Neurohormones in Pain and Headache Management: New and Emerging Concepts

The authors discuss a special set of neurohormones with pain-related functions, which if tapped for their intrinsic use, may diminish the need for opioids.

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The recent discovery and awareness that the central nervous system (CNS) makes specific hormones for intrinsic use in addition to those for peripheral use is a profound finding that is critical to clinical pain and headache management. Some neurohormones provide the physiologic effects of neuroprotection and neurogenesis that are essential for pain reduction, prevention, and treatment.

Following is an attempt to provide an early status report on what we do (and don't) know about the function of neurohormones relative to pain management. Be clearly advised that this report is elementary and, undoubtedly, will be subject to expansion and revision as more basic science and clinical experience are accumulated. This review looks at 8 neurohormones that are in early clinical use.

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Definition of Neurohormones

The CNS, including the pituitary gland, produces numerous hormones, but relatively few are known to have pain-related functions within the CNS.[1–22] For the purposes of this article, we define a neurohormone as a hormone that is produced, retained, and has functions within the CNS that promote pain control. Additional hormones surely will be found.

Table 1 lists the 8 neurohormones that have been identified as affecting pain. Five of these are called neurosteroids because they have the steroid moiety (4 carbon rings) as part of their chemical structure.[9–10] These are dehydroepiandrosterone (DHEA), estradiol, pregnenolone, progesterone, and testosterone. The 3 remaining neurohormones are human chorionic gonadotropin (HCG), human growth hormone (HGH), and oxytocin.

Table 1. Neurohormones Involved in Pain Management
Neurosteroids
• Dehydroepiandrosterone
• Estradiol
• Pregnenolone
• Progesterone
• Testosterone
Non-steroids
• Human Chorionic Gonadotropin
• Human Growth Hormone
• Oxytocin

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We did not include hormones that are produced in the peripheral endocrine system and then transported by arterial blood into the CNS for biologic actions, such as cortisol, epinephrine, thyroid hormones, or insulin.[11–13] Also excluded from discussion are endorphins, prolactin, melatonin, vitamins (ie, D2 and D3), dopamine, cytokines, and various releasing hormones because, although they may have a pain modulatory function, they are generally considered neurotransmitters or neuromodulators. At this time, many of these hormones cannot be readily measured in serum or formulated into compounds.

Neurohormones appear to have 3 basic pain control functions: analgesia or pain modulation; neuroprotection of CNS cells; and neurogenesis, defined as re-growth of damaged tissue.[14–21] Table 2 outlines the biologic actions of neurohormones. Neurohormones likely exert some neuromodulatory and transmission effects, and some appear to have direct analgesic properties. For example, oxytocin is known to surge during childbirth as a component of natural anesthesia.

Table 2. Characteristics of Neurohormones
• Produced inside the CNS with no pituitary or peripheral gland control
• Secreted into bloodstream and spinal fluid
• Maintain blood-brain barrier and cellular integrity
• Inhibit NMDA and GABA receptors; may enhance the latter system
• Prevent apoptosis and cellular death (neuroprotection)
• Suppress microglial cell activation and neuroinflammation
• Maintain analgesic receptors and prevent hyperalgesia
• Promote growth of damaged neurons and glial cells (neurogenesis)

CNS, central nervous system; **GABA**, γ-aminobutyric acid; **NMDA**, *N*-methyl-D-aspartate receptor

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Serum Testing: Why, When, and How

One of the best uses of hormone profiles is for chronic pain patients who have not responded to a standard treatment regimen and continue to have uncontrolled pain.[22] A hormone profile can measure all 5 neurosteroids; HCG, HGH, and oxytocin testing usually are only available through specialty labs that use early-phase testing protocols with non-standard assays.

A serum concentration of a hormone, such as pregnenolone, progesterone, or DHEA, has adrenal and gonadal sources, as well as CNS sources. Thus, it is unknown how much of a serum neurohormone concentration is from CNS versus peripheral sources. However, pain control requires hormone homeostasis in both the CNS and periphery, so a low serum level can be treated without concern as to which sources are not producing enough. Results from a hormone profile will give the practitioner some clues as to why a treatment regimen is not effective and provide enough information so the clinician can take measures to help the patient adjust, or modify, his or her regimen to attain better pain control.[22] For example, serum testing is recommended before starting DHEA, pregnenolone, progesterone, testosterone, and estradiol.

Our recommendation is that hormone administration be restricted to patients who show serum deficiencies. A goal of hormone administration should be to bring serum concentrations into the normal or optimal range.

Neurohormones

Progesterone and Allopregnanolone

Although a great deal of basic science and animal research has been conducted on neurohormones,[23–53] prior to 2010 there was little interest in neurohormones other than testosterone for pain management. In 2010, Kilts et al observed that nearly half of veterans returning from the Middle East who experienced persistent pain had low serum levels of allopregnanolone,[23] a metabolite of progesterone.[25,29,43] It was theorized that the pain experienced by the veterans was due to a lack of progesterone, which has been shown in multiple studies to reduce neuroinflammation, oxidative stress, and brain damage in animals.[24,27,33,39] Progesterone also may be a precursor of cortisol, the central hormone in the stress response.

Progesterone is being studied in cerebral vascular accidents and traumatic brain injury (TBI).[39–42] Our preliminary open-label investigation of progesterone is encouraging, but no specific recommendations on its clinical use can be made yet.[27] However, it is important to take a broader look at the pain patient's hormonal status and measure it, even in young men and women. Progesterone cannot be considered ONLY the "baby" hormone anymore!

Dehydroepiandrosterone

DHEA is, on a quantitative basis, the most plentiful hormone in the human body. It circulates in abundance in the form of a sulfated reserve (DHEA-S).[54–73] DHEA, the levels of which decline with age,[59] has been well studied and used as a dietary and hormonal supplement for hyperlipidemia and cardiovascular disorders.[68–73] It also has been a favorite anti-aging and stress-relieving dietary supplement.

Enthusiasm for use of DHEA in pain management began in 1994, when it was found to suppress pain and pain flares in patients with systemic lupus erythematosus (SLE).[68] Since that time, a number of studies have confirmed its effectiveness in SLE. It clearly possesses anti-inflammatory properties and suppresses interleukin 10 synthesis in women with SLE.

In addition to having peripheral anti-inflammatory actions, DHEA also has been shown to be produced in the CNS and have additional critical properties related to pain management.[56] It is neuroprotective and inhibits tumor necrosis factor alpha (TNF-a) and CNS inflammatory markers by inhibiting production of monocytes, astrocytes, and microglial cells. Its neuroprotective action in the CNS is at least partially attributed to conversion to estrogen and estradiol.[54]

In our experience, serum DHEA and DHEA-S levels regularly are found to be low in patients with severe chronic pain and headache.[22] Many pain practitioners recommend DHEA as a dietary supplement, beginning with replenishment dosing. Some rheumatologists routinely prescribe 200 mg a day in SLE

patients because this dosage has been found to suppress inflammation and prevent pain flares in SLE. To date, no studies have reported that DHEA at this dosage is effective in other causes of chronic pain.

Pregnenolone

Pregnenolone is a hormone that is of interest in pain management. [74–99] Low levels of pregnenolone have been found in patients with headaches, migraines, chronic pain, and TBI.[76,79,89,98] It has multiple effects and properties that compel its consideration in all chronic pain patients. First, its history is interesting and instructive. It was first discovered and researched in the 1940s, with studies on energy, stress, and painful rheumatologic conditions.[93–97] Although reports of pregnenolone effectiveness in rheumatoid arthritis (RA) were quite positive, the commercial development of cortisone and prednisone put an end to further investigation of pregnenolone as an analgesic and anti-inflammatory agent.

Pregnenolone has been called the “grandmother” of hormones, secondary to cholesterol, its parent compound. Pregnenolone, which is synthesized in the CNS, adrenals, and gonads from cholesterol, is the most plentiful hormone in the CNS. It converts to progesterone, allopregnanolone, and DHEA.

Pregnenolone’s reported pain-related functions in the CNS include neuroprotection; antagonism of the N-methyl-D-aspartate (NMDA) receptor, glutamate, and other receptor subtypes; inhibition and augmentation of the g-aminobutyric acid (GABA) receptor; and suppression of microglial neuroinflammatory responses.[88–92] Of particular interest are studies showing that spinal cord injury resolution is enhanced by pregnenolone.[76]

Serum assays are available through local commercial laboratories, and pregnenolone supplements are available without prescription from reliable commercial sources.[22] Serum levels in severe chronic pain and headache patients may be extremely low, according to our preliminary testing in our patients. Little is known about replacement or sub-replacement dosages. We normally recommend a starting dosage of 25 to 100 mg per day. Dosages can then be titrated upward or maintained to achieve a desired effect, such as reduced pain and opioid use, or increased mobility and energy. As much as 600 mg a day was used in the 1940s.[94,95]

Estradiol and Estrogens

Estrogens are produced in the adrenals, gonads, and CNS and peripheral nerves, as well as in microglia.[100–121]Estrogens are believed to modulate NMDA receptors and have some influence on inhibitory descending pain pathways. They, like the other CNS steroids and neurohormones, may suppress glial cell activity and neuroinflammation.[105,106,112]

Painful symptoms of menopause and migraine have been treated successfully with estrogen derivatives,[101,107] but most treatments use synthetic estrogenic substances that are not identical to the naturally occurring hormones. A monthly or bimonthly estrogen injection, primarily in women, is still common practice throughout the United States; more rarely, patients are prescribed implanted replacement pellets of estradiol. Although no one questions the analgesic and pain management potential of estrogens, there has been no consistent identifiable adoption of estradiol or estrogens into contemporary pain management.

There are 2 basic reasons for the lack of use of estradiol and other estrogens in pain management: 1) serum tests are too variable because estradiol levels depend upon age, sex, and menstrual status; and 2) exactly how estrogens modulate pain is extremely complex. For example, estradiol can increase migraine/headache severity in some women but can dramatically reduce or improve it in others.[100,111,117,118]

Without reliable serum ranges of a hormone, it is problematic to replace or replenish it. When a hormone exerts multiple and sometimes opposing analgesic effects, it is problematic to select appropriate patients for treatment. Part of the complexity is that estrogen receptors are located throughout the body, including in the joints, peripheral nerve endings, and CNS. Further, there are 3 derivatives of estrogens in humans: estradiol, estrone, and estriol. It is not known if 1 of these 3 has more relevance to pain/headache management.

The most exacting research with estrogens has been in patients with pain/migraines and RA. Although it is clear that estrogens may influence severity and treatment of these painful disorders, there is no specific consensus or recommendation relative to dosage, as exists partially with DHEA and SLE, and perhaps pregnenolone. Patients with a low estradiol serum level, appropriate for time of cycle and post-menopausal factors, may be given clinical consideration for a trial of low-dose, short-term estradiol. Male estradiol serum levels are available through commercial test laboratories, and low-dose trials in a few men with chronic pain syndrome suggest that further trials should be done. Estrogen should not be considered a “female” drug in pain management, nor should testosterone be considered a “male” drug.[103,104]

Testosterone

Testosterone is the hormone that is most often addressed in pain management.[122–129]It is included here primarily because there are enzymatic mechanisms in the CNS that can produce testosterone and the other sex steroids.[123] In the CNS, the neurosteroids are highly interconnected and may even metabolize to one another. We know that testosterone is produced in peripheral organs, adrenals, and gonads, and migrates into the CNS, but we are unable to identify any studies that show any appreciable testosterone production in the CNS. Testosterone production is under pituitary control.

Testosterone has well-known analgesic effects, and pain patients who demonstrate serum deficiencies and undergo replacement report better pain and headache/migraine control.[122–127] Unfortunately, testosterone levels are decreased in both genders when opioids are used for pain control. This data is well-known. Unfortunately, testosterone is not always tested for in patients with chronic pain, headaches and/or migraines, and mood and sleep disorders, especially women. We recommend short clinical trials of testosterone in both sexes when low serum levels are detected.[126]

Human Growth Hormone

Little is known about the relevance of HGH[130–133]to pain and headache management. The increasing interest in neurogenesis and curative measures likely will lead to much more interest in this neurohormone. The paucity of knowledge likely is related to its lack of availability and extreme expense. In recent years, the little available commercial supply essentially has been restricted to use in pituitary deficiencies, primarily in pediatric and head trauma patients.

Bennett et al published a few reports on use of HGH in fibromyalgia patients.[130,131] In a double-blind study, HGH provided significant pain relief.[131,133] In 2015, Thomas Romano, MD, PhD, reported at the Academy of Integrative Pain Management (formerly American Academy of Pain Management) in San Antonio, Texas, that patients with fibromyalgia had low serum levels of insulin-dependent growth factor (IGF) and were, therefore, deficient in HGH secretion, providing a rationale for its use in pain management.[134]

Recently, HGH secretagogues and pure HGH have become more widely available and less expensive, with potential indications for chronic debilitating diseases. We have begun preliminary clinical trials but, as of yet, have little to report; however, JCK has anecdotal, positive data indicating that using HGH to improve IGF1 levels improved headaches and fatigue in patients with post-concussive TBI.

Human Chorionic Gonadotropin (HCG)

HCG originally was named because it was believed to be produced only in the placenta of pregnant women.[135–145]Later, it was clearly determined that HCG is produced daily in the pituitary glands of males and females.[135–138] Although it formerly was believed that HCG's primary function was to maintain placental integrity, it is now known that it is composed of 2 separate chemical units, each with a unique biologic function.[138,141–145] One unit provides hormone stimulation and the other angiogenesis and neurogenesis. One hormone unit of HCG actually is a long chain of amino acids that incorporates duplicates of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH).

One of the uses of HCG is treatment of hypogonadism. In the pain management arena, deficiencies of testosterone, estradiol, progesterone, and thyroid hormone are common, and HCG may elevate 1 or more of these hormones.

The authors find HCG to be a safe alternative to testosterone replacement in females. The angiogenesis/neurogenesis unit appears to be of clinical benefit in many patients with chronic pain. Open-label trials indicate that HCG may reduce pain and opioid use, enhance energy and mental function, and promote a generalized feeling of well-being.[135]

Compounding pharmacies throughout the country now supply HCG as a sublingual troche, sublingual solution, or subcutaneous injection. Starting dosages are 125 to 250 units 2 to 3 times a week.

Oxytocin

Preliminary studies of oxytocin,[146–158] including one small, double-blind study, indicate that oxytocin has analgesic properties and has a place in both acute and chronic pain management.[147–151,157] Although its mechanism of action is unclear, it appears to act by inhibition of some neurons that connect the brain and spinal cord.[146,153–155] Oxytocin is, like the other neurohormones, becoming accessible through local compounding pharmacies. It can be used intranasally or sublingually. Starting doses range from 20 to 40 units a day.

Summary

Over the last 2 decades, research has shown that the CNS produces and retains a special set of neurohormones that have pain control functions. In addition, almost all neuroprotective and neurogenic biologic mechanisms are under some hormonal control. The revelation that a number of hormones with pain-related functions are produced in the CNS without apparent pituitary control compels pain management clinicians to investigate the use of these hormones in clinical practice. DHEA has found solid footing in SLE patients at a dose of about 200 mg per day to reduce pain intensity and flares. Testosterone testing and replacement are now commonplace in pain management since low serum levels are associated with inferior pain control, especially in the setting of opioid management of pain.

There are practitioners throughout the country who are attempting to determine how best to clinically use neurohormones. To date, there are no serious reported complications. Open-label observations suggest that neurohormones are a good adjunct to symptomatic pain/headache care. They appear to reduce baseline pain and flares, diminish the need for opioids, and, possibly, produce some neurogenesis and healing properties.

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