glands outside the CNS are cortisol, pregnenolone, dehydroepiandrosterone (DHEA), progesterone, testosterone, estrogen, and thyroid.[31-52] (Table One) Among the primary pain control functions of these hormones are immune and anti-inflammatory actions, cellular protection, tissue regeneration, glucose control, and modulation of central nervous system (CNS) receptors, blood brain barrier, and nerve conduction.[53-63] (Table Two) Given the CNS effects of certain hormones, analgesics including antidepressants, neuropathic agents, and opioids may not achieve maximal analgesic responses without hormone homeostasis.[19,33,37,42,49-53]

THE RELEASING HORMONES

Pain signals that reach the brain from any injury in the peripheral nervous system activate three releasing hormones in the hypothalamus.[8,9,15,48] (Figure One) They are corticotropin releasing hormone (CRH), gonadal releasing hormone (GRH), and thyroid releasing hormone (TRH).[8,9,12,48] These three hormones, in turn, cause the anterior pituitary to release into the serum adrenal corticotropin hormone (ACTH), follicle stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulating hormone (TSH). The end organs for stimulation are the adrenals, gonads, and thyroid which release into the serum hormones necessary for pain control including cortisol, pregnenolone, DHEA, testosterone, progesterone, estrogen, triiodothyronine (T_3), and thyroxine (T_4). (Table One) Adrenalin and other catecholamines are also released from the adrenal medulla, but it is only partially a result of ACTH stimulation. Serum concentrations of the pituitary and end-organ hormones can now be assayed in commercial laboratories and replacement hormones are also now readily available. Consequently, the old saying that pain "can't be measured" needs to be modified. Serum levels of the pituitary and end-organ hormones noted here serve as biomarkers for uncontrolled pain.[3,7,30,66] (See Table Three) In other words, it may not be possible to quantitate pain, per se, but it is now possible to determine if pain severity has reached a level that it has activated the HPATG.[29,66] It should be noted that commercial assays for the hypothalamic releasing hormones (CRH, GRH, TRH) are in the developmental stages, and, when available, will provide an even more direct, assessment of brain overstimulation by pain.[48]

Pain is a stressor and raises hormone levels.

THE STIMULATION PHASE

It is important to note that only severe pain will stimulate the HPATG to the point that the end-organs produce and secrete enough hormones to raise serum levels above normal.[29,67] (Figure One) Studies show that patients with mild or intermittent pain, such as common degenerative

TABLE TWO

MAJOR PAIN CONTROL MECHANISMS OF HORMONES

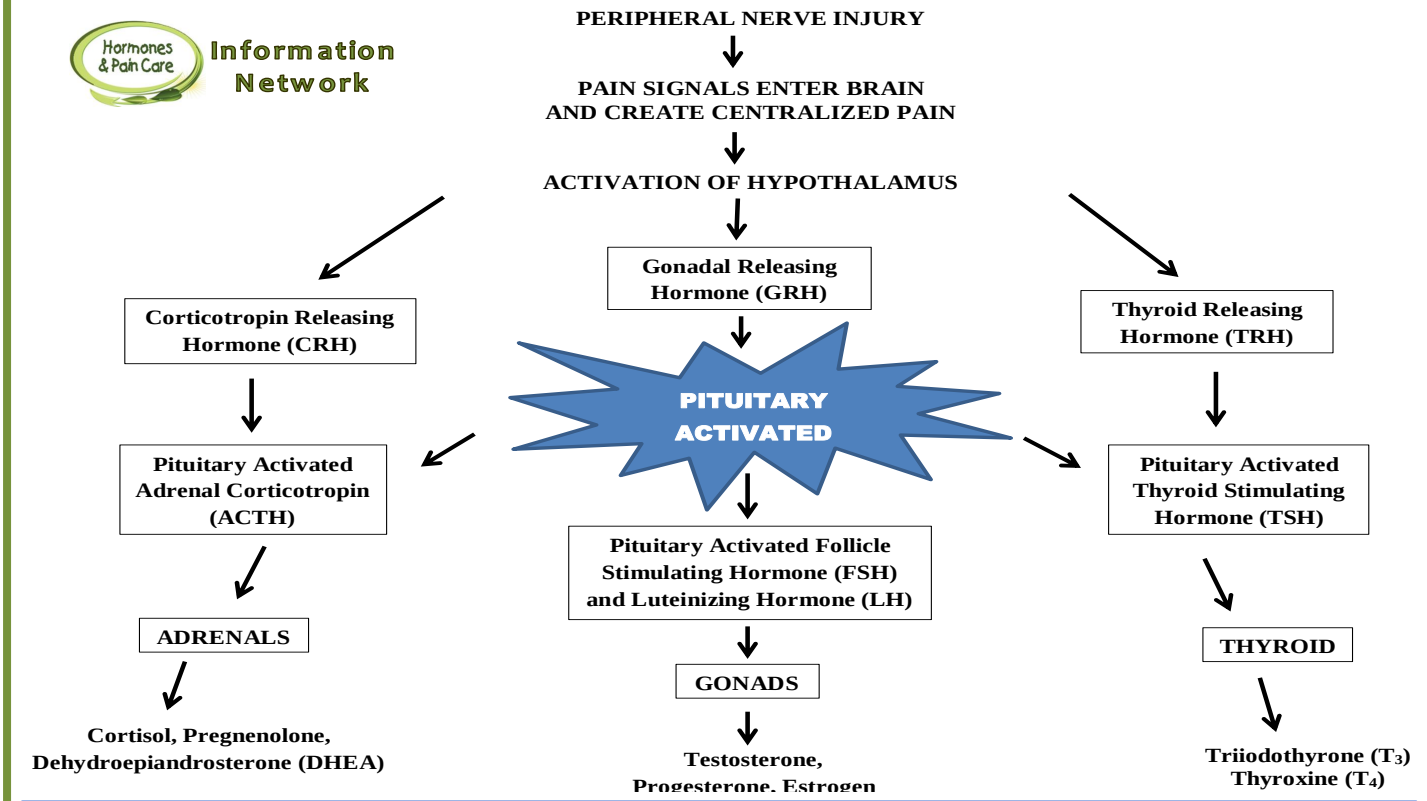
- IMMUNOREACITY
- ANTI-INFLAMMATORY ACTION
- TISSUE REGENERATION
- CELLULAR PROTECTION
- GLUCOSE CONTROL
- CELLULAR METABOLISM
- CNS FUNCTIONS
  - ✓ Receptor Binding
  - ✓ Nerve Conduction
  - ✓ Maintenance of Blood Brain Barrier

arthritis, have normal hormone serum levels.[67] This is an excellent practical point for the pain practitioner since normal serum hormone levels usually mean the patient's pain is not in need of much enhanced therapy with high risk treatment such as long-acting opioid drugs or invasive interventions.[68-76] Put another way, hormone serum levels are excellent biomarkers that help separate severe from mild pain. If end-organ serum hormone levels are above normal, however, enhanced pain control treatment will be needed.[77] If hormones are below normal levels, it is prudent to replace the hormones and achieve homeostasis before embarking on a therapeutic regimen that has risks, such as opioid-induced endocrine suppression.[23,68-77]

THE DEPLETION PHASE

If tissues in the hypothalamus, pituitary, adrenals, gonads, or thyroid cannot keep up with the demands of severe pain, serum levels of some hormones may drop below normal levels.[10,29,66] (Figure Two) Based on clinical experience, to date, the most common end-organ hormones to diminish in the serum due to uncontrolled pain are cortisol, pregnenolone, testosterone and DHEA.[29,30,77] It is noted that thyroid depletion occurs, but is quite uncommon based on today's testing technology.[21] Also, some clinicians believe that thyroid depletion should be assessed by symptoms rather than today's assays for T_3 and T_4.[26] Once pain is controlled and/or hormones are replaced, serum levels will almost always return to normal. It is emphasized that only severe pain

FIGURE ONE
PAIN STIMULATION OF THE HORMONE SYSTEM



Pain stimulation causes adrenal, gonad and thyroid hormones to elevate in the serum. If pain goes uncontrolled for a considerable time period, hormonal depletion may occur and serum levels will drop below normal.

will stimulate HPATG to the point that the end-organs will not produce enough hormones to maintain homeostasis.[67]

CORTISOL ABNORMALITIES: THE MOST SERIOUS HORMONE COMPLICATIONS

Chronic cortisol abnormalities, either too high or too low, over an extended time period are the major hormonal problems in chronic pain patients. Although the prevalence of cortisol abnormalities in chronic pain patients is unknown, the recognition of excess and deficient cortisol states is starting to be done in pain patients.[7,10,29] Extended periods of exposure to excess cortisol, often referred to as Cushing's Syndrome, named after Harvey Cushing who first described the clinical signs and symptoms in patients with pituitary tumors, has serious complications.[78-80,84] They include osteoporosis, hypertension, hyperlipidemia, and mental deficiencies. (Table Three) Heretofore, many of these complications in pain patients were simply viewed as unrelated, random events. Table Three lists the complications of hypercortisolemia.[84] The major ones that manifest in pain patients are osteoporosis, joint degeneration, tooth decay, hypertension, hyperlipidemia, obesity, and mental deterioration.[77-84]

The disease originally described by Cushing was due to pituitary adenomas which we now know constantly secretes ACTH and raises serum cortisol levels.[78,79,80,84] In chronic pain patients, hypercortisolemia is usually episodic and only occurs during flares or periods of under-treatment that force the hypothalamus and pituitary to temporarily secrete ACTH and cortisol. Physiologically, however, it makes little difference if high serum cortisol levels are intermittent or constant, because chronic pain patients may experience high cortisol levels, even if intermittent, over long time periods and sustain complications. It is very likely that joint degeneration, renal stones, vertebral collapse, hypertension, dementia, and hyperlipidemia so commonly observed in chronic pain patients, is the result of intermittent hypercortisolemia over an extended period of time. Of particular concern is that hypercortisolemia causes calcium resorption which is the apparent cause of osteoporosis, dental erosion, joint degeneration, nephrolithiasis (renal stones) and vertebral collapse. Pain practitioners must be alert and recognize these complications and evaluate patients for cortisol abnormalities.

Pain, for too long, lowers hormone levels.

FIGURE TWO

WHY SERUM HORMONE LEVELS DROP WITH SEVERE, UNCONTROLLED PAIN

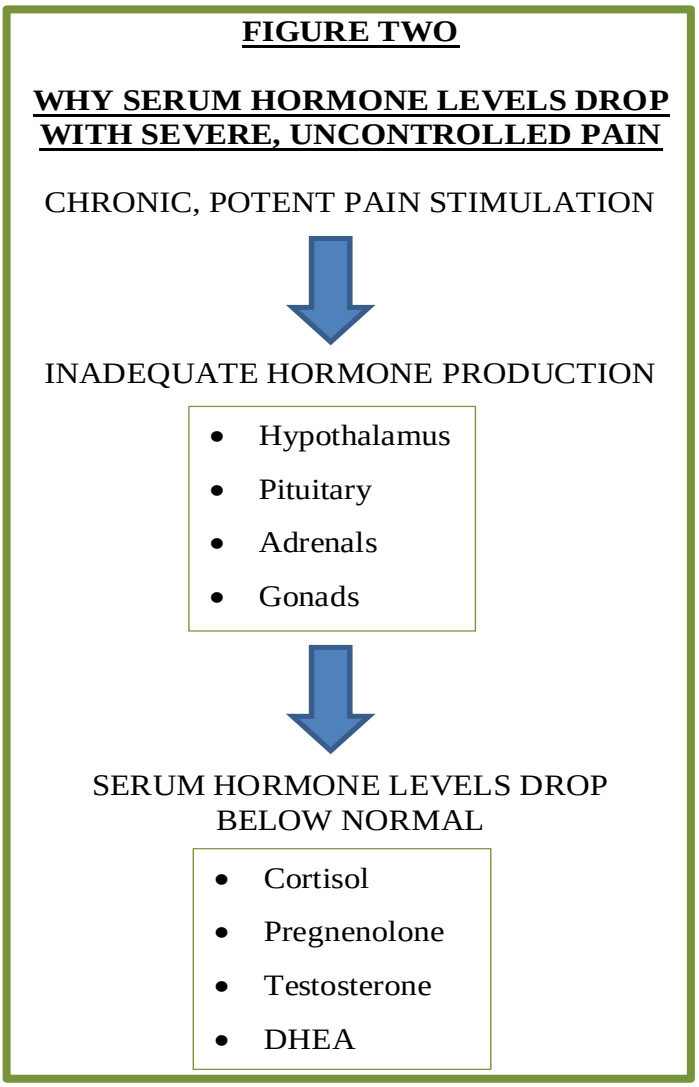


TABLE THREE CLINICAL FEATURES OF CUSHING'S SYNDROME	
FEATURES	**PROPORTION % PATIENTS**
Obesity Or Weight Gain	95%
Facial Plethora	90%
Decreased Libido	90%
Rounded Face	90%
Thin Skin	85%
Menstrual Irregularity	80%
Hypertension	75%
Hirsutism	75%
Depression	70%
Easy Bruising	65%
Glucose Intolerance	60%
Weakness	60%
Osteopenia/Fracture Dental Erosion	50%
Nephrolithiasis	50%
Adopted from Newell-Price J, Bertango X, Grossman AS, Nieman L. Cushing Syndrome. Lancet 2006;362:1605-1617.[84]	

Long term hypocortisolemia, often known as Addison's Disease, has a different set of complications. Hypocortisolemia produces weight loss, muscle wasting, mental apathy, hypotension, and if not detected and treated, may cause sudden death. In patients who take opioids, testosterone is the major hormone suppressed, although opioids may also suppress cortisol.

Adrenal insufficiency was first described by Thomas Addison in 1855.[85] Serum testing and even the name cortisol were not yet invented. His treatise was called, "On the Constitutional and Local Effect of Disease of the Supra-Renal Capsules". He reported on 11 patients who died from severe disease of the supra renal capsules now called the "adrenal glands", and who had a similar clinical history of weight loss, muscle wasting, lowered blood pressure, decreased mental ability, yellowish hue to the skin, and pigmentation around scars, gums, axillae, and skin creases.[85] Interestingly, 2 of his 11 cases had severe pain. One had facial and the other extremity neuropathy. Severe, chronic pain may cause significant cortisol suppression, and a typical Addison's clinical profile will ensue. (Table Four) Pain practitioners should suspect this condition if such symptoms as weight loss, muscle wasting, hypotension, and brown pigmentation on the skin are present. Hydrocortisone replacement in hypocortisolemia as well as enhanced pain control is essential. It can even be a simple life-saving endeavor.[73,77,86] (See Table Four)

Too much or too little cortisol has severe complications.

Serum cortisol deficiency may cause death.

SERUM TESTING AND REPLACEMENT

Due to the two phases of pain's effect on the HPATG, stimulation and depletion, practitioners should be prepared for either too high or too low serum hormone levels when they are assayed. Shown here is a series of serum cortisol levels in 40 intractable pain patients referred to my clinic. (Table Five) Note that some are high, low, and normal. In particular, it should be noted that one individual had a cortisol concentration of less than 1.0 mcg/dl. This is clearly a dangerous sign, as it indicates that the patient's adrenals are nearly non-functional.[83] Death may suddenly occur in this situation. The author regards a cortisol of less than 1.0 mcg/dl to be considered a life-threatening emergency that requires immediate hormone replacement with hydrocortisone.

Replacement or partial replacement of hydrocortisone, pregnenolone, DHEA, or testosterone is rightfully emerging as a new procedure in pain treatment.[77,83] The benefits appear numerous. In early reports, less medication, particularly opioids, is required if hormone serum levels are normal prior to initiation.[77,86,87] The author highly recommends that hormone testing and necessary replacement be done before long-acting opioids and other high risk measures be instituted.

Opioids most commonly suppress testosterone and estrogen.

OPIOID SUPPRESSION OF HORMONES

Opioids, particularly those that are long-acting or delivered by the intrathecal route, may suppress some hormone production.[68-76] Suppressed levels of testosterone are the most common problem with opioid administration, but cortisol, pregnenolone, and DHEA may also be suppressed.[69,72] For unclear reasons, the thyroid hormones T_3 and T_4 are seldom suppressed.[25,72] The predilection for testosterone suppression is believed to be due to opioid's tendency to preferentially suppress GRH.[72] Testosterone suppression with long-acting and intrathecal opioids approaches 75-85% of patients.[68,72,74,76] Given this extremely high prevalence, patients who take long-acting opioids need to be regularly screened for testosterone, as well as pregnenolone, DHEA, and cortisol. Replacement of these hormones should be done as low serum levels of any of these hormones may be associated with poor pain control including symptoms of allodynia and hyperalgesia.[86,87] In a patient who takes opioids, a low serum hormone concentration may be due to opioids, pain, or both. Consequently, in clinical practice, hormone replacement may have to be done without knowing precisely which mechanism is primarily responsible for hormone deficiencies.

TABLE FOUR

COMMON FEATURES OF HYPOCORTISOLEMIA IN PAIN PATIENTS

WEAKNESS

WEIGHT LOSS

MUSCLE WASTING

ANOREXIA

HYPOTENSION

MENTAL APATHY

TACHYCARDIA

YELLOWISH HUE OF SKIN

PIGMENTATION AROUND SKIN CREASES OR SCARS

These symptoms were reported in Addison's original 1855 description of patients who died of adrenal failure.[85]

SUMMARY

The basic physiologic effect of pain on the endocrine system is one of severe stress. Pain initially stimulates the HPATG system to produce and secrete extra hormones from the adrenals, gonads, and thyroid. Hormones including cortisol, pregnenolone, DHEA, testosterone, and thyroid (T_3 and T_4) travel from their producing glands to distinct tissue targets including injured nerves and the CNS. Hormones provide immunologic, anti-inflammatory, and regenerative properties for cellular protection and healing. In the stimulation phase of severe pain, serum hormone levels are elevated. If pain goes unabated for too long, the hormonal system is unable to keep up with the stress of pain, and hormone production may be decreased causing serum hormone levels drop below normal.

The most serious hormone complications of severe chronic pain are hyper-and hypocortisolemia. Chronic hypercortisolemia has numerous complications related to increased calcium resorption and include osteopenia, joint degeneration, tooth decay, degenerative arthritis, vertebral collapse, and renal stones. Hypocortisolemia may occur in severe under-treated pain, and it may drop below 1.0 mcg/dl which may be too low to sustain life. Low serum cortisol levels are clinically manifested by weight loss, muscle wasting, weakness, hypotension, and pigmentation around scars and skin creases.

Hormone serum levels serve as biomarkers for uncontrolled pain. Before embarking on therapy with long-acting opioids and other pain treatment modalities with risk, an assessment should be made as to whether a chronic pain patient has normal serum levels of cortisol, pregnenolone, DHEA, and testosterone as a minimal hormone assessment. Early clinical experience indicates that opioids and possibly other treatments may be spared if hormonal homeostasis is achieved prior to institution of high risk therapies.

TABLE FIVE

CORTISOL SERUM CONCENTRATIONS IN 40 CONSECUTIVE ADMISSIONS TO TREATMENT

NORMAL RANGE 5 to 20 mcg/dl

1. 1.1	**11. 28.9**	**21. 6.2**	**31. 4.7**
2. 4.9	**12. 11.6**	**22. 4.0**	**32. 16.2**
3. 2.2	**13. 24.1**	**23. 4.3**	**33. 4.3**
4. 2.2	**14. 3.9**	**24. 30.1**	**34. 29.8**
5. 13.0	**15. 28.9**	**25. 1.3**	**35. 22.7**
6. 28.5	**16. 32.5**	**26. 16.1**	**36. 25.8**
7. 0.6	**17. 29.0**	**27. 18.5**	**37. 18.7**
8. 4.3	**18. 27.3**	**28. 9.6**	**38. 9.0**
9. 3.7	**19. 19.2**	**29. 3.4**	**39. 21.8**
10. 5.0	**20. 8.6**	**30. 10.8**	**40. 19.8**

Patients were referred, under-treated and claimed their pain to be disabling and constant. Note that some levels are above and below normal range indicating uncontrolled pain. Patient number 7 has such a low level that adrenal failure and death could occur without immediate hydrocortisone replacement.

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