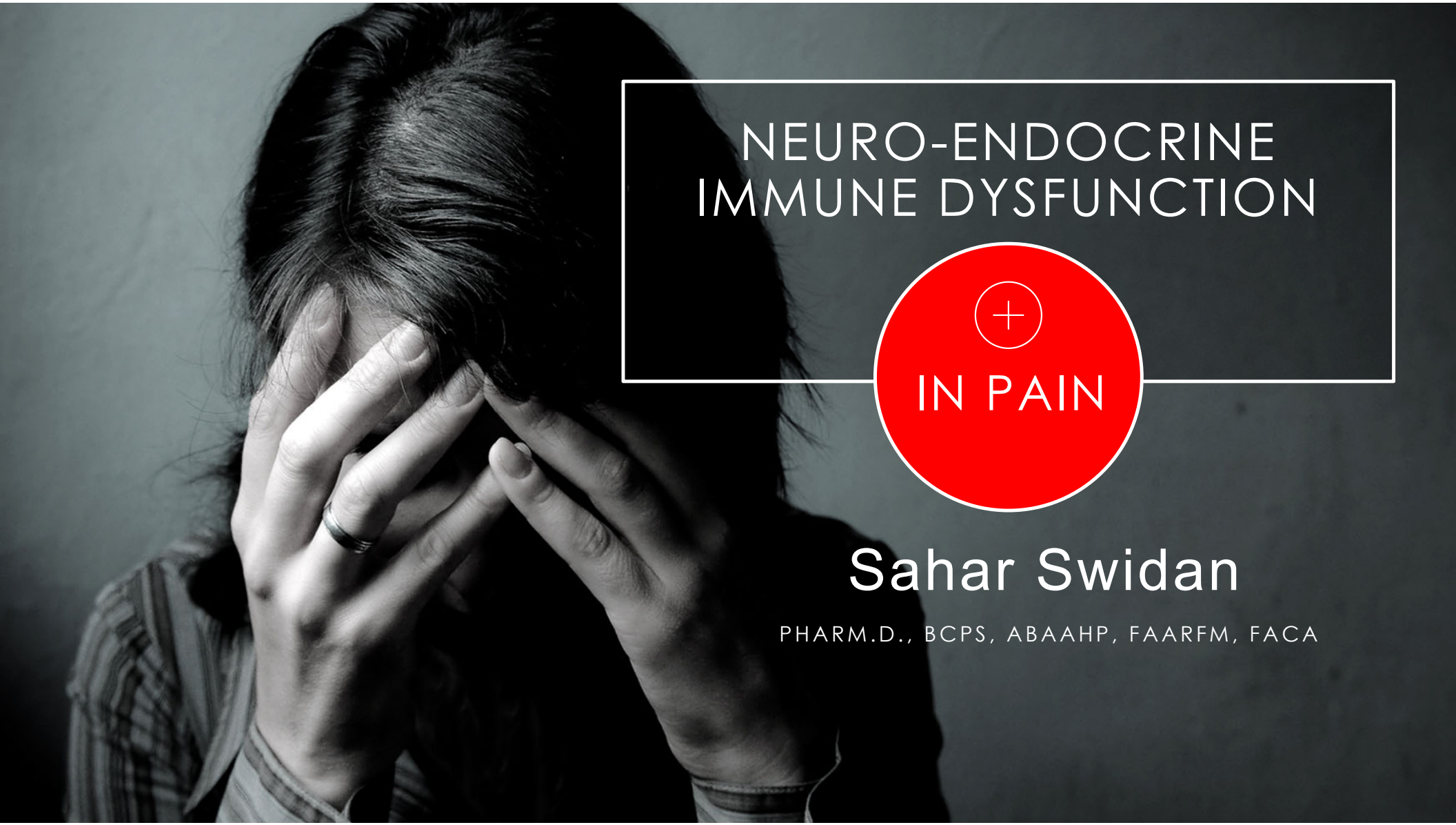
NEURO-ENDOCRINE
IMMUNE DYSFUNCTION
+
IN PAIN
Sahar Swidan
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DISCLOSURES

- Disclosure of Financial Relationships:
- Employment-Pharmacy Solutions
- Speaker-Amgen, Biohaven, A4M
-

Off-Label Usage

- "None"

OBJECTIVES

- Review Neuro-Endocrine-Immune connections
- Outline the dysregulation we observe in pain patients
- Discuss various therapeutics to aid in the treatment of pain

Chapter 1

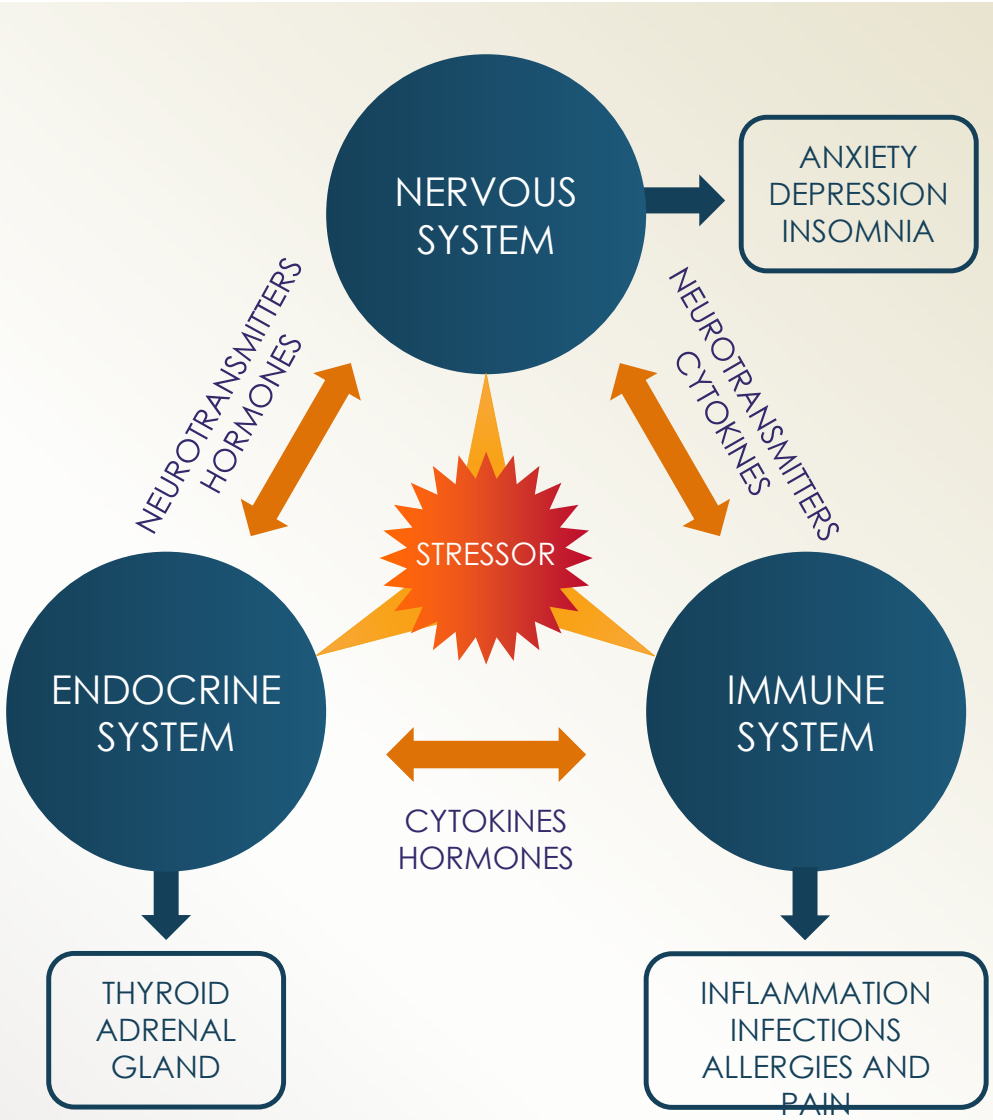
THE NEUROENDOCRINE, NERVOUS AND IMMUNE SYSTEMS

NEUROENDOCRINE SYSTEM

- Neuroendocrine system is the sum of glands, hormones, and target tissues/organs involved in the control of bodily functions (including behaviors)
- The immune, endocrine, and nervous system are highly integrated

NEUROENDOCRINE-IMMUNE INTERACTION

- 2 pathways that link brain and immune system
  - Autonomic nervous system
  - HPA axis
- Neuroendocrine hormones influence immune function via:
  - Release of mediators into circulation
  - Direct innervation of the llymphoid organs



NEUROENDOCRINE AND THE IMMUNE SYSTEM

- Both of these systems utilize a number of similar ligands and receptors to provide an intra- and inter-system network of communication
- Communication of these two systems is essential for maintaining physiological homeostasis
- Receptors for immune-derived cytokines, chemokines, and growth factors have been identified on neuronal cells and within endocrine organs under normal physiological condition in response to stress and disease
  - Homeostasis and negative feedback maintained between the immune system and central nervous system

NEUROENDOCRINE AND THE IMMUNE SYSTEM

- The immune system is able to synthesize and secrete several hormones with immunomodulatory properties that reduce or inhibit any exacerbated inflammatory response
  - Lymphocytes and macrophages produce endogenous opioid peptides and catecholamines such as NE and epinephrine

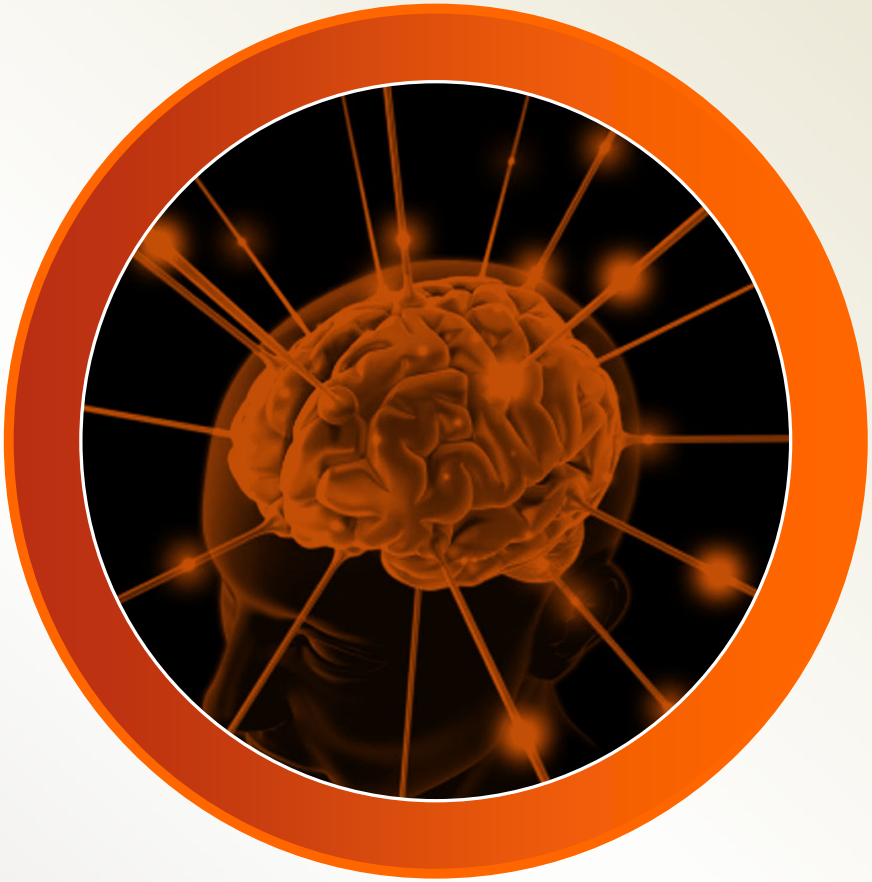
- Human lymphocytes secrete growth hormone and monocytes secrete the brain-derived neurotrophic factor (BDNF), whose expression is up-regulated by flogisitic mediatory such as TNF-alpha and IL-6

NEUROENDOCRINE AND THE IMMUNE SYSTEM

- Lymphocytes, monocytes, and various other immune cell subsets express receptors for many of these ligands include a variety of neurotransmitters and neuropeptides

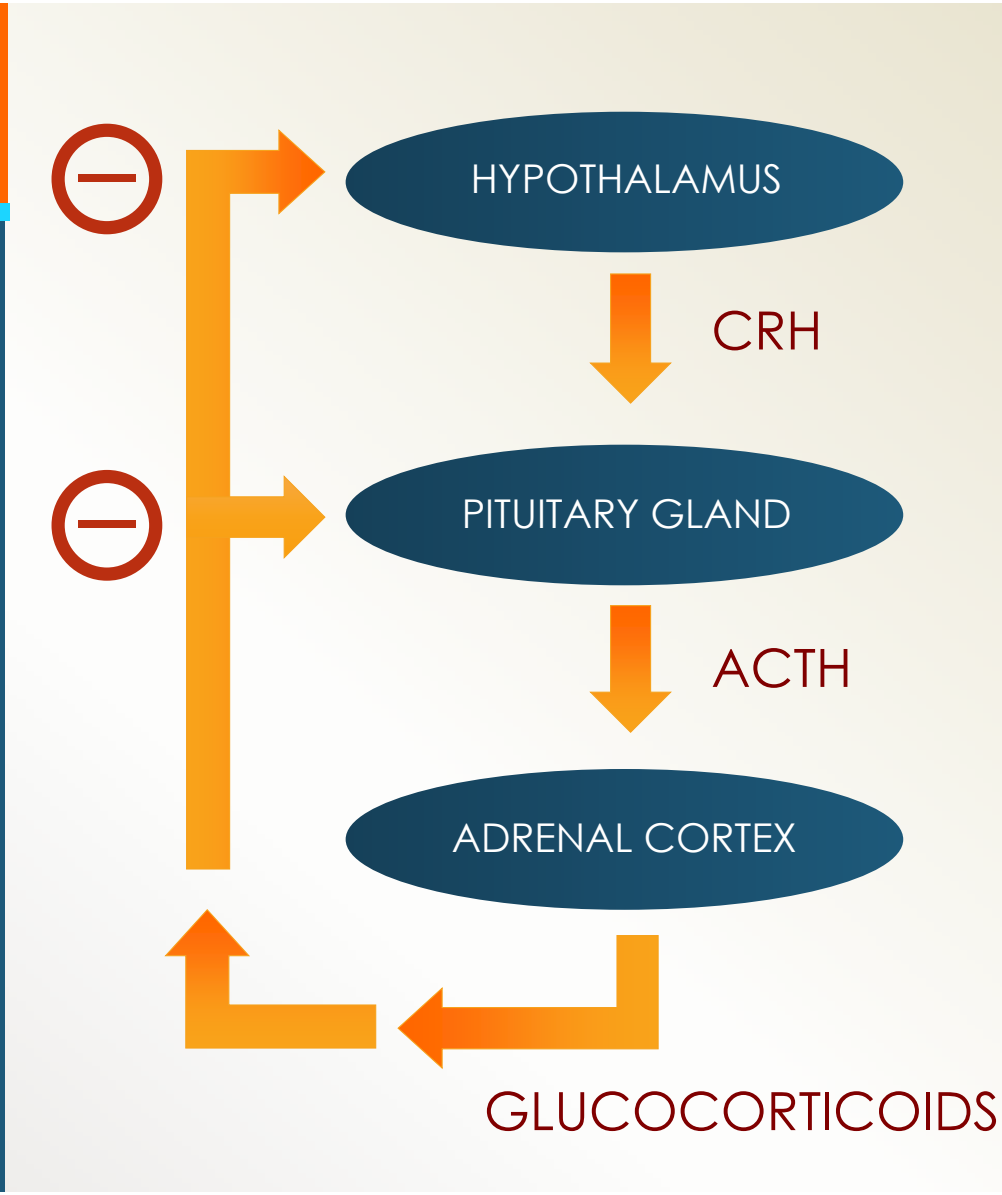
- Corticosteroids
- Insulin
- Prolactin
- Growth Hormone
- Somatostatins
- Estrogens
- Testosterone

- Leptin
- Ghrelin
- Opioids
- Corticosteroids
- Neuropeptide Y
- Vasoactive intestinal peptide (VIP



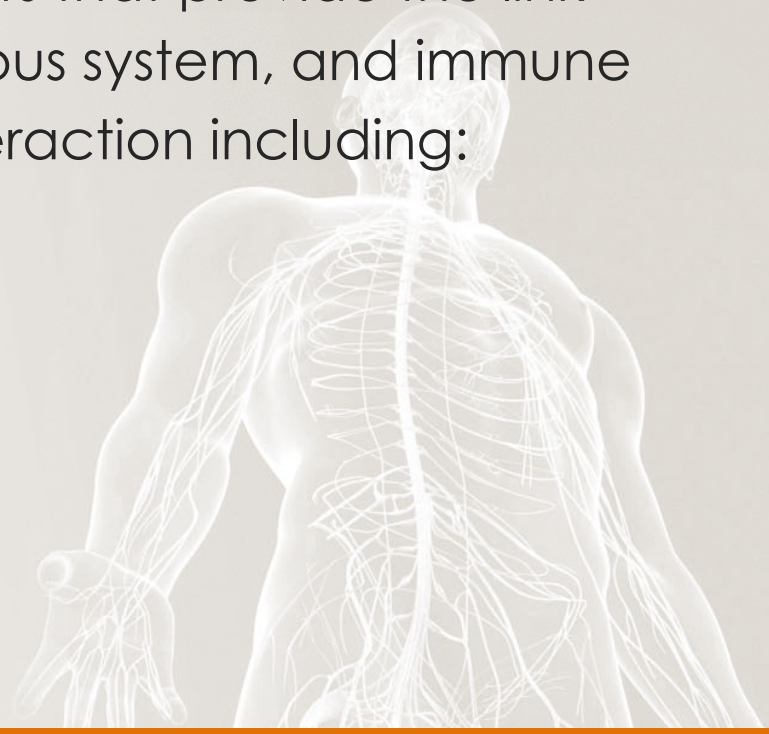
NEGATIVE FEEDBACK LOOP

- Regulatory networks of the negative feedback loops maintains homeostasis between the immune and central nervous system
- Disturbances in this system may lead to immune activation or suppression, depending on the systems affected and the nature of the stimuli



NEUROENDOCRINE AXES

- Hormonal and neuropeptide mediators that provide the link between the endocrine, central nervous system, and immune systems constitute specific axes of interaction including:
  - Hypothalamic-pituitary-adrenal (HPA) axis
  - Hypothalamic-pituitary-gonadal (HPG) axis
  - Hypothalamic-pituitary-thyroid (HPT) axis
  - Hypothalamic-growth-hormone axis

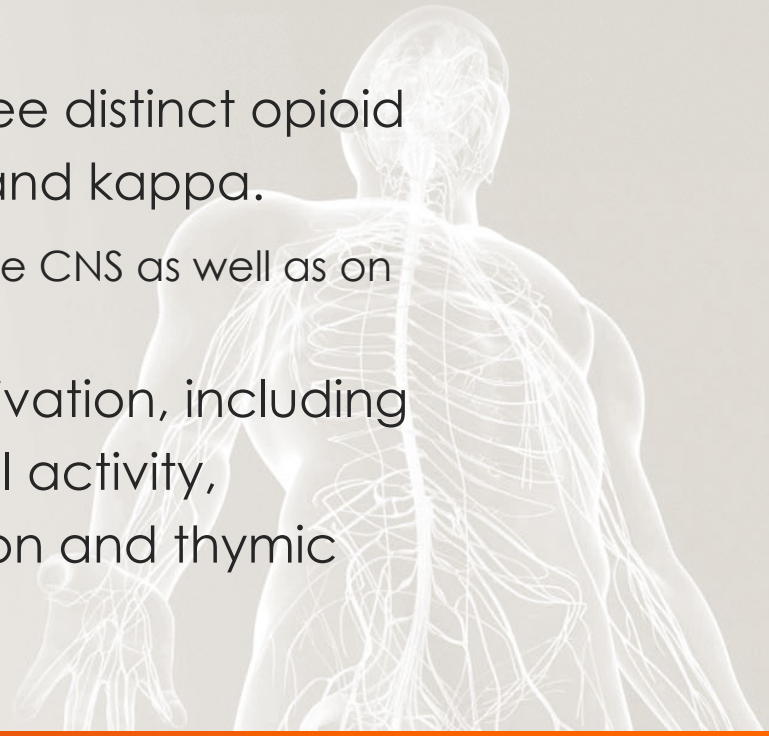


MULTIDIRECTIONAL COMMUNICATION

- Autonomic nervous system communicates with the lymphoid compartment through the release of norepinephrine and acetylcholine from the sympathetic and parasympathetic nerves
- Administration of exogenous steroidal hormones and opioid-based drugs can influence immune function and susceptibility to infections
- There is multidirectional communication networks within the body that permit the transmission of signals between various systems during times of stress, injury, disease, infection, metabolic alterations, and complications

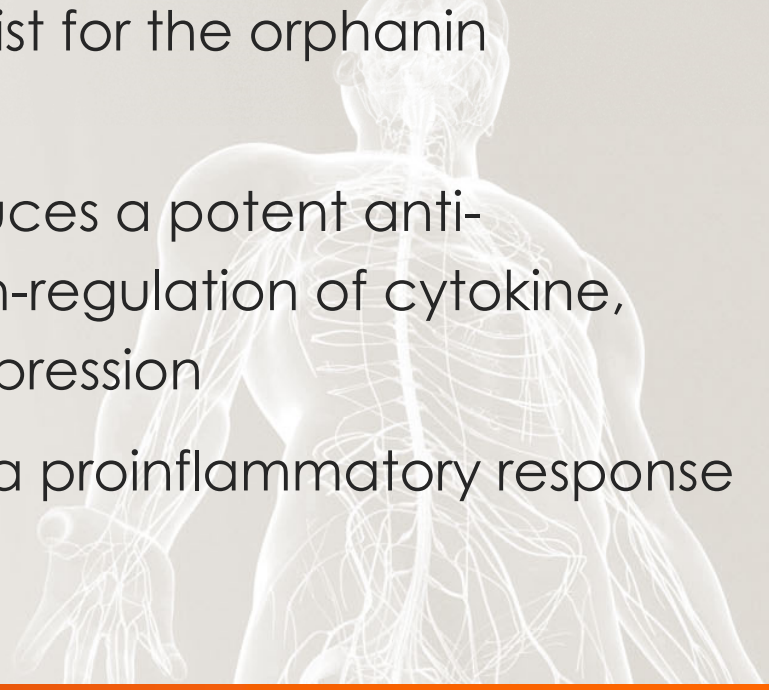
OPIOIDS

- Opioids regulate the function of cells involved in the immune response
- Opioids mediate their effects through three distinct opioid receptor classes designated, mu, delta, and kappa.
  - The receptors are widely expressed through the CNS as well as on immune cells
- Can modulate immune function and activation, including antibody responses, phagocytosis, NK cell activity, cytokine, and cytokine receptor expression and thymic development and function



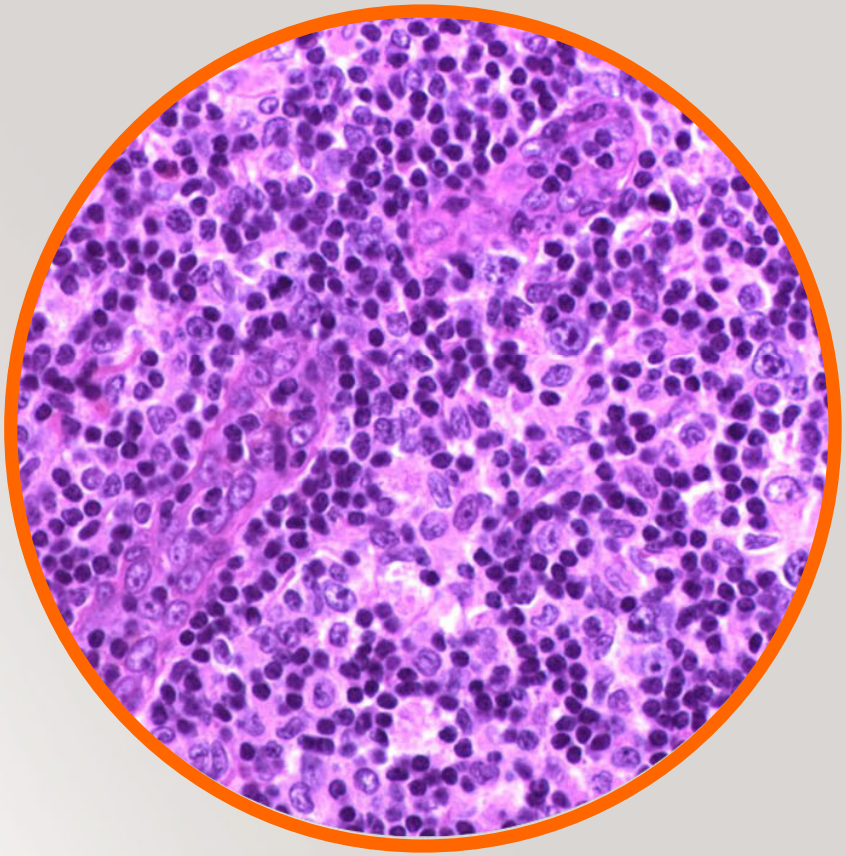
REGULATION AND ACTIVATION

- Regulation of cytokine, chemokine, and cytokine receptor expression is a critical component of the immunomodulatory activity of the opioids and nociceptin the natural agonist for the orphanin FQ/nociceptin receptor
- Activation of kappa opioid receptor induces a potent anti-inflammatory response through the down-regulation of cytokine, chemokine, and chemokine receptor expression
- Activation of the mu receptor promotes a proinflammatory response



NEUROENDOCRINE MODULATION OF IMMUNE RESPONSES

- Most lymphoid tissues possess sympathetic innervation
- Lymphocytes express receptors for a variety of hormones, neurotransmitters, and neuropeptides
  - Examples: steroids, catecholamines, encephalins, endorphins
  - When release in vivo during stress, most of them are immunosuppressive



NEUROENDOCRINE MODULATION OF IMMUNE RESPONSES

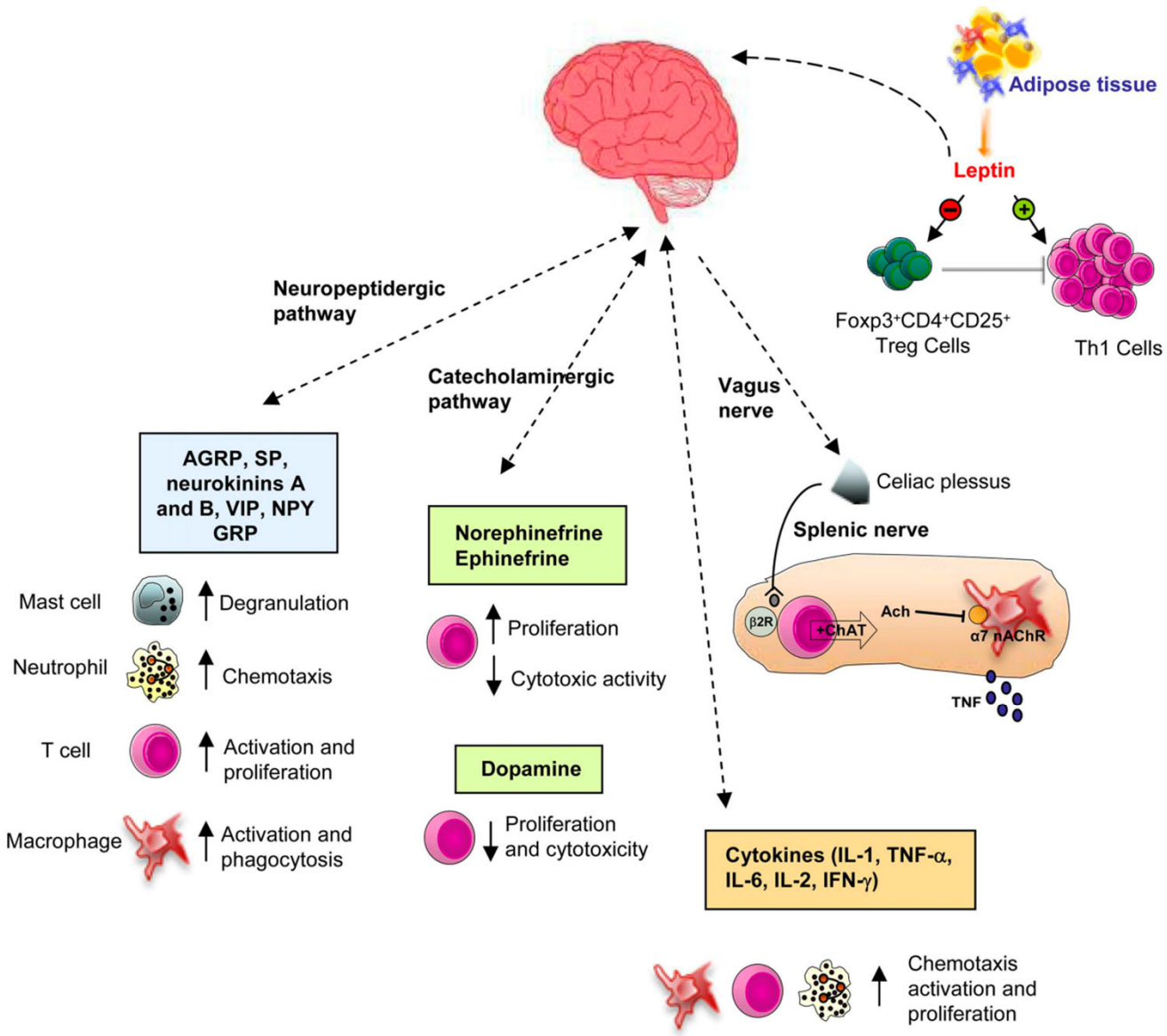
- IL-1 and IL-6 cytokines act as stimulants of adrenal corticosteroid production
- Both IL-1 and IL-6 are synthesized by neurons and glial cells and, in addition by cells in the pituitary and adrenal glands

PRO-INFLAMMATORY CYTOKINES

- IL-6, IL-1beta, and TNF-alpha are inflammatory cytokines that are released into sites such as:
  - Joints
  - Active inflammatory cells: monocytes, macrophages, and T cells
- These inflammatory cytokines get into these areas via autocrine and paracrine mechanisms and by upregulating adhesion molecule expression
- These cytokines also trigger a cascade of neuroendocrine mechanisms that regulate the body's response and the eventual termination of inflammation by 3 major pathways

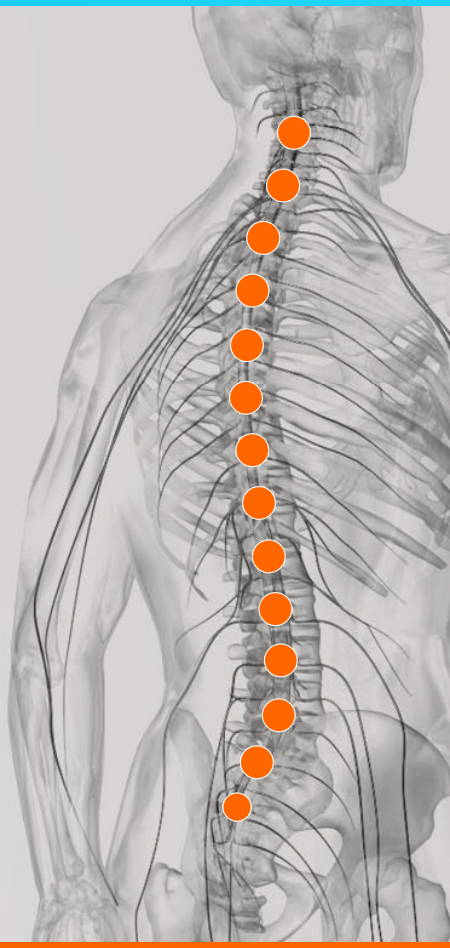
THREE MAJOR PATHWAYS

- Mechanism 1
  - Activation of the sympathetic nervous system to increase catecholamine and bradykinin release which enhances corticosteroid release by the adrenal glands
- Mechanism 2
  - Generation of fever and the adoption of adaptive behavior conductive to recovery
- Mechanism 3
  - Variety of neuropeptides that are involved in the stress response, including corticotrophin release hormone (CRH), adrenocorticotrophic hormone (ACTH), and prolactin are also released

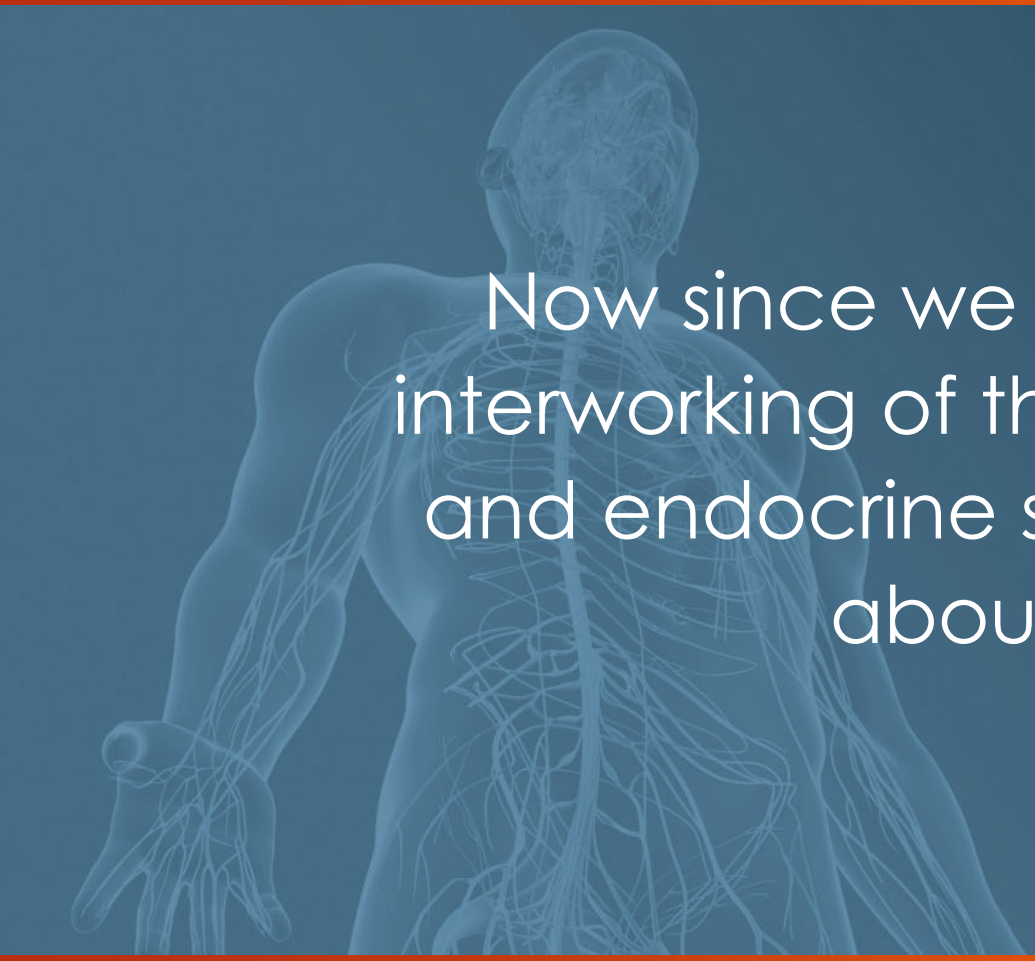

Adipose tissue
Leptin
Foxp3+CD4+CD25+
Treg Cells
Th1 Cells
Neuropeptidergic pathway
Catecholaminergic pathway
Vagus nerve
AGRP, SP, neurokinins A and B, VIP, NPY GRP
Mast cell
Degranulation
Neutrophil
Chemotaxis
T cell
Activation and proliferation
Macrophage
Activation and phagocytosis
Norephinefrine Ephinefrine
Proliferation
Cytotoxic activity
Dopamine
Proliferation and cytotoxicity
Celiac plessus
Splenic nerve
β2R
+ChAT
Ach
α7 nAChR
TNF
Cytokines (IL-1, TNF-α, IL-6, IL-2, IFN-γ)
Chemotaxis activation and proliferation

SPINO-BULB-SPINAL PATHWAY

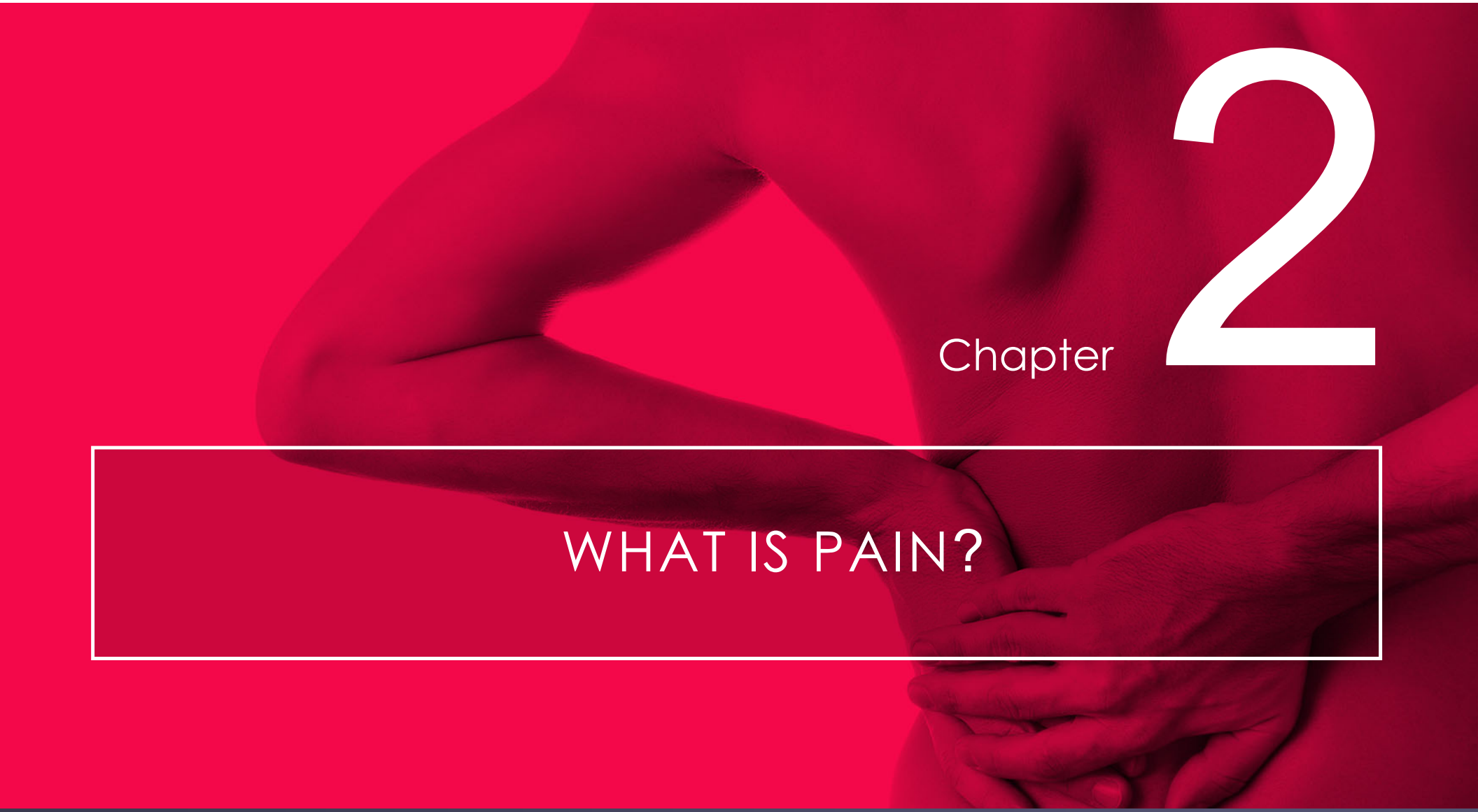
- The nociceptive-neuroendocrine reflex pathway is inhibited by the activity in vagal afferent neurons
- This inhibition occurs in the spinal cord, most likely in the spinal segments close to the nociceptive afferent input
- The descending inhibitor pathway, activated by activity in vagal afferents, project through the dorsolateral spinal funiculus ipsilateral to the nociceptive spinal input
- The excitatory spino-bulbo-spinal pathways is activated by the nociceptive input, leading to an endogenous positive feedback loop between nociceptive afferent input and sympathetic preganglionic output to the adrenal medulla
  - This is under inhibitory control from the viscera via activity in vagal neurons



NOW…



Now since we understand the interworking of the immune system and endocrine system, let's learn about pain!

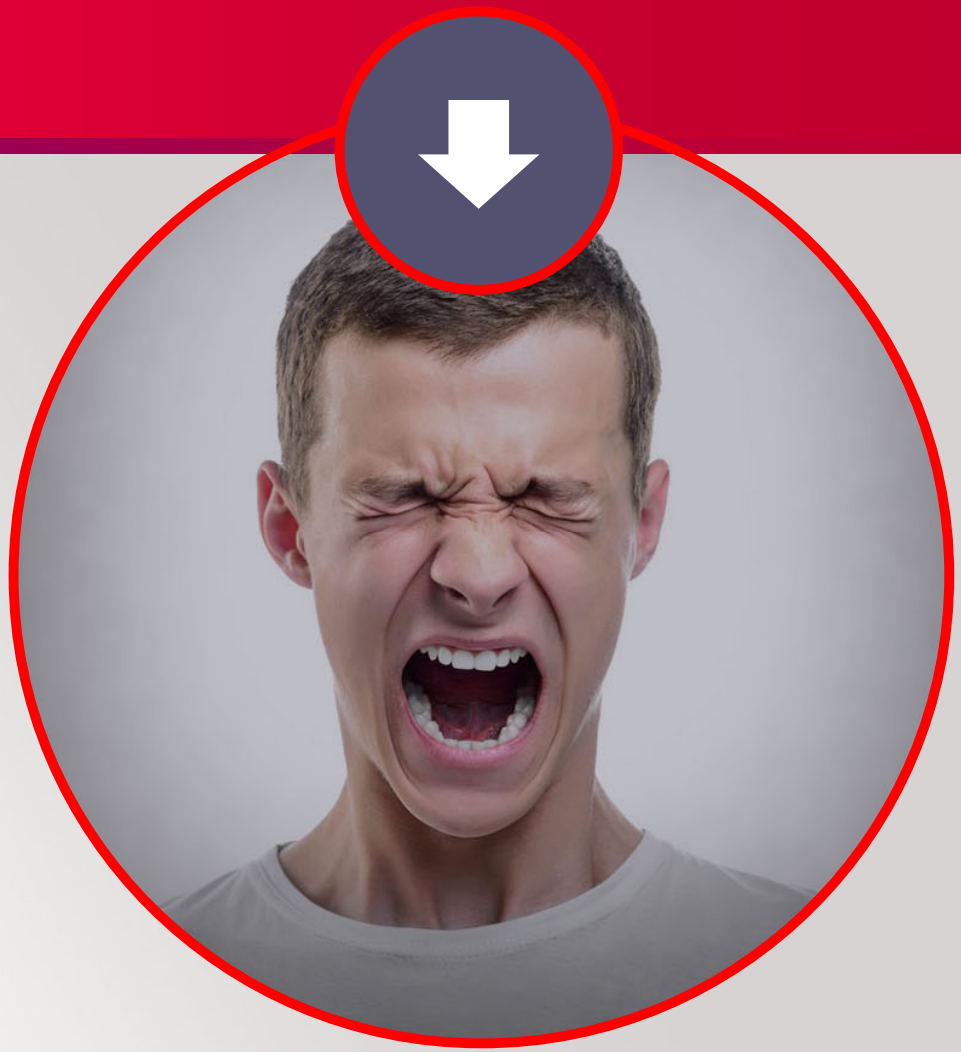


Chapter 2

WHAT IS PAIN?

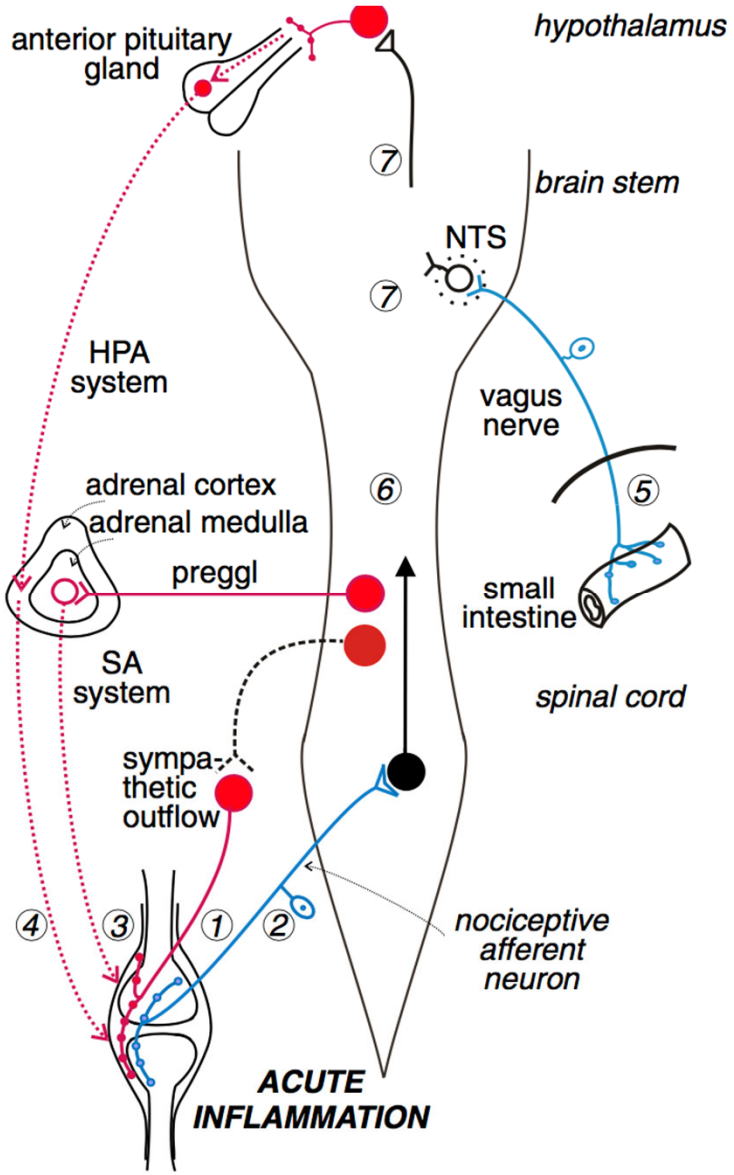
PAIN

- Pain is the most common reason patients seek medical care
- Pain has sensory and emotional components and is often classified as acute or chronic



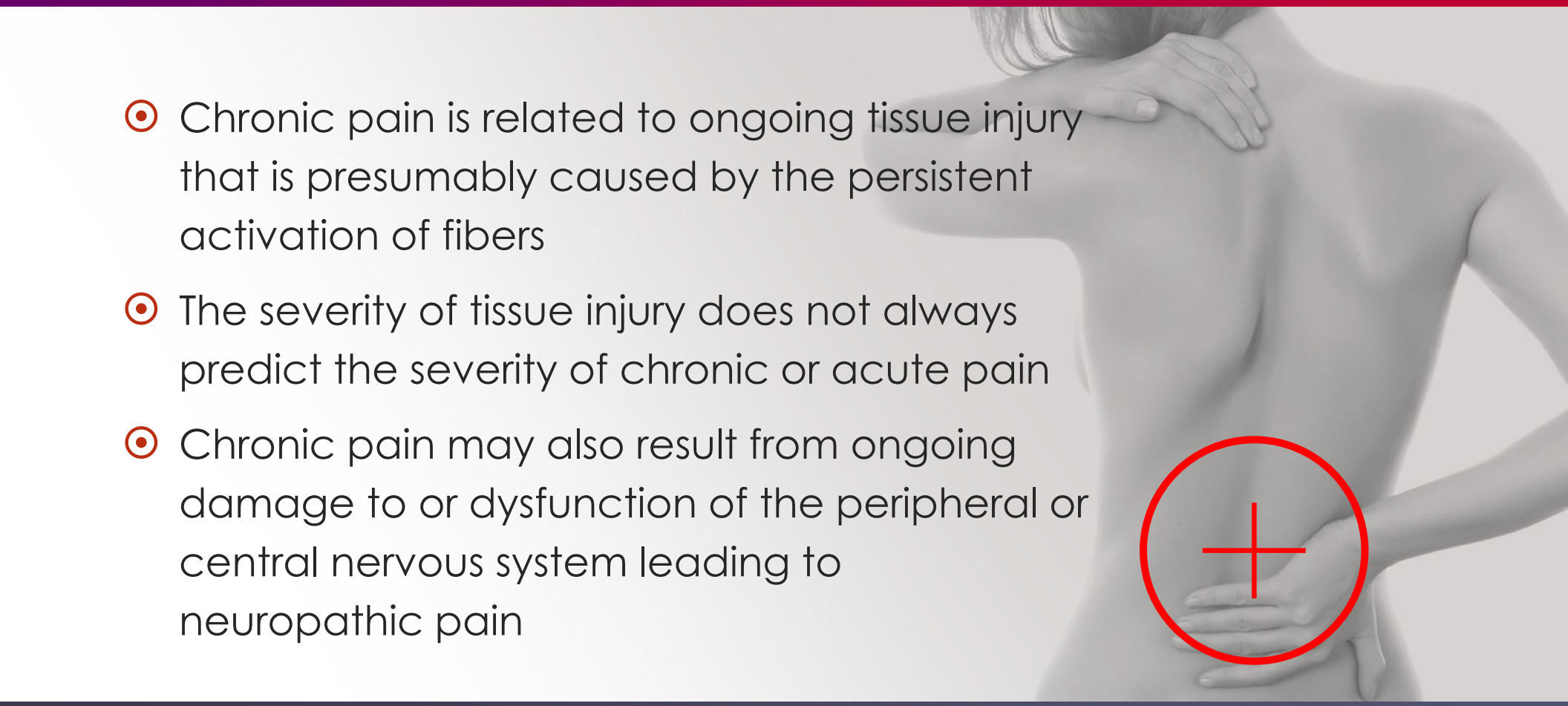
ACUTE PAIN

- Acute pain occurs in response to tissue injury
- It results from the activation of peripheral pain receptors and their specific A delta and C sensory nerve fibers (nociceptors)



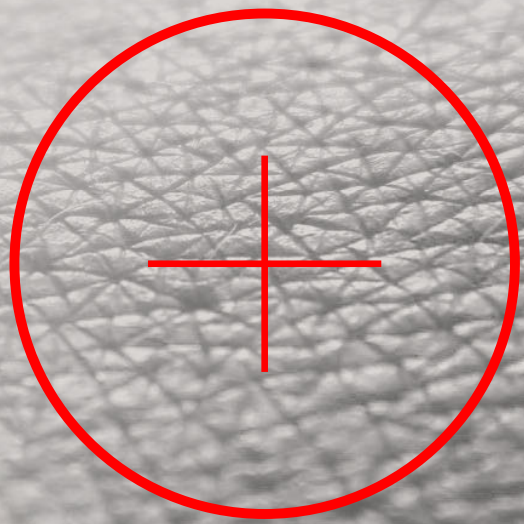
CHRONIC PAIN

- Chronic pain is related to ongoing tissue injury that is presumably caused by the persistent activation of fibers
- The severity of tissue injury does not always predict the severity of chronic or acute pain
- Chronic pain may also result from ongoing damage to or dysfunction of the peripheral or central nervous system leading to neuropathic pain



NOCICEPTIVE PAIN

- Can be somatic or visceral
  - **Somatic pain** receptors are located in the skin, subcutaneous tissue, fascia, other connective tissues, periosteum, endosteum, and joint capsules
    - Simulation of these receptors produce sharp or dull pain, but burning is NOT common if the skin or subcutaneous tissues are involved
  - **Visceral pain** is due to obstruction of a hollow organ that is poorly localized, deep, and cramping and may be referred to remote cutaneous sites
    - Visceral pain due to injury of organ capsules or other deep CT may be more localized and sharp



PSYCHOLOGICAL FACTORS

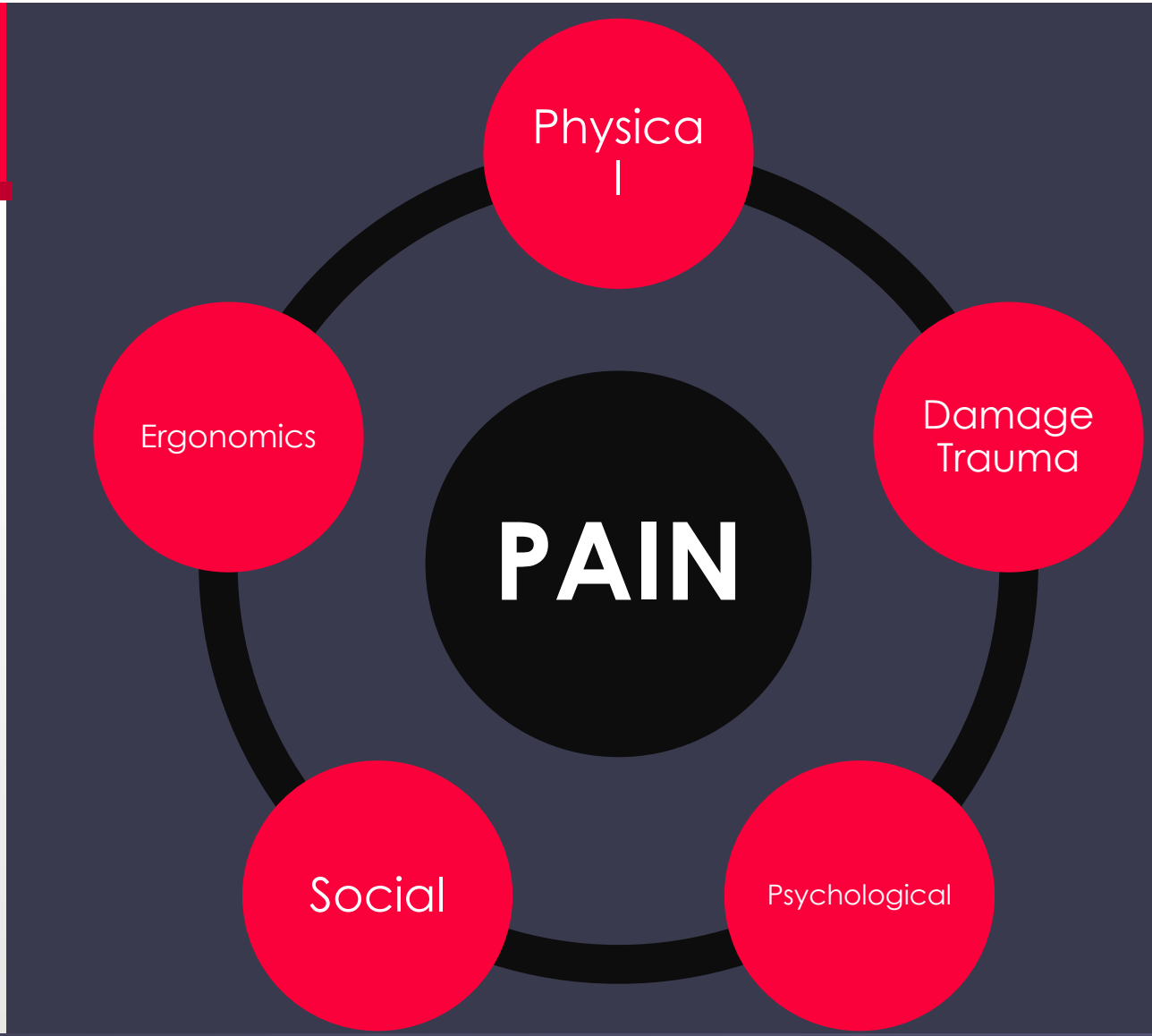
- Psychological factors modulate pain intensity to a highly variable degree
- Thoughts and emotion have an important role in the perception of pain
- Many patients who have chronic pain can have psychological distress, especially depression or anxiety

COGNITIVE

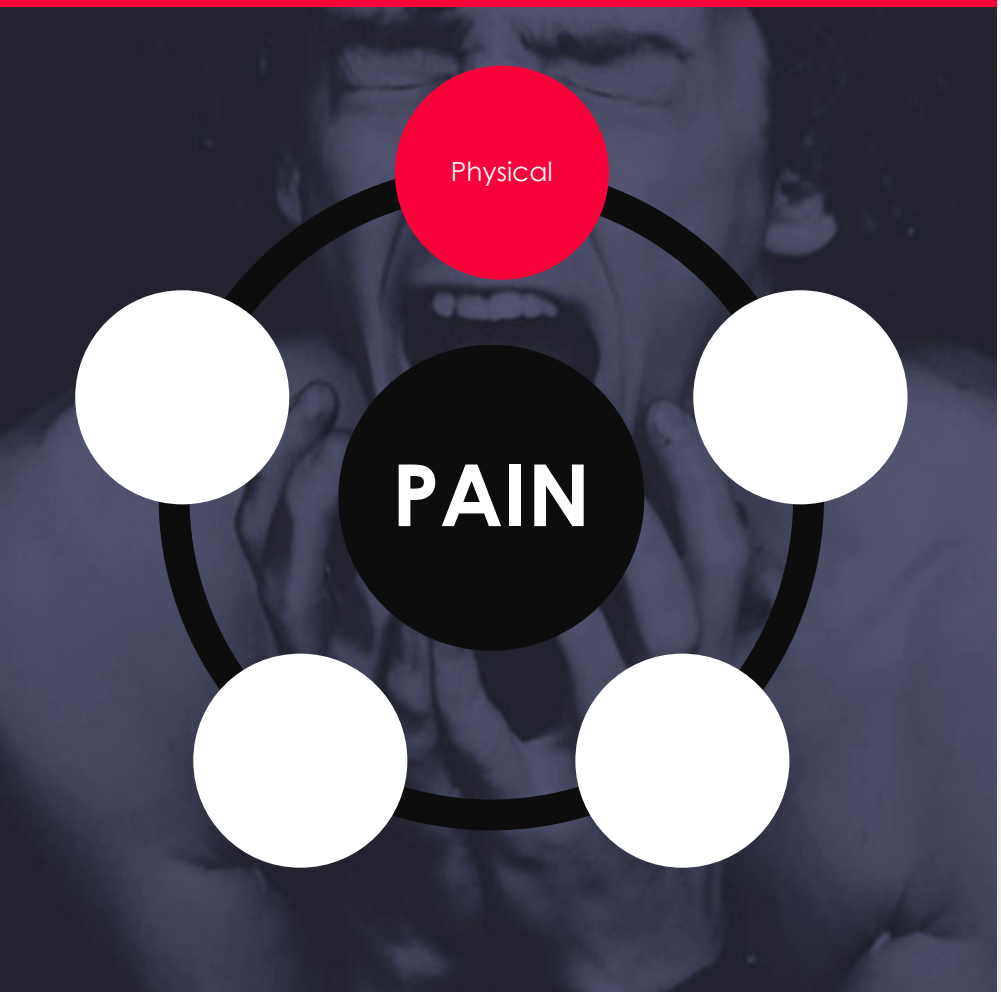
- Pain impairs multiple cognitive domains including attention, memory, concentration, and content of thought, possibly by demanding cognitive resources

MULTIFACTORIAL PAIN

- Many pain syndromes are multifactorial
- Example: chronic lower back pain and most cancer pain syndromes have predominant nociceptive component but also may involve neuropathic pain (due to nerve damage)

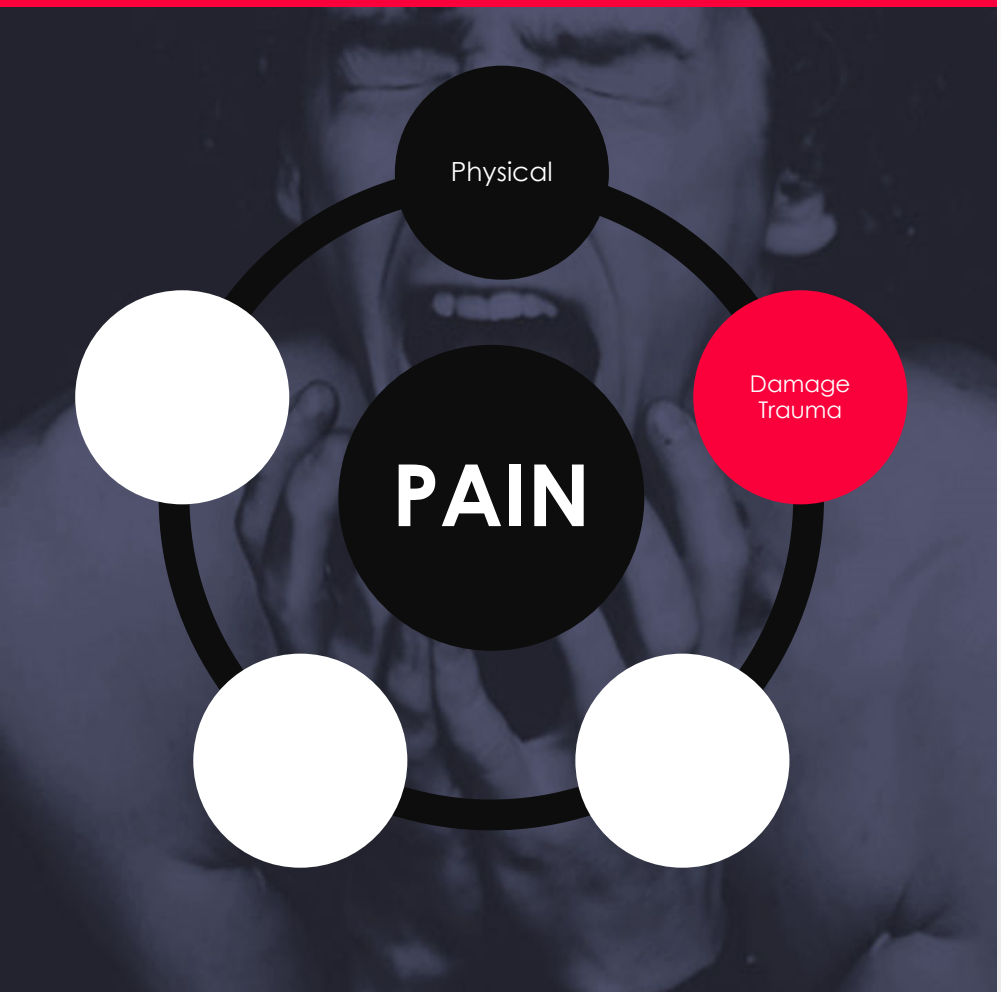


PHYSICAL PAIN



- Muscle
- Weakness
- Control / imbalance
- Tightness

DAMAGE AND TRAUMA PAIN

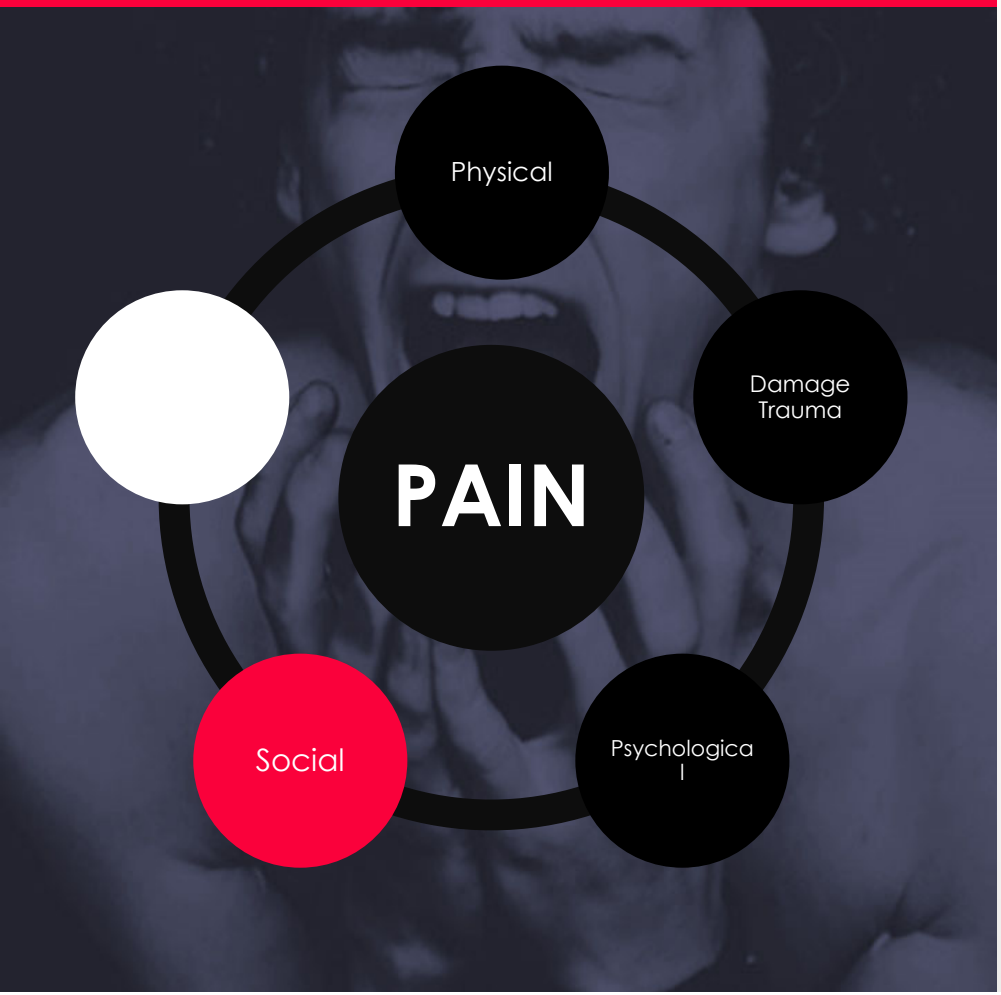


- Structural pathology
- IVD
- Facet joint
- SIJ
- Neural tissue
- Myofascial
- Connective tissue
- Genetic factors

PSYCHOLOGICAL PAIN

- Fear
- Anxiety
- Catastrophisation
- Context
- Depression / Negative thoughts and feelings
- Stress
- Poor sleep
- Poor education and mis-information
- No control
- Hyper vigilence

SOCIAL PAIN

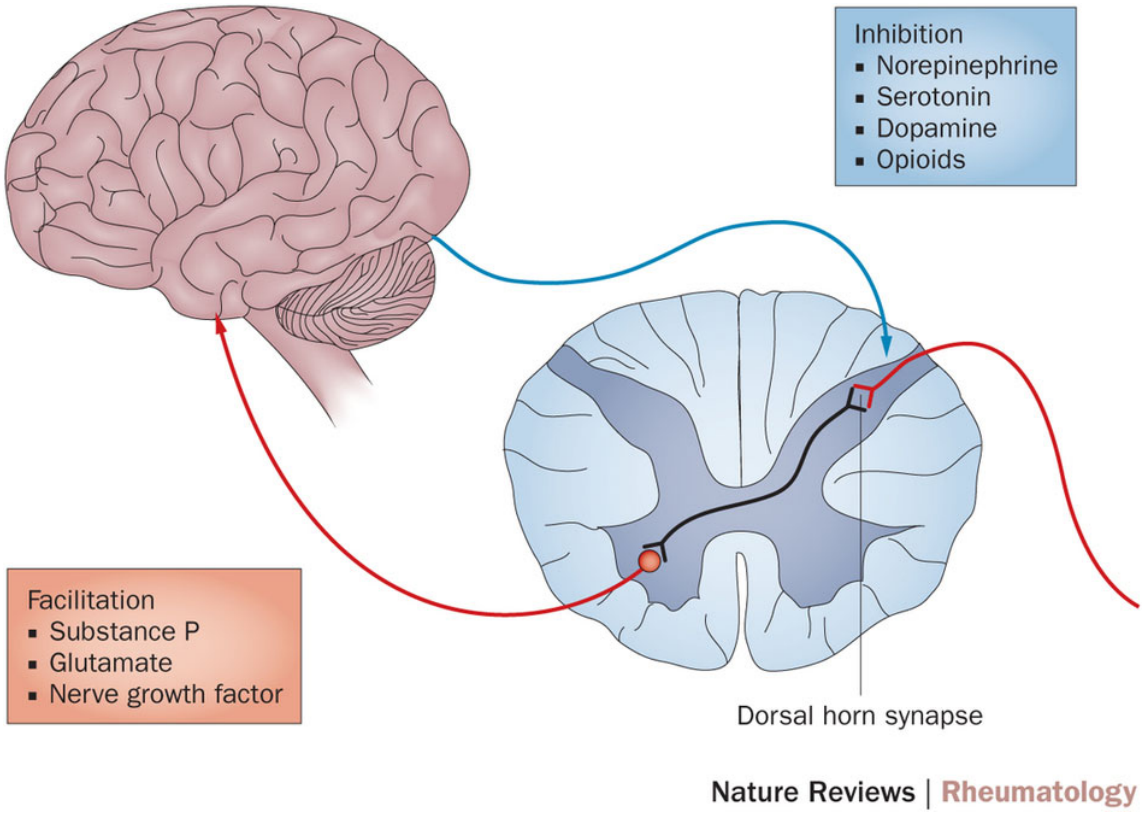


- Past experiences
- Context
- Culture
- Work
- Attitudes of health professionals and others
- Family support
- Socioeconomic
- Lifestyle - Nutrition and activity levels

ERGONOMIC PAIN

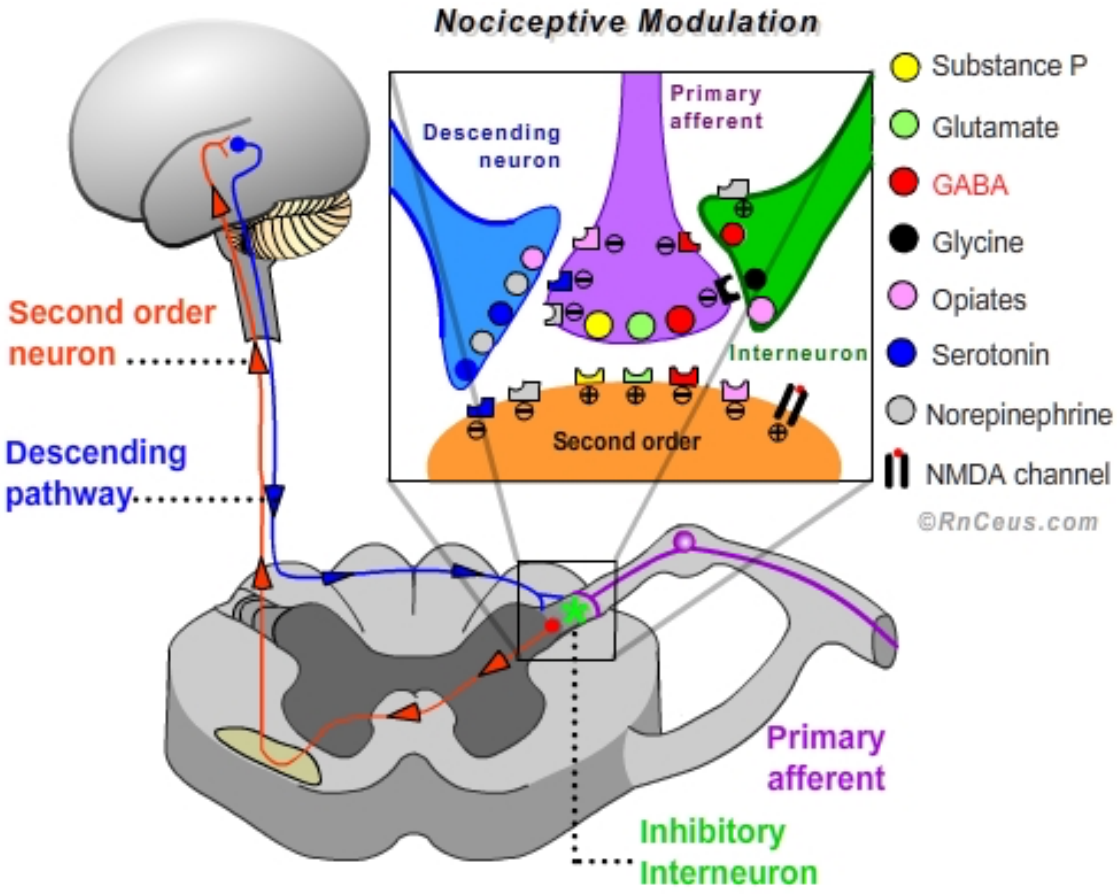
- Prolonged or repetitive poor posture

PAIN TRANSMISSION AND MODULATION



- Pain fibers enter the spinal cord at the dorsal root ganglia and synapse in the dorsal horn
- From here, fibers cross to the other side and travel up the lateral columns to the thalamus and then to the cerebral cortex
- Repetitive stimulation can sensitize neurons in the dorsal horn of the spinal cord so that a lesser peripheral stimulus causes pain
- Peripheral nerves and nerves at other levels of the CNS may also be sensitized, producing long-term synaptic changes in cortical receptive fields (remodeling) that maintains exaggerated pain perception

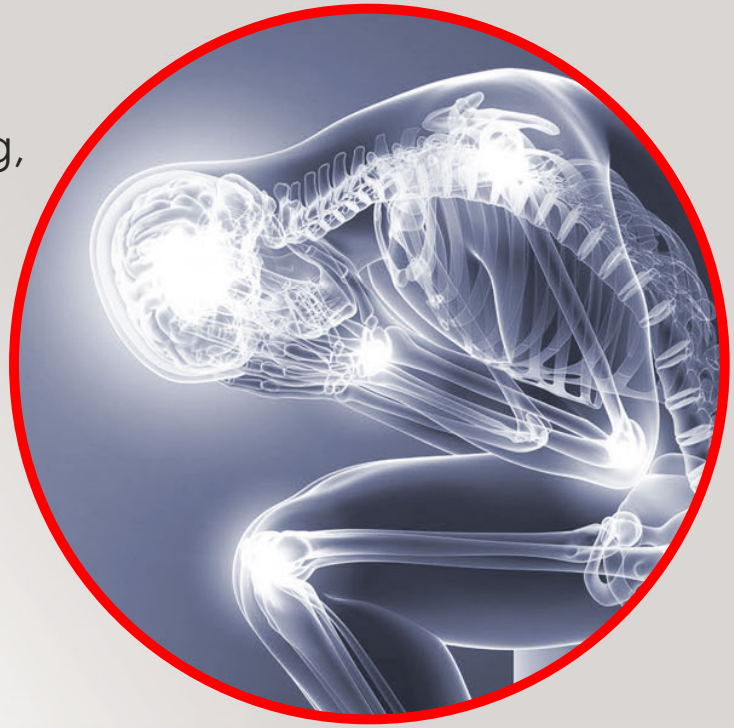
PAIN TRANSMISSION AND MODULATION



- Substances released when tissue is injured, including those involved in the inflammatory cascade, sensitize peripheral nociceptors
- These substances include vasoactive peptides (e,g. calcitonin related protein, substance P, neurokinin A) and other mediators (prostaglandin E2, serotonin, bradykinin, epinephrine)
  - AS YOU CAN SEE THESE EXAMPLES ARE FROM BOTH THE IMMUNE SYSTEM AND THE ENDOCRINE SYSTEM

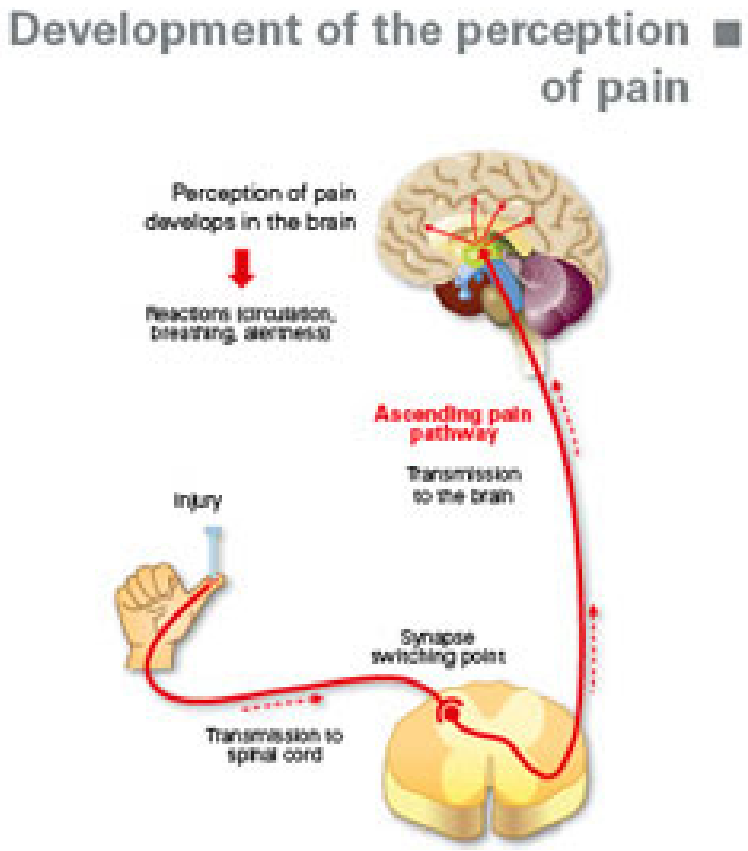
PAIN TRANSMISSION AND MODULATION

- Pain signal is modulated at many point in both segmental and descending pathways by many neurochemical modulators, including endorphins (eg, enkephalin) and monoamines (e.g. serotonin, NE)
- These mediators interact in poorly understood ways to increase, sustain, shorten, or reduce the perception of and response to pain
- They mediate the potential benefit of the CNS-active drugs (e.g. opioids, antidepressants, anticonvulsants, membrane stabilizers) that interact with specific receptors and neurochemicals in the treatment of chronic pain



PAIN TRANSMISSION AND MODULATION

- Psychological factors are important modulators
- They have an affect on how patients speak about pain and how they behave in response to it
- They also generate neural output that modulates neurotransmission along pain pathways
- Psychologic reaction to protracted pain interacts with other CNS factors to induce long-term changes in pain perception



EVALUATION OF PAIN

- Clinicians should evaluate the cause, severity, and nature of pain and its affect on activities, mood, cognition, and sleep
- Evaluation of the cause of acute pain differs from that of chronic pain
- Patient's level of function should be assessed, focusing on activities of daily living, employment, avocations, and personal relationships

EVALUATION OF PAIN

- History should include the following information:
  - Quality (e.g. burning, cramping, aching, deep, superficial, shooting)
  - Severity
  - Location
  - Radiation pattern
  - Duration
  - Timing (including pattern and degree of fluctuation and frequency of remissions)
  - Exacerbating and relieving factors

EVALUATION OF PAIN

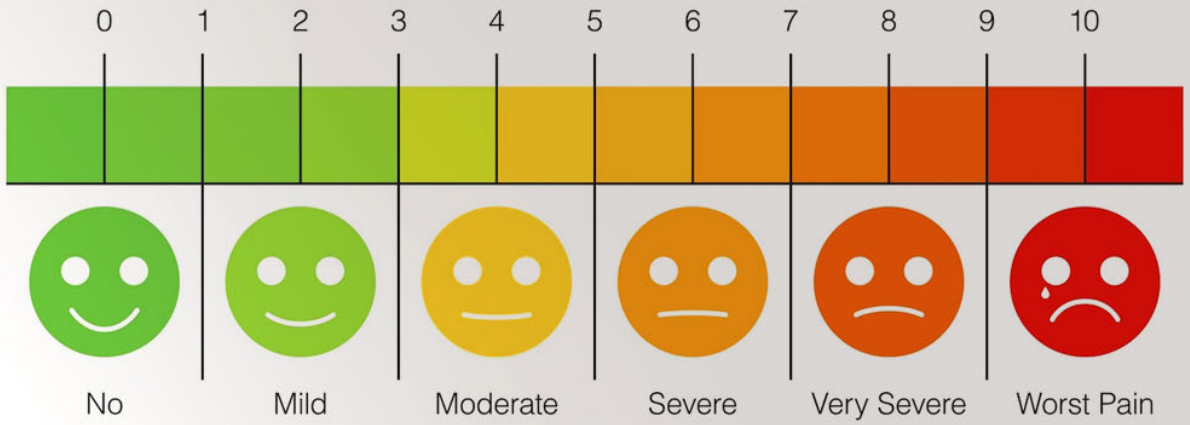
- What pain means to the patient should be determined, with an emphasis on psychological issues, depression, and anxiety
- Reporting pain is more socially acceptable than reporting anxiety or depression, and appropriate therapy often depends on sorting out these issues first
- Pain and suffering should be distinguished, especially in cancer patients
  - Suffering may be due as much to loss of function and fear of impending death as to pain

EVALUATION

- Evaluating the patient's current management of the pain is also important
- Patients and sometimes family members and caregivers should be asked about the use, efficacy, and adverse effects of prescription and OTC drugs
- Also other treatments and about alcohol and recreational or illicit drug use
- This can give a background on the abuse potential and ways that the clinician may want to approach the use of drugs to manage a patient's pain knowing their history

PAIN SEVERITY

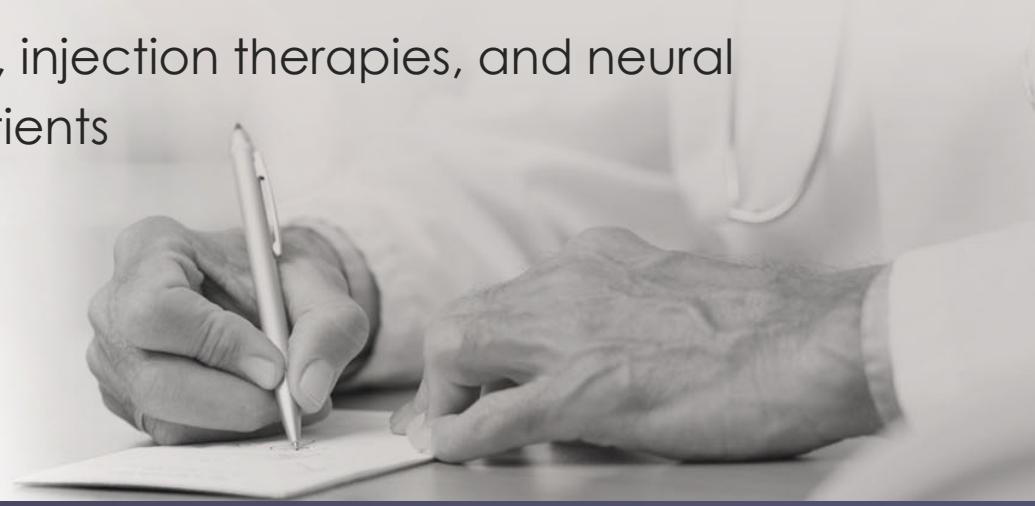
- Pain severity should be assessed before and after potentially painful interventions
- Pain severity should be assessed before and after potentially painful interventions
- Self-reporting is the gold standard in patients that are able to communicate verbally
  - External signs of pain and distress are secondary (non-verbal indicators)
    - First for those that have a difficult time communicating (young children)



- Verbal category scales, numeric scales, and the Visual Analog Scale (CAS) are used

TREATMENT OF PAIN

- Treatment should be multimodal – use of non-opioid and opioid analgesics (when needed)
- Antidepressants, anticonvulsants, and other CNS-active drugs may also be used for chronic or neuropathic pain and are the first-line therapy for some conditions
- Neuraxial infusion, nerve stimulation, injection therapies, and neural blockade can help for selected patients
- Cognitive behavioral interventions may reduce pain and pain-related disability and help patients cope

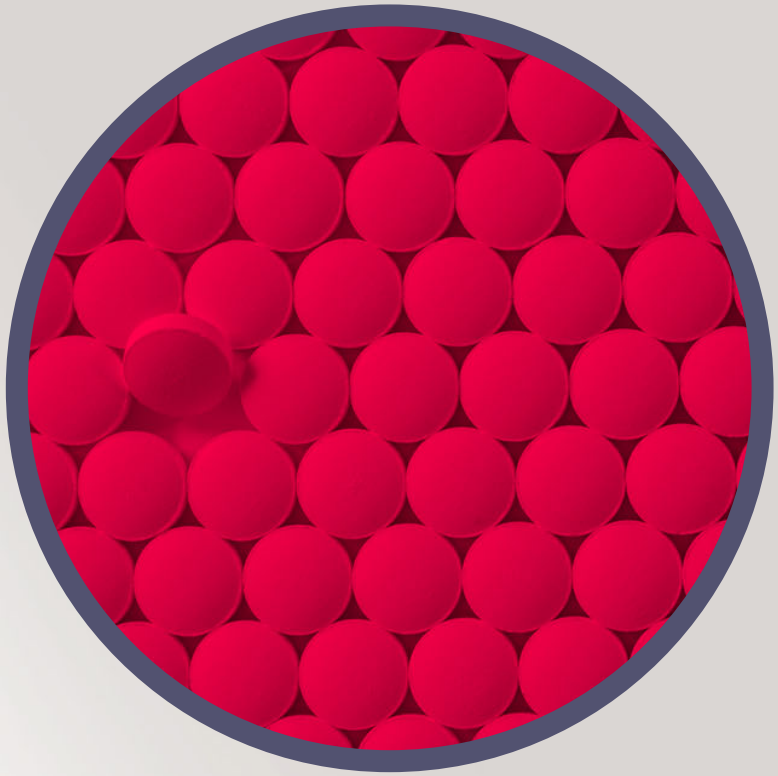


NON-OPIOID ANALGESICS

- Acetaminophen and NSAIDs are often effective for **mild to moderate** pain as monotherapy
- Non-opioids do not cause dependence or tolerance
- Acetaminophen has no anti-inflammatory or antiplatelet effects and does not cause gastric irritation
- NSAIDs should be used cautiously in patients with renal insufficiency, cardiovascular disease, and conditions that increased bleeding/ulcers in the GI tract

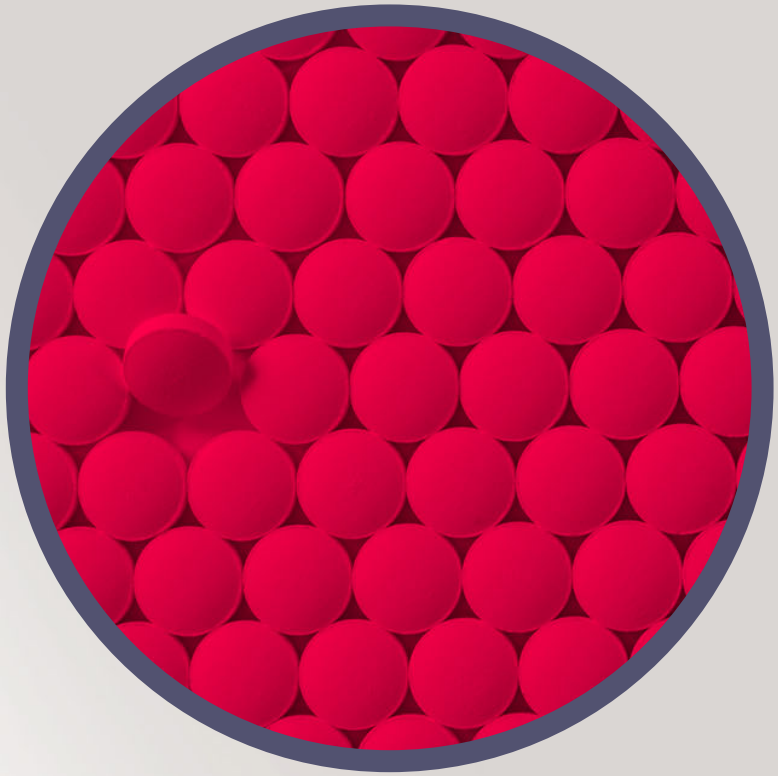
OPIOID ANALGESICS

- Opioid is a generic term for natural or synthetic substances that bind to specific opioid receptors in the CNS that producing an agonist action
- Opioids are also called narcotics – a term originally used to refer to any psychoactive substance that induces sleep
- Opioids have both analgesic and sleep-inducing effects, but the 2 effects are distinct from one another



OPIOID ANALGESICS

- Some opioids used for analgesia have both agonist and antagonist actions
  - Those with known abuse may benefit more from an agonist-antagonist drug rather than a pure agonist
- Agonist-antagonist drugs have a ceiling effect for analgesia and induce a withdrawal syndrome in patients already psychically dependent on opioids
- Acute pain is best treated with short-acting pure agonists
- Chronic pain is best treated with long acting opioids



OPIOID ANALGESICS

- Adverse effects
  - Sedation and mental clouding
  - Nausea and vomiting
  - Itching
  - Respiratory depression (rare with appropriate doses)
- Use in caution in the following patients:
  - Hepatic disorders
  - COPD
  - Neurologic disorders
  - Severe renal insufficiency

OPIOID ANALGESICS

- Constipation is common among people who take opioids for more than a few days
- Prevention in patients using dietary fiber and a stimulant laxative should be giving
- Persisting constipation can be managed with different pharmacotherapy and patients should consult a physician if no bowel movements have been made within 48 hours of being on an opioid analgesic

OPIOID ANALGESICS

- Opioids can cause neuroendocrine effects, typically reversible hypogonadism:
  - Fatigue
  - Loss of libido
  - Infertility due to low levels of sex hormones
  - Amenorrhea in women

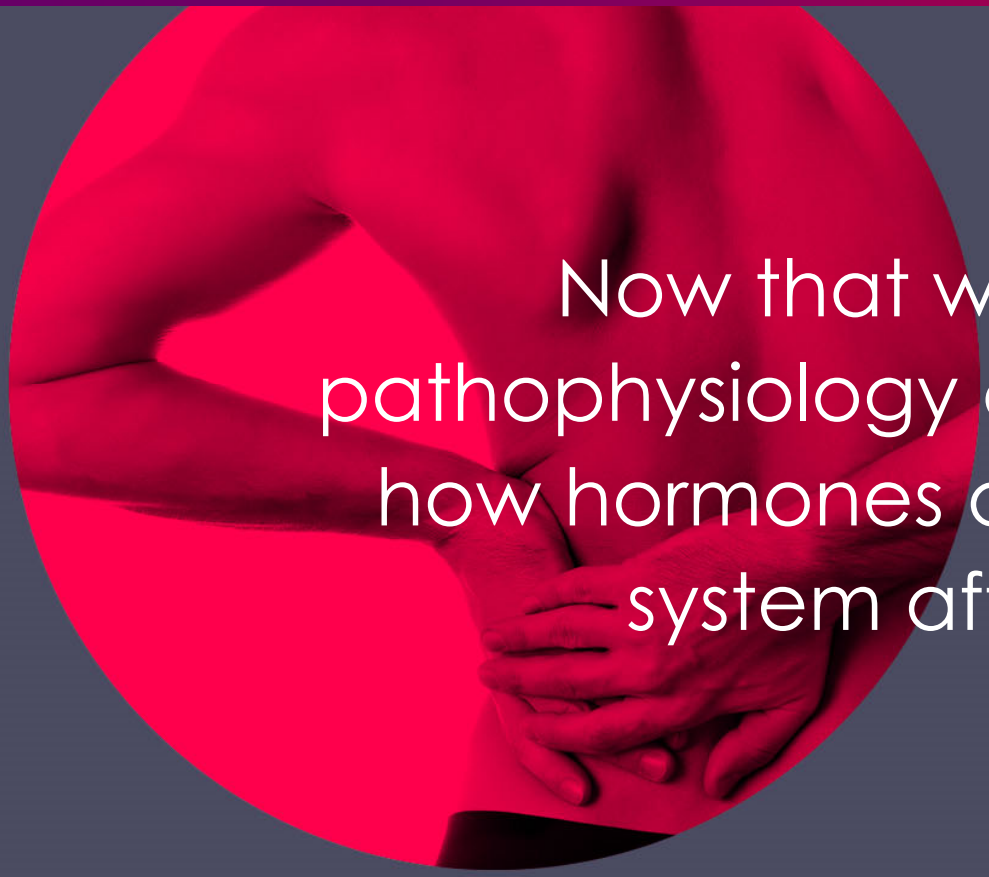
OPIOID MISUSE, DIVERSION, AND ABUSE

- Opioids are the leading cause of accidental death and fatal drug overdose in the US
- **Opioid misuse** may be intentional or unintentional. It includes any use that contradicts medical advice or deviates from what is prescribed
- **Diversion** involves selling or giving a prescribed drug to others
- **Abuse** refers to recreational or nontherapeutic use
- **Addiction**, typically marked by impaired control and craving, refers to compulsive use despite harm and negative consequences

ADJUVANT ANALGESIC DRUGS

- Many drugs are used as adjuvant analgesics, including anticonvulsants and antidepressants
- They most notably relieve neuropathic pain
  - Gabapentin
  - Pregabalin
  - Duloxetine

NOW…



Now that we know the pathophysiology of pain, let's learn how hormones and the immune system affect pain!

Chapter 3

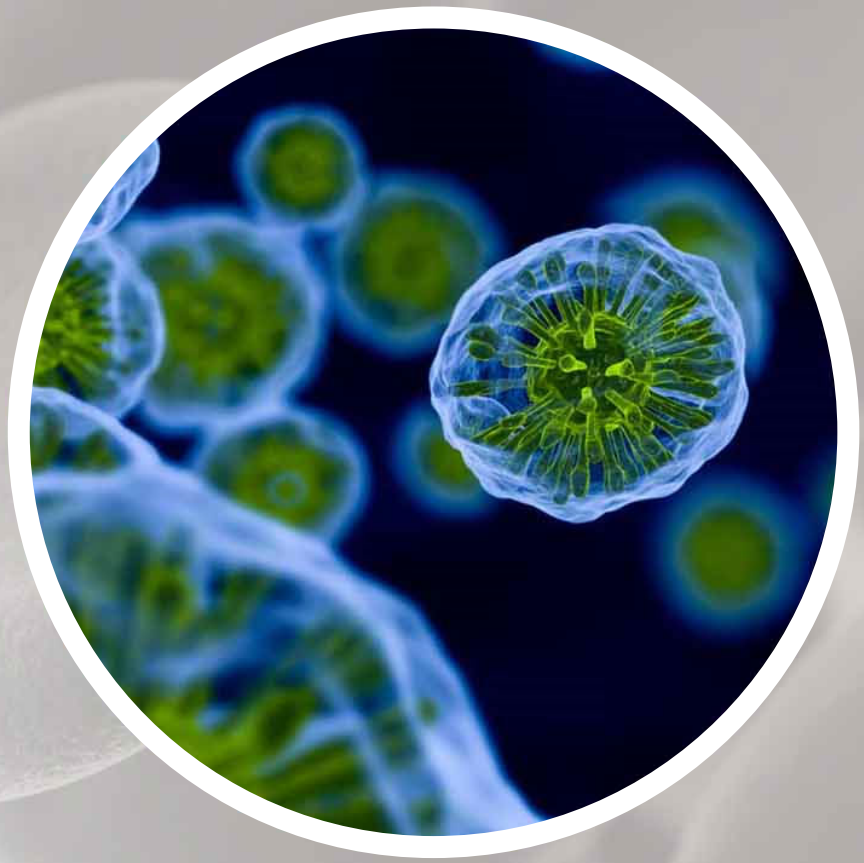
PAIN AND THE IMMUNE SYSTEM

INFLAMMATION AND PERIPHERAL NOCICEPTOR SENSITIZATION

- Upon injury, inflammation is triggered by immune activation of pattern-recognition receptors including toll-like receptors (TLR)
  - Recognize and bind to invading pathogens or endogenous molecules released from damaged cells
- TLRs are expressed in immune cells, including monocytes, macrophages, dendritic cells
- Binding to TLRs followed by activation of nuclear factors kB signal and release inflammatory cytokines

INFLAMMATION AND PERIPHERAL NOCICEPTOR SENSITIZATION

- Resident immune cells, mast cells and macrophages are also activated within minutes of injury and release proinflammatory cytokines
  - Cytokines, chemokines, effectors of the complement cascade and vasodilators, including vasoactive amines and bradykinin
- Blood-borne neutrophils, monocytes, and T lymphocytes adhere to the vessel walls, extravasate and accumulate at the site of injury
- These immune cells contribute to peripheral nociceptive sensitization by releasing soluble factors and interacting directly with nociceptors



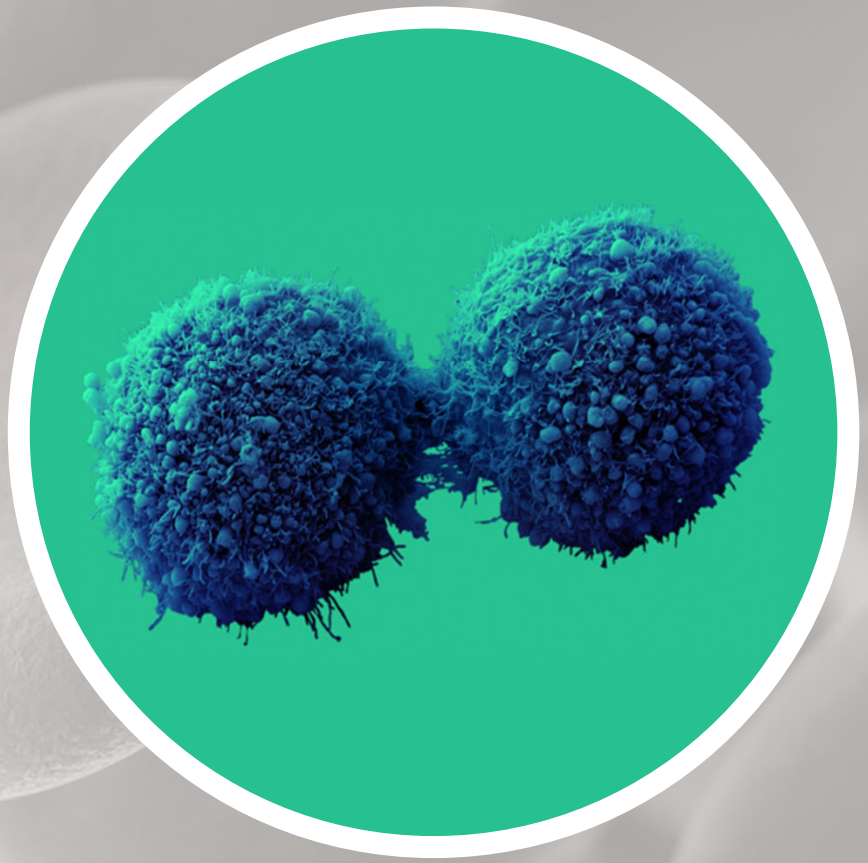
INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- Mast cells are granulated resident immune cells that are divided into mucosal and connective tissue subtypes and are found close to capillaries
- They participate in innate host defenses and allergic reactions and are degranulated within minutes of an inflammatory reaction
  - Results in the release of histamine, bradykinin, and other mediators that contribute to vasodilation

INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- Degranulation of masts cells requires direct interaction between mast cells and peripheral nerve terminals, mediated by the calcium-dependent adhesion molecule N-cadherin

- N-cadherin is expressed in both mast cells and primary sensory neurons and is cleaved by mellatoproteinase MT5-MMP which is expressed by neurons



INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- Mast cells are found close to primary nociceptive neurons and contribute to nociceptor sensitization
- Mast cells degranulation also contributes to the rapid onset of nerve growth factor-induced thermal hyperalgesia
- Histamine plays an important role in mediatory cell-induced nociceptor activation
- TNF-alpha does not seem to be required for mast-cell dependent pain

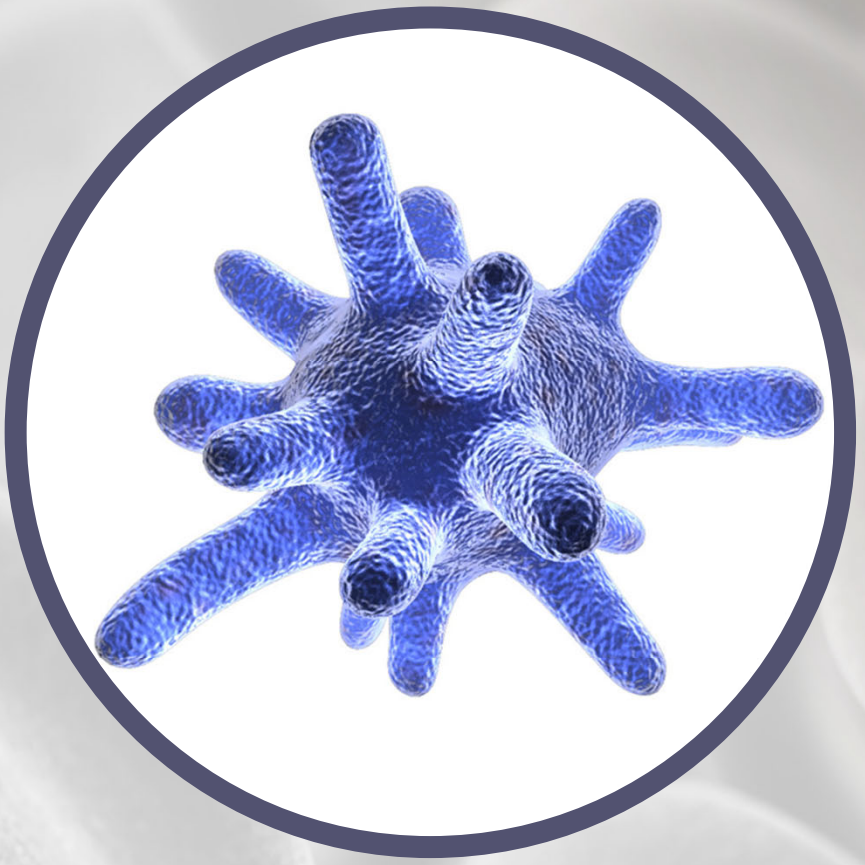
INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- Macrophages are derived from circulating monocytes and are maintained by the local proliferation and maturation of blood monocytes after diapedesis
- Migrating blood monocytes are required to the site of injury and mature within hours to increase the proportion of macrophages in the inflamed area within days to weeks
- Resident macrophages become phagocytic almost immediately after injury

INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- The number of macrophages is increased at the site of nerve injury
  - Correlates to the development of mechanical allodynia, pain induced by a normally non-noxious stimulus, after nerve injury
- Recruitment of macrophages after nerve injury is mediated by several inflammatory cytokines
  - TNF-alpha released from Schwann cells immediately after nerve injury, induce MMP-9
  - MMP-9 then promotes migration of macrophage to the injured site via breakdown of the blood-brain-barrier
  - IL-15, which acts on B cells and promotes T cell proliferation, is upregulated in nerves a few hours after injury

INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

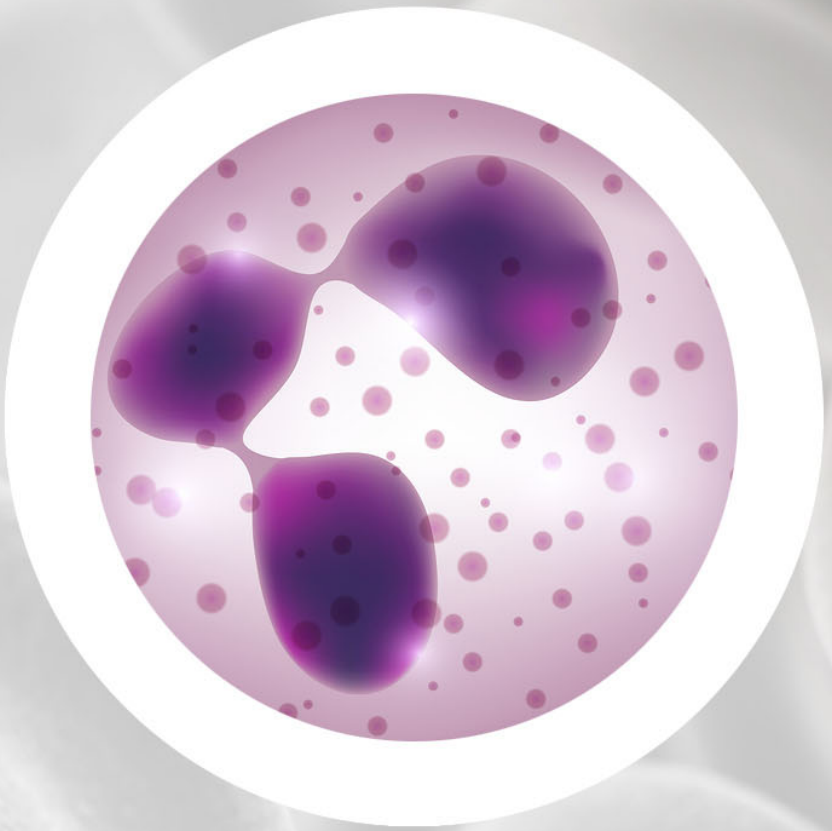


- Following recruitment and activation, macrophages contribute to nociceptor sensitization by releasing several soluble mediators
  - Expression of chemokine macrophage inflammatory protein-1alpha (MIP-1alpha) and its receptors CCR1 and CCR5 is increased in macrophages and Schwann cells after partial ligation of the sciatic nerve and contribute to the development of neuropathic pain

INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- Depletion of circulating monocytes and macrophages by liposome-encapsulated clodronate partially reduces thermal and mechanical hyperalgesia, without altering mechanical allodynia
- This suggests that macrophage may only have a minor role in neuropathic pain
- Resident macrophages have an important role in polymorphonuclear leukocyte infiltration and acute inflammation, as demonstrated by conditional macrophage ablation

INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS



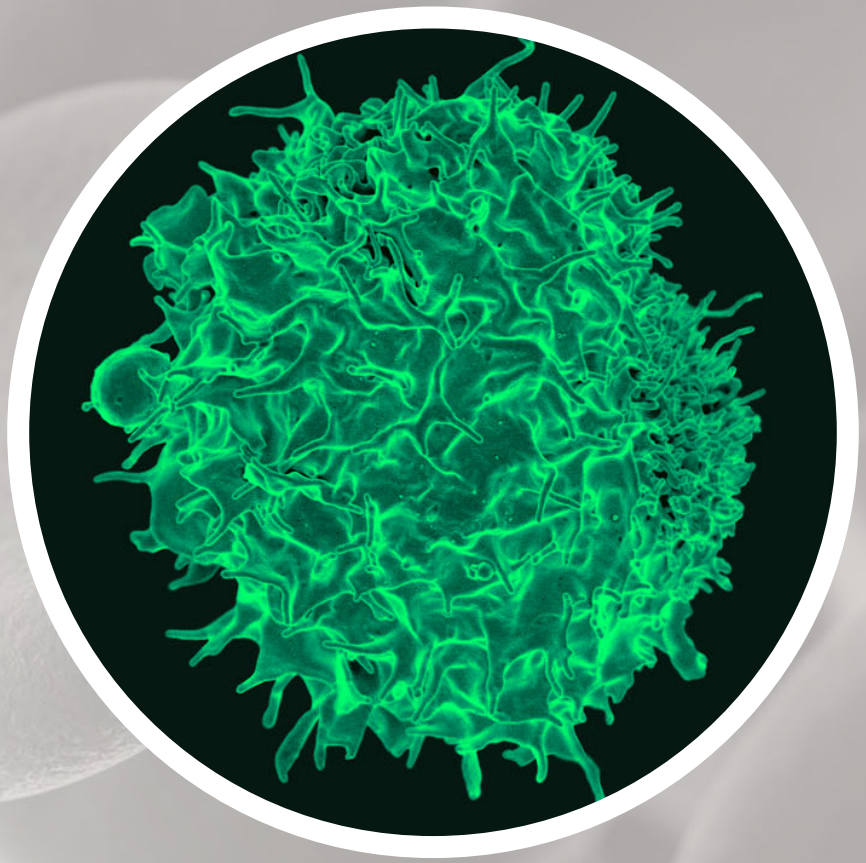
- Neutrophils are the most abundant polymorphonucelar leukocytes
- Neutrophil migration is associated with inflammatory pain
- Within the first hour of onset of inflammation, neutrophils migrate through the vascular endothelium and accumulate at the site of injury
- Nerve terminals influence neutrophil recruitment through neurogenic inflammation
  - Release vasoactive peptides substance P and calcitonin gene-related peptide (CGRP) at peripheral branches
  - IL-1 can also bind nerve terminals and induce substance P release and migration of polymorphonuclear leukocytes

INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- Mast cell degranulation is also facilitated by substance P and CGRP
- Synergistic neuroimmune interactions, in which multiple soluble mediators can amplify a response and increase the recruitment of cells, facilitate sensitization and the emergence of a chronic pain state

INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- Lymphocytes contribute to the sensitization of peripheral nociceptors
- T cells infiltrate the sciatic nerve and dorsal root ganglion after nerve injury
- Hyperalgesia and allodynia induced by nerve injury are markedly attenuated or abrogated when T cells are lacking
- Among the subset of T cells, type 1 and 2 helper T cells have been shown to have different roles in neuropathic pain



INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- TH1 cells facilitate neuropathic pain behavior by releasing proinflammatory cytokines
- TH2 cells inhibit it by releasing anti-inflammatory cytokines
- Natural killer cells are recruited to the site of injury, but they do not seem to be involved in neuropathic pain because there is no difference in the number of NK cells
- B cells also show no change in people with chronic pain and do not seem to contribute to the development of neuropathic pain

INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

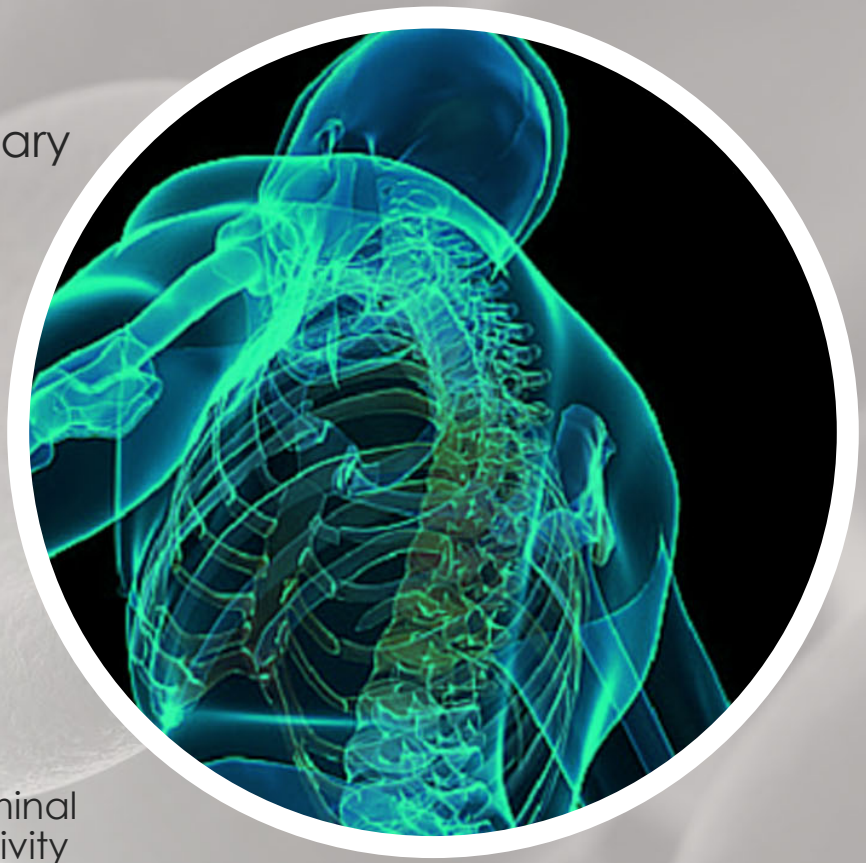
- The complement system is an important part of innate defense
- Effectors of the complement cascade attack microbes, activate mast cells and basophils, and promote chemotaxis of leukocytes
- These proteins are normally present in the blood but can leak out to inflamed tissue

INTERACTIONS BETWEEN IMMUNE CELLS AND NOCICEPTORS

- Complement system has a role in inflammatory hyperalgesia and neuropathic pain
- C5a, an analphyatoxin, is an important effector of the complement system and upon binding the C5aR1 receptors on neutrophils it becomes a potent neutrophil attractant
- Complement components also have a direct effect on nociceptors
  - Application of C5a or C3a to peripheral nerves sensitizes C fiber nociceptors
  - This effect may be mediated by direct effect of binding C5a receptors, as C5a receptor mRNA is expressed in primary sensory neurons

NEURON-TO-GLIA SIGNALING

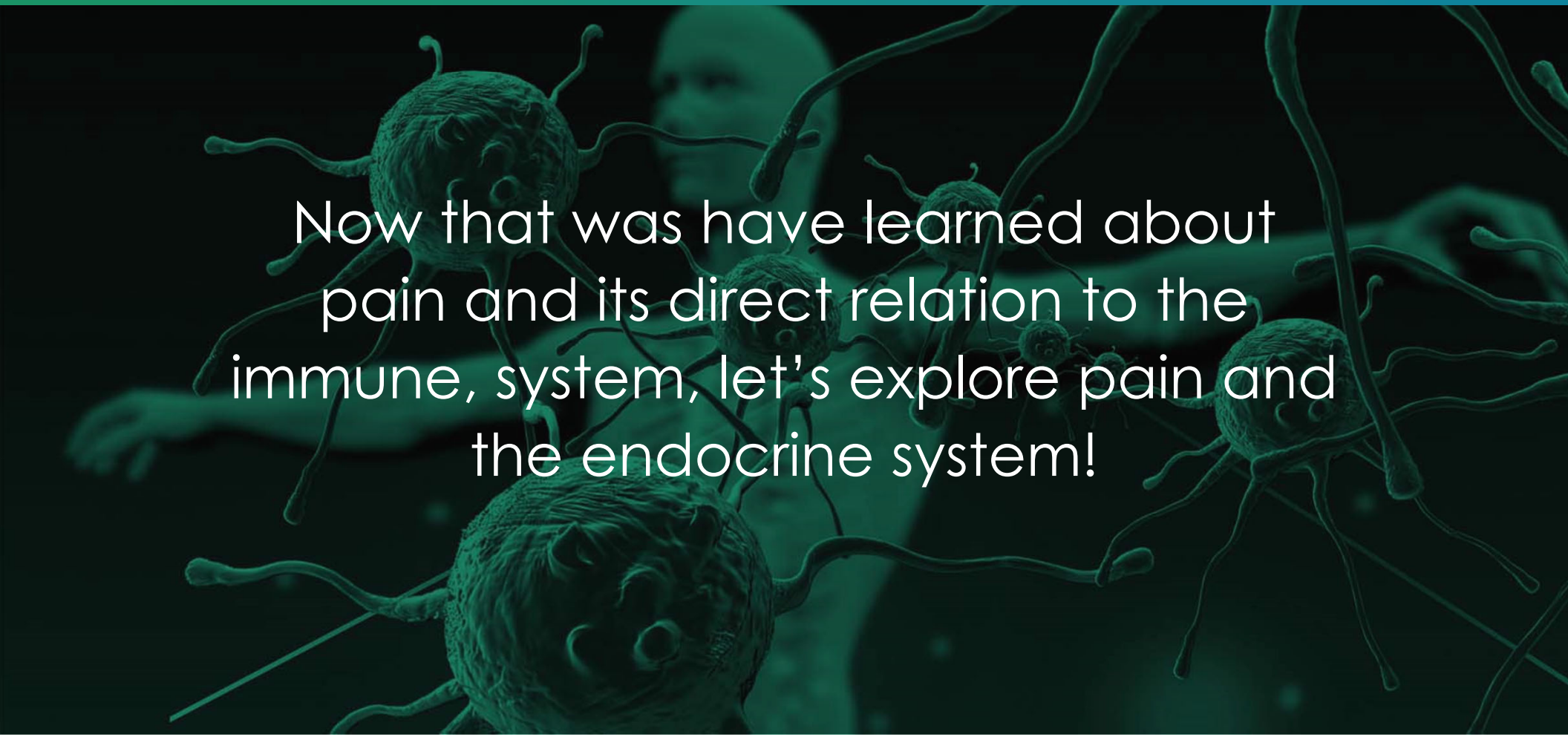
- Neurotransmitters, neuromodulators, and inflammatory mediators are released from primary afferent terminal into the spinal cord
- CCL2 is packaged into large dense-core vesicles in dorsal root ganglia neurons, suggesting that it can be released in a manner similar to a neurotransmitter
- Upon an arrival of a nerve impulse, neural and immune mediators such as glutamate, ATP, substance P, CGRP, BDNF, IL-6, and CCL2 are released
  - These act on receptors on the postsynaptic nerve terminal and on migroglia and astrocytes, modulating glial activity



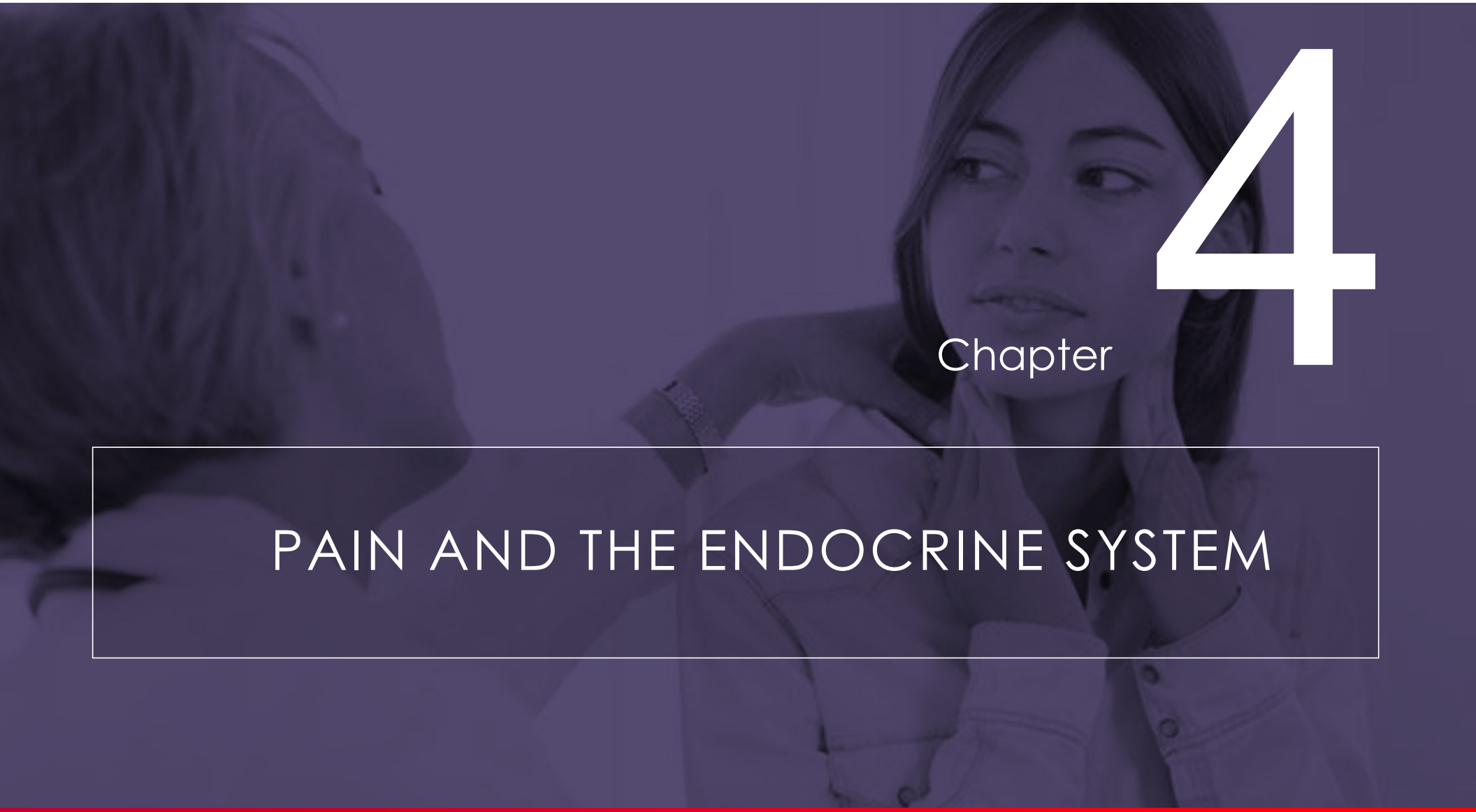
GLIA-CYTOKINE-NEURON INTERACTIONS

- Both microglia and astrocytes release substances that influence neuronal activity
- Activated microglia release several mediators that act on neurons and sensitize nociceptors
- CX3CL1 is expressed in primary sensory neurons and dorsal horn neurons
  - CX3CL1 is normally anchored to the cell membrane by a mucin stalk that can be cleaved by protease activity
  - Upon primary afferent stimulation the lysosomal cysteine protease cathepsin S is released from microglia and cleaves CX3CL1
  - This in turn activates its receptor on microglia leading to phosphorylation of p38 MAPK in microglia

NOW…

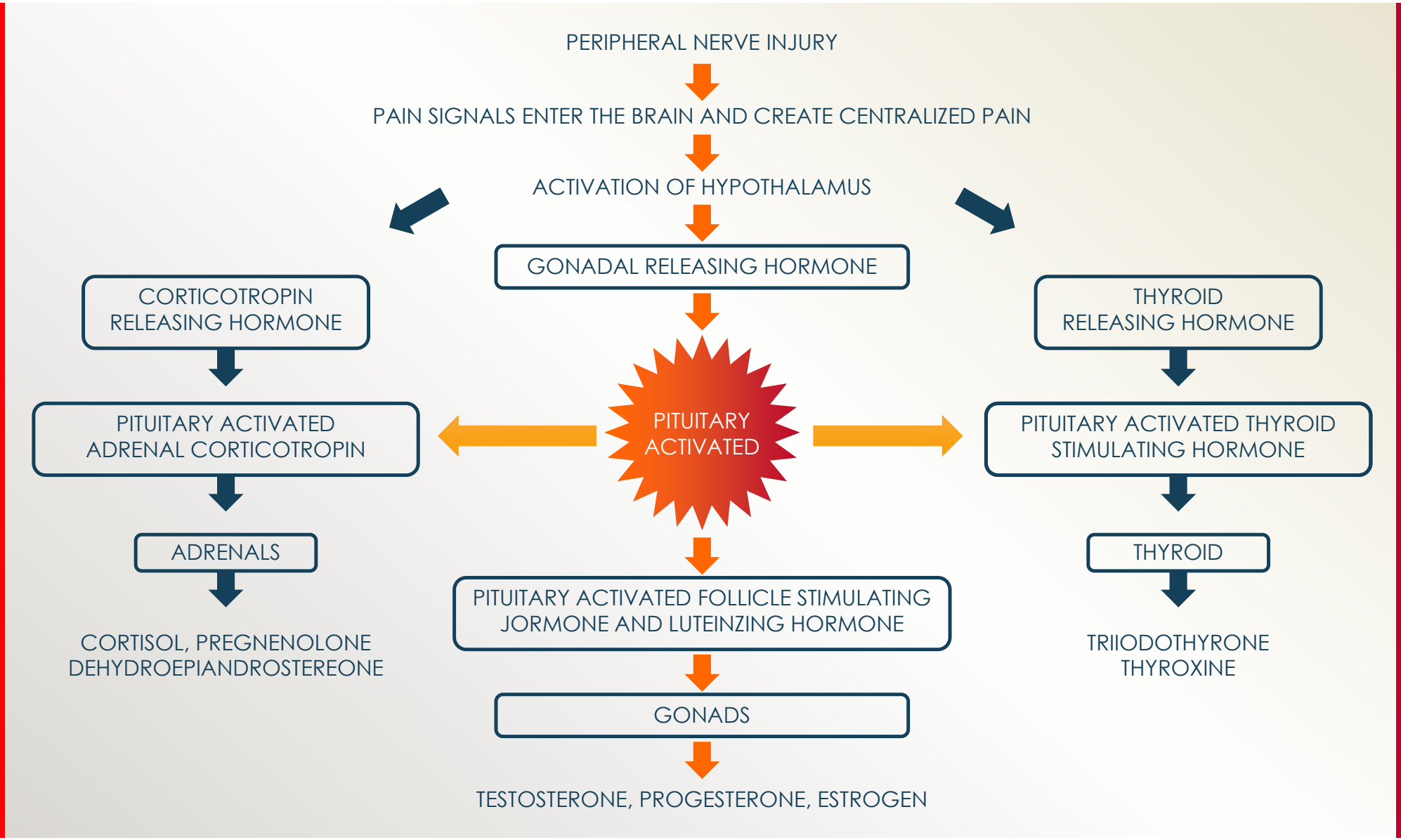


Now that was have learned about pain and its direct relation to the immune, system, let's explore pain and the endocrine system!



Chapter 4

PAIN AND THE ENDOCRINE SYSTEM


PERIPHERAL NERVE INJURY
PAIN SIGNALS ENTER THE BRAIN AND CREATE CENTRALIZED PAIN
ACTIVATION OF HYPOTHALAMUS
GONADAL RELEASING HORMONE
CORTICOTROPIN RELEASING HORMONE
THYROID RELEASING HORMONE
PITUITARY ACTIVATED ADRENAL CORTICOTROPIN
PITUITARY ACTIVATED
PITUITARY ACTIVATED THYROID STIMULATING HORMONE
ADRENALS
THYROID
PITUITARY ACTIVATED FOLLICLE STIMULATING JORMONE AND LUTEINZING HORMONE
CORTISOL, PREGNENOLONE DEHYDROEPIANDROSTEREONE
TRIIODOTHYRONE THYROXINE
GONADS
TESTOSTERONE, PROGESTERONE, ESTROGEN

HORMONE FUNCTIONS IN PAIN CONTROL

- Adequate pain control may not be achieved without homeostasis of certain hormones
- **Hormonal homeostasis** – maintenance of a hormone within a normal serum range
- Critical pain-control hormones that are produced in the glands outside of the CNS:
  - Cortisol
  - Pregnenolone
  - DHEA
  - Progesterone
  - Testosterone
  - Estrogen
  - Thyroid

HORMONE FUNCTIONS IN PAIN CONTROL

- Pain control functions of these hormones:
  - Anti-inflammatory actions
  - Cellular protection
  - Tissue regeneration
  - Glucose control
  - Modulation of CNS receptors, blood-brain-barrier, and nerve conduction

HORMONES AND THEIR INTERACTION WITH THE PAIN EXPERIENCE

- Sex differences in the prevalence of painful condition appear after puberty
- Variation in symptoms severity across the menstrual cycle occurs in a number of clinical pain conditions
- Sex steroid hormones act at a number of sites in both the peripheral and central nervous system and in both reproductive and non-reproductive tissues
- Sex steroid hormones have traditionally been thought to alter transcription however, there is evidence that there are also non-genomic effects
- Sex steroid hormones can have organizational effects from as early as in utero
- The relationship between sex hormones and pain is complex

CLINICAL PAIN

- Dramatic changes in sex hormones occur around puberty and it is at that point that sex differences in clinical pain conditions begin to be observed
- The timing of puberty is very variable between individuals and most recent studies that control for the stage of pubertal development rather than chronological age have shown an association with pain
- For both sexes, the probability of experiencing a painful condition increases with increasing pubertal development

CLINICAL PAIN

Women

- The greatest reports of pain symptoms appear to occur at times of low or rapidly falling estrogen levels
  - The use of combined oral contraceptive to give a more constant hormonal level can improve these symptoms
- Complete abolition of hormonal fluctuation with gonadotropin releasing hormone antagonists (GnRHa) can improve the symptoms of IBS and IC
- Hypo-estrogenic state can worsen headaches and migraines, although achieving a steady hormonal state with GnRHa and additional low-dose estradiol has been shown to improve migraines
- Women with high testosterone levels have more work-related neck and shoulder injuries

CLINICAL PAIN IN PREGNANCY

- During pregnancy, cyclical fluctuations in hormones cease and instead a steady increase in the levels of both progesterone and estrogen is seen towards term which then fall rapidly after delivery
- Concentrations in the number of steroid hormones also vary from the non-pregnant state and may have an effect on painful conditions, including prolactin and relaxin
- Many clinical pain condition improve during pregnancy including arthritis, migraine, pelvic pain, rheumatoid arthritis
- Pregnancy can also be associated with the development of pain and symptoms of SLE usually worsen in pregnancy

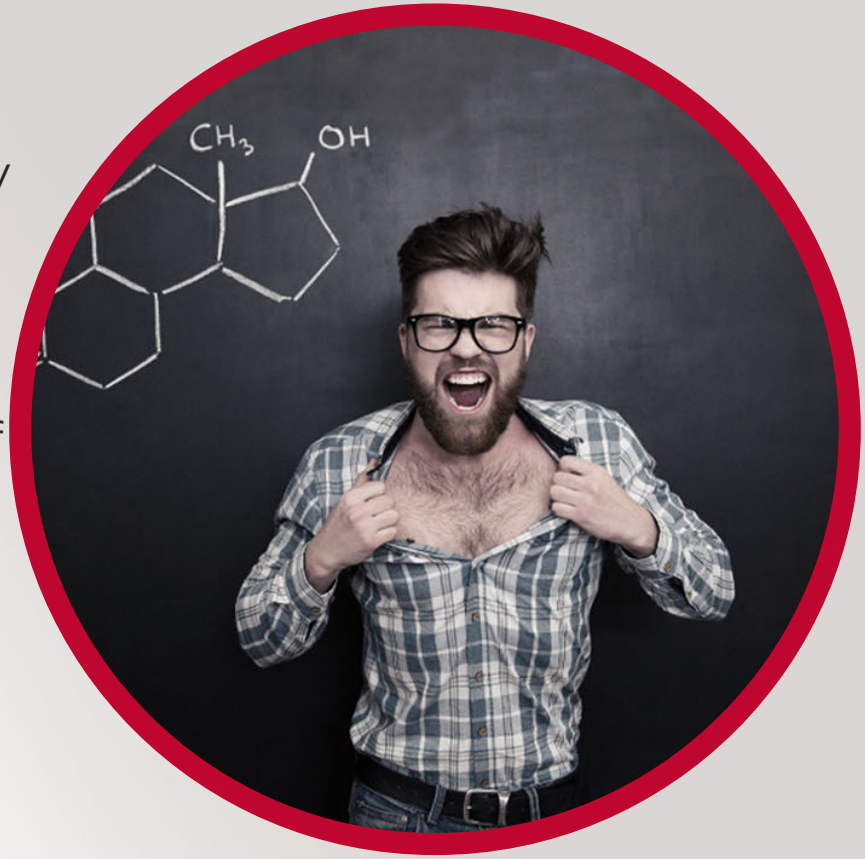
CLINICAL PAIN - MENOPAUSE

- After menopause, levels of estrogen and progesterone are very low
  - Sex differences in pain become much less marked
- Use of HRT in postmenopausal women has been associated with the development of pain conditions including back and TMJ pain

CLINICAL PAIN

Men

- From puberty onwards, men have significantly higher levels of testosterone and its metabolites as compared to women
- Testosterone appears to have an analgesic effect protecting against the development of painful conditions
- Rheumatoid arthritis patients (both male and female) have been shown to have lower androgen levels than their sex-matched controls
  - Androgen administration improves their symptoms



NON-REPRODUCTIVE ACTIONS OF STEROID HORMONES

	Estrogen	Progesterone	Testosterone
Brain	↑Mu-opioid receptor availability ↑Hippocampal excitability ↑5-HT ↓Noradrenaline ↑↓anxiety/stress	Anxiolytic Sedative Analgesic Anticonvulsant Modulate GABA Promote myelination Mediate male aggression towards infants	Analgesic ↑↓seizure threshold ↑Noradrenaline Mediate aggressive behaviour Organisational effects on sexually dimorphic behaviours Modulate endogenous opioids Regulate aromatase activity
Spinal Cord	Modulate dorsal horn response to pain	Mediate hypersensitivity after nerve root damage Neuroprotective	Modulate dorsal horn response in neuropathic pain
Peripheral Nerve	Sensitise uterine and cervical afferents ↑glutamatergic nociceptor activity	Neuroprotective	Facilitate release of ACh
Immune System	Δ T and B cell proliferation and phenotype Δ cytokine and immunoglobulin balance	Anti-inflammatory Modulate immune response	↓cellular immune response
Musculoskel-etal System	↑bone deposition ↑muscle mass recovery following disuse	↑bone deposition Smooth muscle relaxant	↑bone density and strength ↑muscle mass
Cardiovascular System	Δ NO synthesis Δ vasodilation	↑vasodilation	↑vasoconstriction

NEW TARGETS FOR PAIN

NALTREXONE

- FDA-approved indications
  - Treatment of alcohol dependence
  - For the prevention of opioid dependence relapse after opioid detoxification
- Dose
  - 12.5 mg to 150 mg PO

PHARMACOKINETICS

- Duration of onset
  - Oral: up to 3 days
- Absorption
  - Bioavailability: 5-40%
- Distribution
  - Vd(IV): 1350 L
  - Protein binding: 21%

PHARMACOKINETICS

- Metabolism
  - Extensive hepatic metabolism
  - Active metabolite: 6-beta-naltrexol
- Elimination
  - Half life: 4 hours
  - Half life Beta: 5-10 days
  - 53-79% renal excretion, including metabolites

CONTRAINDICATIONS

- Acute hepatitis
- Liver failure
- Recent or current opioid/alcohol ingestion

WHAT IS LOW DOSE NALTREXONE (LDN)

- Naltrexone belongs to a class of drugs known as opioid antagonists
- Naltrexone blocks opiate drugs from binding to the opioid receptors, which can result in increased **endorphin** and **enkephalin** release.
  - Endorphins and enkephalins are the body's natural painkillers.
  - These natural peptide chemicals produced in your body interact with receptors in your brain to help you feel focused, less impacted by pain and put you in a better mood.

HISTORY OF NALTREXONE ...

NALTREXONE – 50mg-200mg

- 1963 – Synthesized
- 1967 – Patented
- 1984 – FDA Approval for Heroin Addiction = 50mg dose
- 1991 – Yale studies, Alcoholism. 2x successful as placebo
- 1995 – FDA approval for alcoholism
- 2003 – Vitriol
- 2005 – Yale studies Obesity | Contrave
- FDA approval orphan drug Autism

HISTORY OF LDN...

LOW-DOSE NALTREXONE 0.5mg – 4.5mg

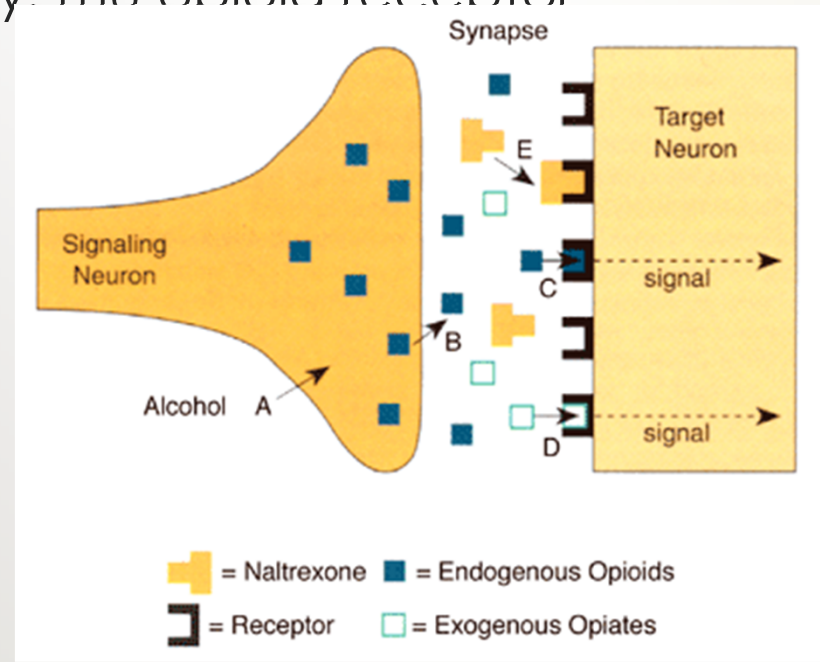
- 1985 – Dr. Bihari – Harvard MD, treatment of AIDS patient
  - AIDS patients 20% normal endorphin levels
  - KEY DISCOVERY – 1% normal dose paradoxical effect
    300% increase in endorphin levels
  - Best success rate in the country
- 2007 1st LDN Research Article – Crohn's Disease, Penn State
- 2009 Fibromyalgia – Stanford Medical School
- PUBMED = 230 LDN Articles

MANY DISEASES ARE EXPRESSIONS OF A MALFUNCTIONING IMMUNE SYSTEM

- Immune system is regulated by endorphins
- Endorphins have a primary action on opiate receptors
- Briefly blocking opiate receptors up-regulates endorphins
- Acts in an immunomodulatory way to correct the immune system
- Cell growth (proliferation) can be mediated by endorphins
- Cell proliferation may be suppressed by endorphins

MECHANISM OF ACTION

- Antagonist of opiate receptors
- Highest affinity: mu opioid receptor



NALTREXONE AND TOLL LIKE RECEPTORS (TLRS)

- Naltrexone is an antagonist of TLRs
- TLRs lead to production of pro-inflammatory cytokines when activated
- Pro-inflammatory cytokines increase inflammation
- Pro-inflammatory cytokines increase pain

HOW DOES LDN HELP YOUR IMMUNE SYSTEM, REDUCE PAIN, INFLAMMATION AND AUTOIMMUNE CONDITIONS ?

- Down regulates inflammatory cytokine release, oncogene expression and auto-immune cascades
- In the Central Nervous System **(CNS)**
  - Reduces toll-like receptor (TLR) signaling and glial cell activation resulting in reduced inflammatory cytokines and reduced neuro-inflammation
- In the Peripheral Nervous System **(PNS)**
  - Modulates T & B lymphocyte production (example: gut inflammation)
  - Reduces inflammatory cytokines (IL6, IL12, TNF alpha)
  - Suppresses tumor growth factor (NF-kB)

When taken at bedtime, the short acting LDN binds to the receptors which leads to a brief blockade of opioid receptors between 2 am and 4 am. This blockade is believed to up-regulate vital elements of the immune system by causing an increase in endorphin and enkephalin production

NALTREXONE AND TOLL LIKE RECEPTORS (TLRS)

- Naltrexone is an antagonist of TLRs
- TLR Activation leads to production of **NF-ķB** (inflammatory signaling pathway)
  - NF-ķB linked to expression of cancer oncogenes
    - Cancer oncogenes turn off natural cell death mechanism
    - Leads to uncontrolled growth of cancer cells

NALTREXONE INHIBITS IL-6 AND TNF-ALPHA

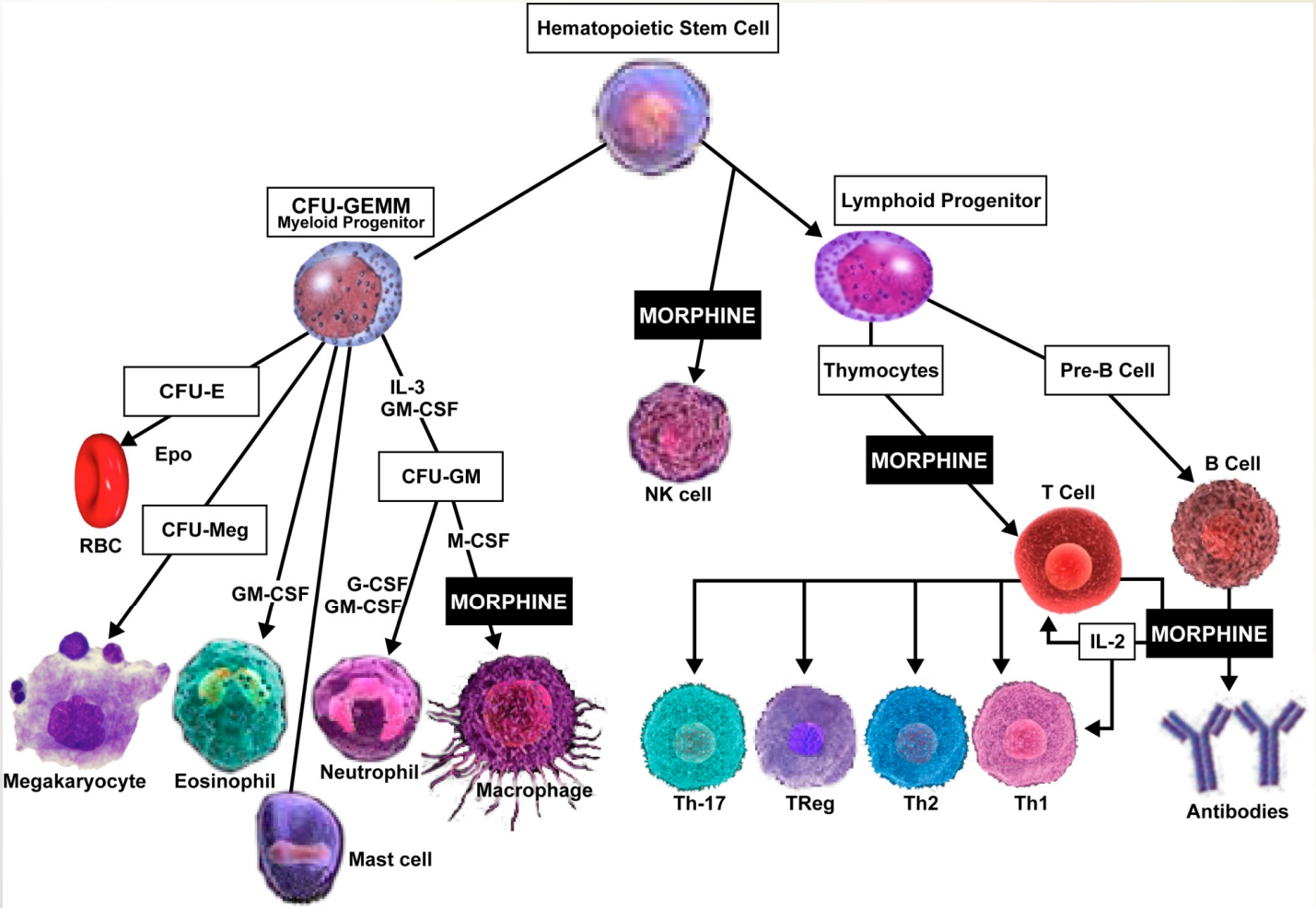
- Analyzed effects of LDN on IL-6 secretion by peripheral blood mononuclear cells
  - In vitro following stimulation with ligands for TLR4 and for intracellular receptors TLR7, TLR8, and TLR9
- Naltrexone did not affect cell viability or induce apoptosis of PBMC
- Intracellular staining showed that naltrexone inhibited production of IL-6 and TNF-alpha by monocyte and plasmacytoid dendritic cell subsets
  - Within PBMC population following treatment with ligands for TLR7/8 and TL9, respectively

NALTREXONE INHIBITS IL-6 AND TNF-ALPHA

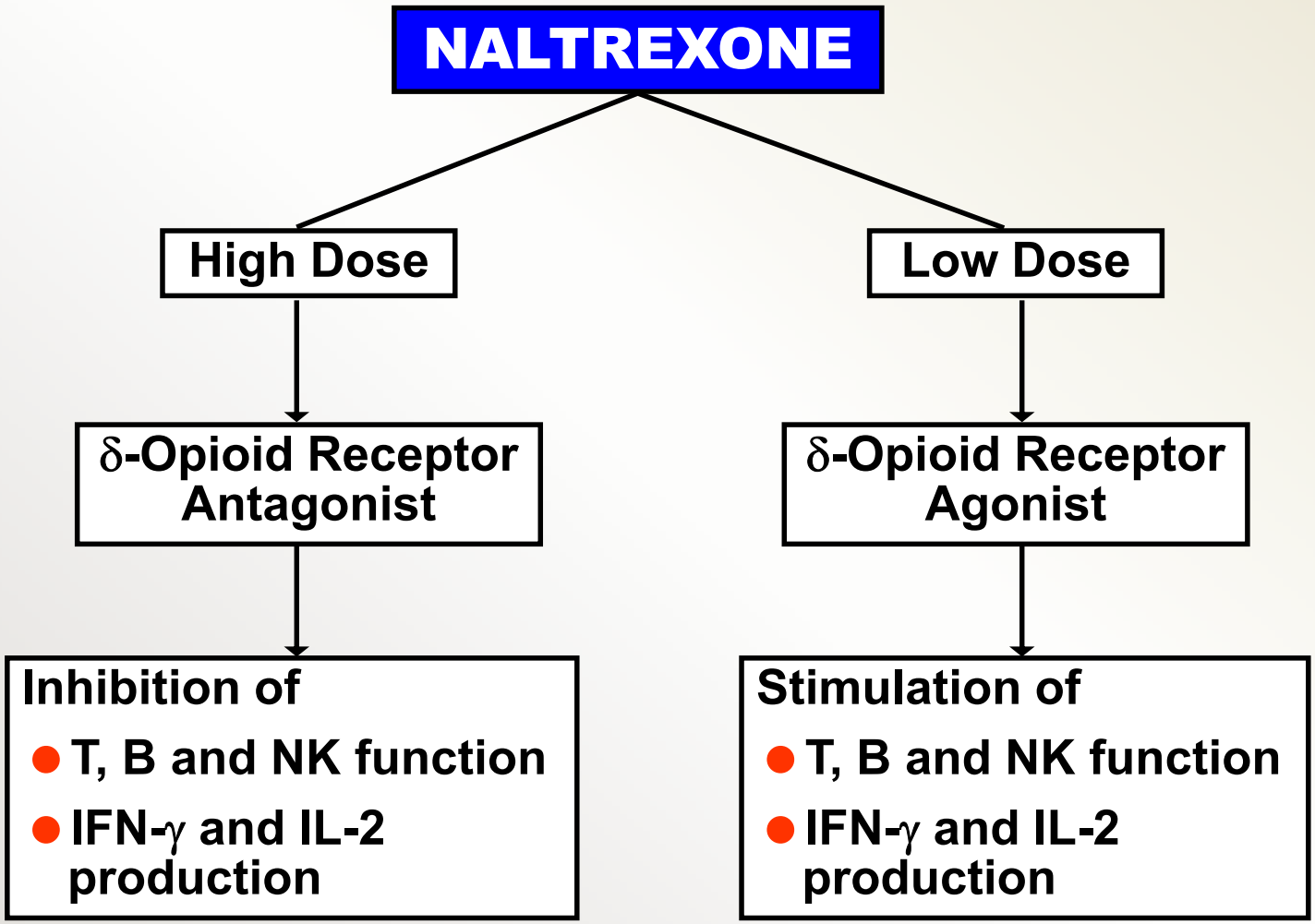
- Naltrexone inhibited IL-6 production in isolated monocytes and B cells after TLR7/8 and TLR9 stimulation
- Findings indicate that naltrexone has potential to modulate the secretion of inflammatory cytokines in response to intracellular TLR activity
  - May have potential for use as an immunomodulator

LOW DOSE NALTREXONE

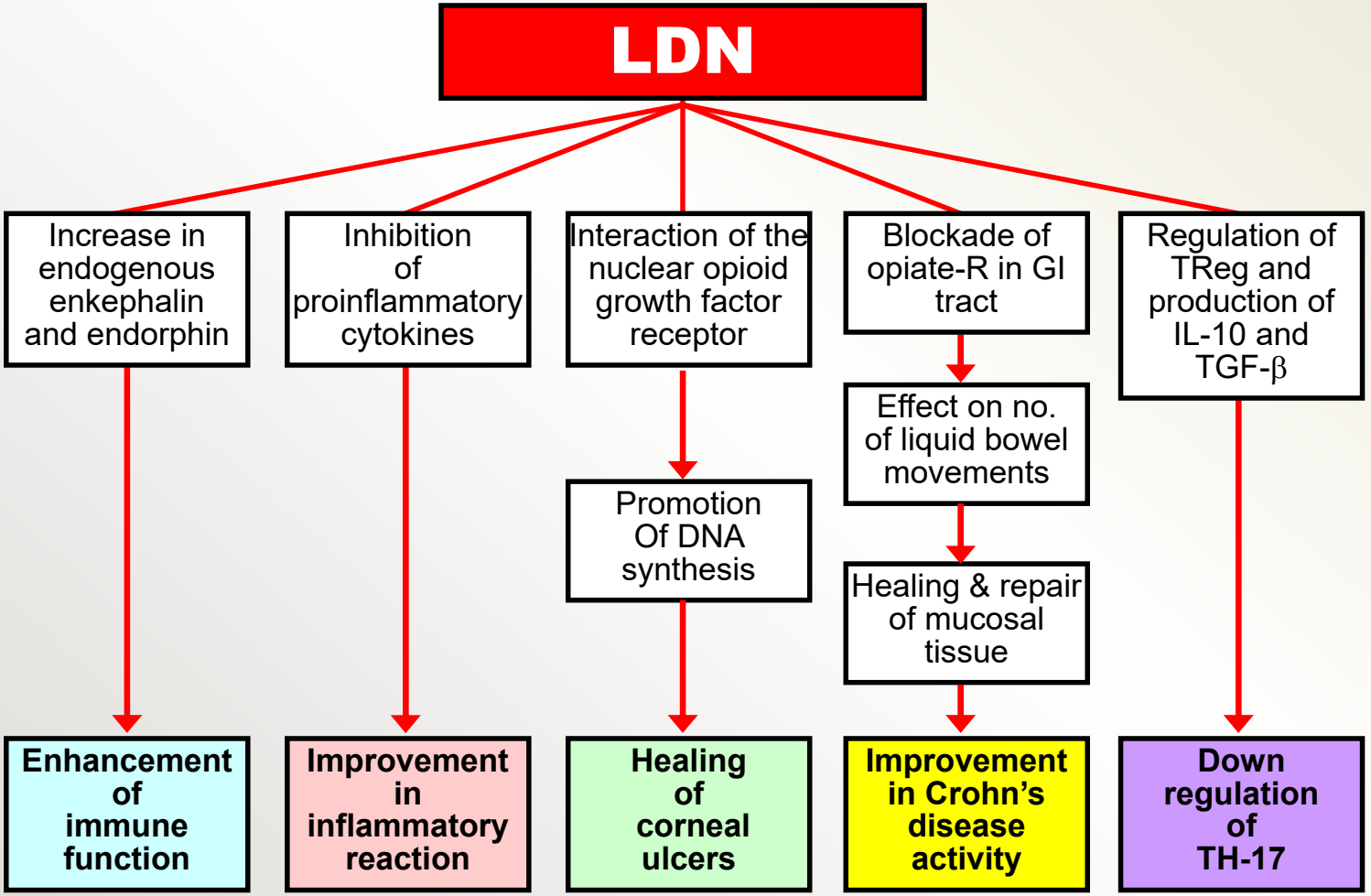
Effects of Opioids on the Immune System



Schematic representation of the hematopoietic system showing the differentiation pathways sensitive to opioids.
from Effects of Opioids on the Immune System – Roy S. and Loh H.H., Neurochemical Research, 21:1375-1386, 1996


NALTREXONE
High Dose
Low Dose
δ-Opioid Receptor Antagonist
δ-Opioid Receptor Agonist
Inhibition of
T, B and NK function
IFN-γ and IL-2 production
Stimulation of
T, B and NK function
IFN-γ and IL-2 production

MECHANISM OF ACTION OF LDN



OPIOID ADDICTION TREATMENTS

OPIOID ADDICTION

- Addiction is defined as chronic, impaired control, compulsive use, continued use despite harm, and craving
- Opioid activates specific opioid neurotransmitter receptors (mu, kappa, delta) which stimulates G protein associated transduction
- Resulted in opioid effects of reward, withdrawal, and analgesia
- Chronic opioid receptor activation will results in molecular effects opposite to those of acute opioid administration

OPIOID CLINICAL MANIFESTATIONS

- Physiological effects of opioid
  - Analgesia
  - Cough suppression
  - Nausea and vomiting
  - Constipation
  - Urinary retention
  - Itching
  - Sedation
  - Respiratory depression
  - Hypotension

OPIOID INTOXICATION

- Rush of euphoria
- Motor retardation
- Sedation
- Slurred Speech
- Impairment of attention or memory
- Miosis

OPIOID OVERDOSE

- Respiratory depression or arrest
- Hypothermia
- Hypotension
- Seizure
- Bradycardia
- Coma
- Death

NALTREXONE

- Orally bioavailable opioid antagonist
- It is FDA approved to use for maintenance of opioid abstinence
- It is used to deter exogenous opioid use by blocking the pleasurable effect of opioids
- It is not used to treat withdrawal because it can cause withdrawal itself
- It also exists in injectable form which is used for reduction of alcohol craving
- Extremely high affinity for mu receptor (100 times that of heroin)
- It displace morphine and heroin from opioid receptor sites and initiate withdrawal in opioid dependent patients
- Naltrexone should NOT be initiated in patients who have not already undergone opioid detoxification or anyone require the use of opioids for pain control

NALTREXONE AND OPIOID DEPENDENCE

Dose Recommendation:

- *Oral:* Initial: 25 mg; if no withdrawal signs occur, administer 50 mg/day thereafter; alternative maintenance regimens may be used and include: 50 mg on weekdays with a 100 mg dose on Saturday; 100 mg every other day; or 150 mg every 3 days (degree of blockade may be reduced with extended dosing interval regimens and doses >50 mg may increase risk of hepatocellular injury)
- *IM:* 380 mg once every 4 weeks

NALTREXONE AND ALCOHOL USE DISORDER

Dose Recommendation

- *Oral:* 50 mg daily; some patients may require doses up to 100 mg/day (APA [Reus 2018]). Alternative maintenance regimens may be used and include: 50 mg on weekdays with a 100 mg dose on Saturday; 100 mg every other day; or 150 mg every 3 days (degree of blockade may be reduced with extended dosing interval regimens and doses >50 mg may increase risk of hepatocellular injury).
- *IM:* 380 mg once every 4 weeks

VARENICLINE, LOW DOSE NALTREXONE, AND THEIR COMBINATION FOR HEAVY-DRINKING SMOKERS

- Heavy-drinking smokers (≥ 10 cigarrets/day) constitute a sizeable and hard-to-treat subgroup of smokers for whom tailored smoking cessation therapies are not yet available
- Double-blind randomized 2 x 2 medication design, testing varenicline alone (1 mg BID), LDN alone (25 mg QD), combination, and placebo
- 130 participants tested after a 9 day titration period designed to reach steady state on the target medication

VARENCLINE, LOW DOSE NALTREXONE, AND THEIR COMBINATION FOR HEAVY-DRINKING SMOKERS

- Testing completed at 12h of nicotine abstinence, after consuming a standard dose of alcohol and after smoking the first cigarette of the day
- Combination of Varencline and LDN was superior to placebo and monotherapy in:
  - Attenuating cigarette craving
  - Cigarette and alcohol "high"
  - Reduction of both cigarettes and alcohol during the 9 day medication titration period

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COMBINATION OF LEVO-TETRAHYDROPALMATINE AND LOW DOSE NALTREXONE: A PROMISING TREATMENT FOR PREVENTION OF COCAINE RELAPSE

- Combination of L-THP and LDN targets both dopaminergic signaling and the regulation of endogenous opioids
  - Majority of pharmaceutics developed for treatment of substance abuse only target one pathway
- Evidence provided that this combination is more potent with fewer unwanted side effects than L-THP alone
- Conclusions
  - Combination has demonstrated significantly greater effect in attenuating drug seeking behavior than L-THP alone
  - Combination does not result in reduction of spontaneous locomotion
  - Combination increases peripheral concentrations of B-endorphin
  - L-THP and LDN appears to upregulate expression of POMC in the arcuate nucleus

COMBINATION OF LEVO-TETRAHYDROPALMATINE AND LOW DOSE NALTREXONE: A PROMISING TREATMENT FOR PREVENTION OF COCAINE RELAPSE

- Pretreatment of L-THP and LDN significantly attenuated cocaine or cue-induced reinstatement of drug-seeking behavior
  - Dose-dependent manner
- Effective combination treatment for prevention of cocaine relapse
- L-THP and LDN mediates release of endogenous opioids and dopamine, allowing dopaminergic signaling in the brain to approach pre-addiction homeostasis
- Treats both behavioral and physiologic symptoms observed during recovery and reduces drug cravings and relapses
- Future studies should explore proposed mechanism of LDN as well as validate efficacy of L-THP and LDN in human trials

NALTREXONE AND PATHOLOGICAL GAMBLING DISORDER (OFF-LABEL USE)

- It is hypothesized that opioid antagonist, naltrexone, produce a reduction of urges to engage in gambling behavior and longer periods of abstinence.
- Its effectiveness was most seen in patients with strong gambling urges
- A dose of 25mg/day as well as 50mg/day doses were found significantly efficient due to intolerable side effects including insomnia and dizziness

Hloch K., Mladenka P., Dosedel M., Adriani W., Zoratto F. The current clinical knowledge on the treatment of gambling disorder: a summary. *Synapse.* 2017. 71(8). doi: 10.1002/syn.21976.

NALTREXONE AND OBESITY

- Naltrexone/bupropion are recently approved in the USA for long-term weight management
- Mu and kappa opioid receptor antagonist and weak norepinephrine and dopamine reuptake inhibitor combination decrease food consumption synergistically
- Both have weight loss as a side effect
- Rodent studies found naltrexone prevents inhibition of alpha-melanocyte-stimulating hormone, a anorexigenic molecuels that decrease food consumption and increase energy expenditure
- The downstream effects include changing the response to food I nthe hypothalamus, cortical and subcortical self-control regulation, internal awareness and memory

Pilitsi E., Farr OM., Polyzos SA., Perakakis N., Nolen-Doerr E., Papathanasiou AE., Mantzoros CS. Pharmacotherapy of obesity: available medications and drugs under investigation. *Metabolism.* 2019. 92:170-192. doi: 10.1016/j.metabol.2018.10.010.

NALTREXONE AND OBESITY

Dosage Recommendation:

- Available in sustained release tablets of 8mg/90mg
- Take one tablet every morning for one week, then titrate to one tablet twice daily for another week, follow by two tablets every morning and one every evening for a third week and finally tow tablets twice daily from the 4th week on
- Monitor for side effects:
  - Transient nausea, headache, constipation, dizziness

Pilitsi E., Farr OM., Polyzos SA., Perakakis N., Nolen-Doerr E., Papathanasiou AE., Mantzoros CS. Pharmacotherapy of obesity: available medications and drugs under investigation. *Metabolism.* 2019. 92:170-192. doi: 10.1016/j.metabol.2018.10.010.

LOW-DOSE NALTREXONE (LDN)

- Naltrexone has two effects:
  - Direct antagonistic effect on mu opioid receptors
  - Antagonism of Toll-like receptor 4 (TLR4)-mediated proinflammatory pathway in macrophages and microglia
- High dose naltrexone (50-100mg daily) is used in FDA-approved indications for opioid dependence and alcohol withdrawal
- Low-dose naltrexone (LDN) refers to dosage range from 1- 5mg daily
- The immunomodulatory action decreases release of proinflammatory cytokines (tumor necrosis factor, interleukin-6, interleukin-12), inhibit T lymphocyte proliferation, down-regulates expression of chemokines receptors and adhesion molecules
- Such mechanism makes them ideal to be used as adjunct therapy for dermatologic conditions

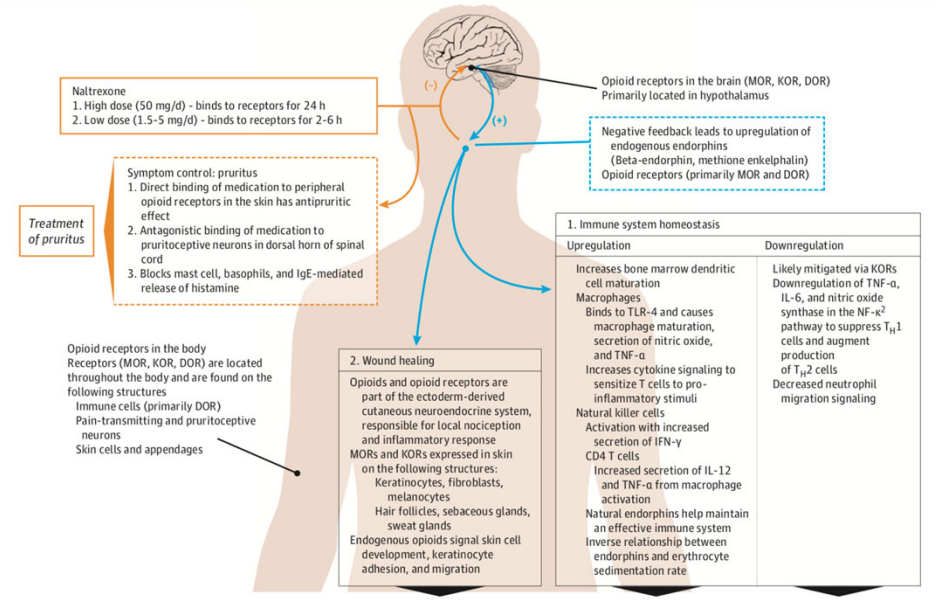
Sikora M., Rakowska A., Olszewska M., Rudnicka L. The use of naltrexone in dermatology. Current evidence and future directions. *Curr Drug Targets.* 2019. doi: 10.2174/1389450120666190318121122.

LDN AND INFLAMMATORY DERMATOLOGIC CONDITIONS

- Naltrexone is found effective in treating pruritus due to:
  - Atopic dermatitis
  - Prurigo nodularis
  - Cholestatsis
  - Burn injury
  - systemic sclerosis
  - Hailey-Hailey disease
  - Lichen planopilaris
- Low dose naltrexone is safer and more effective than higher dose due to lack of opioid involvement in the pathophysiologic mechanisms of these conditions

Ekelem C., Juhasz M., Khera P., Mesinkovska NA. Utility of Naltrexone Treatment for Chronic Inflammatory Dermatologic Conditions: A Systematic Review. JAMA Dermatol. 2018. doi: 10.1001/jamadermatol.2018.4093.

Figure 1. Proposed Mechanisms of Action of Naltrexone on the Immune and Cutaneous Neuroendocrine System



Ekelem C., Juhasz M., Khera P., Mesinkovska NA. Utility of Naltrexone Treatment for Chronic Inflammatory Dermatologic Conditions: A Systematic Review. JAMA Dermatol. 2018. doi: 10.1001/jamadermatol.2018.4093.

USES

- Crohn's Disease
- Multiple Sclerosis
- Fibromyalgia
- Complex Regional Pain Syndrome
- Cancer
- Lyme Disease
- Amyotrophic Lateral Sclerosis
- AIDS/HIV
- Itching
- Eczema and Psoriasis
- Irritable Bowel Syndrome
- Weight loss
- Dry Eyes

Bihari B (2013) Bernard Bihari, MD: low-dose naltrexone for normalizing immune system function
Younger, J, Parkitny, L, Mclain, D. The use of low-dose naltrexone (LDN) as a novel anti-inflamma

THE USE OF LDN AS A NOVEL ANTI-INFLAMMATORY TREATMENT FOR CHRONIC PAIN

- Review of evidence that LDN may operate as a novel anti-inflammatory agent in the central nervous system, via action of microglial cells
- Currently used in fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome
- Effects may be unique to LDN and appears to be independent from naltrexone's better known activity on opioid receptors
- LDN is well tolerated
- LDN may represent on of the first glial cell modulators to be used for the management of chronic pain disorders

LDN FOR MIGRAINE

- No large controlled studies for LDN for migraines
- Only anecdotal evidence
- Dose: 1 mg to 4.5 mg
- Can treat chronic pain syndromes such as fibromyalgia, complex regional pain syndrome, migraine headache, and interstitial cystitis
- MOA: reduce pain by blocking the production of inflammatory substances in the human body

J Pain. 2016;17(4):579.

POTENTIAL SHORT-TERM SIDE EFFECTS

- Insomnia—most common
- Vivid dreams
- Fatigue
- Loss of appetite
- Nausea
- Hair thinning
- Mood swings
- Mild disorientation

POTENTIAL LONG-TERM SIDE EFFECTS

- Possible liver and kidney toxicity
- Possible tolerance to the beneficial rebound effect
- Other unknown sequelae
  - There is a long history of use of naltrexone at FDA approved doses (much higher than used in LDN)

TREATMENT OF PAIN OXYTOCIN

OXYTOCIN

- Released from Posterior Pituitary
  - Similar to Vasopressin
- Prominent in Labor/Delivery/Breast Feeding
- The "CUDDLE HORMONE"
- Engenders Trust/Reduces Anxiety
- Regulates Repetitive Behaviors
  - Treatment for Autism/Schizophrenia

OXYTOCIN BENEFITS

- Releases Endorphins/Reduces Pain
- Fibromyalgia
- Enhances Sexual Desire in Women
- Big Release Following Orgasm

ANALGESIC EFFECTS OF OXYTOCIN

- Analgesic and nociceptive effects thought to be result of interaction with the central endogenous opioid system
- Naloxone can block the analgesic effects of both endogenous and extrinsic oxytocin
- Oxytocin is involved in the modulation of pain experiences
  - One mechanism is thought to be linked to the decreased pain sensitivity by improving mood
- Clinically oxytocin has been used in the treatment of autism, sexual dysfunction, migraine, schizophrenia, drug addiction, and other CNS dysfunctions

Curr Pharm Des. 2015;21(7):906=13.
Neuroscience and Behavioral Reviews. 2015;55:53-67.

ANALGESIC EFFECTS OF OXYTOCIN

- **Somatic nociceptive effects**: Oxytocin indirectly reduces the activity of spinal dorsal horn neurons following application of glutamate
- **Visceral nociceptive effects**: dorsal horn neuronal response to noxious visceral stimulation
- Oxytocin thought the oxytocin receptor appear to be ideal candidates for the treatment of deep tissue pain conditions
- Pain relieving effects of oxytocin, particularly in deep tissue sensation (ischemic pain/muscle pain) or in deep tissue disorders (IBS, migraine)

Curr Pharm Des. 2015;21(7):906=13.

ANALGESIC EFFECTS OF OXYTOCIN

- Exogenously administered oxytocin has been demonstrated to produce minimal toxicity at appropriate doses

- Analgesic effects of exogenous oxytocin through the oxytocin system
  - involves a neuronal mechanism for the transduction of the effects of social support into the neural and physiological changes that modulate the experience of pain

Curr Pharm Des. 2015;21(7):906=13.
Journal of Neuroendocrinology. 2016;28:1-10.

ANALGESIC EFFECTS OF OXYTOCIN

- Has multifunctional actions
  - Anxiety
  - Depression
  - Sexual dysfunction
  - Drug addiction
  - Chronic pain
- More studies need to be done to address long-term analgesic efficacy, long-term safety and toxicity, as well as important assessments related to mechanism of action

Curr Pharm Des. 2015;21(7):906=13.

OXYTOCIN FOR MIGRAINE

- Oxytocin receptors are present on CGRP-expressing trigeminal neurons
  - Administration of oxytocin inhibits the firing of trigeminal ganglia neurons and the release of CGRP
- Intranasal oxytocin may be useful for the treatment of migraine headaches
  - Dose-dependent analgesic effect
  - This has not been shown to occur with IV administration

Headache. 2017;57:64-75.

OXYTOCIN

- Blood level peaks at ovulation
- Levels decline with age
- Estrogen and T3 essential for oxytocin production
- 5-10 units SL daily (1mg = 450 units)
- Can lower ACTH production –
  - If Patient feels worse, could be cortisol deficient

KETAMINE

BACKGROUND

- Ketamine first synthesized in 1960s as alternative to phencyclinde
- Initially, used as a dissociative anesthetic
- Limited use in contemporary anesthesia due to side effects, namely psychedelic symptoms (Niesters et al. 2013)
- More commonly used in animal anesthesia (Morgan, Curran 2012)
- At subanesthetic doses, produces analgesia

PHARMACOLOGY

- A non-competitive antagonist of the NMDA receptor – blocks glutamate action
- S(+) isomer has higher affinity for NMDA receptor than R(-) isomer (Morgan, Curran 2012)
- Also interacts with monoaminergic, muscarinic, and opioidergic receptors (Niesters et al. 2013)

PSYCHIATRIC EFFECTS

- Emergence symptoms after IV infusion – hallucinations, delusions, 'out-of-body' experiences
- Induces transient symptoms of schizophrenia in healthy patients but no evidence linking chronic ketamine use to diagnosis of psychiatric disorders
- Frequent users exhibited profound impairment of long and short term memory (Morgan, Curran 2012)

REWARD AND DEPENDENCE

- Increases dopaminergic modulation in the brain (similar to other addictive substances) → activates reward pathway
- Interaction with μ opioid receptors may contribute to its rewarding properties
- Some case reports of ketamine dependence but no large scale studies undertaken so incidence of ketamine dependence is unknown
- Frequent users report increasing dose over time (tolerance) (Morgan, Curran 2012)

ROLE IN PAIN MANAGEMENT

- Antagonism of NMDA receptor thought to modulate pain
- Potent analgesic at sub-anesthetic doses (0.5-1 mg/kg/hr) that prevents sensitization of spinal neurons to painful stimuli (Morgan, Curran et al. 2012)
- Roles in acute, chronic, and cancer/palliative care pain

INTRANASAL KETAMINE IN DEPRESSION

- 24 patients with major depression; 18 completed 2 days
- DB, PC, Crossover Study
- 50mg intranasal ketamine vs. placebo
- 8/18 in ketamine responded after 24 hours vs 1/18 in placebo
- Effective with minimal adverse effects

Biol Psychiatry. 2014 December 15; 76(12): 970–976.
doi:10.1016/j.biopsych.2014.03.026

INTRANASAL KETAMINE FOR PAIN

- Cross sectional/observational study/8 years and older
- Moderate to Severe Pain on VAS
- Pain scores and VS recorded Q15min
- Side effects/Sedation level/Patient satisfaction recorded

World J Emerg Med 2015;7(1):19–24

INTRANASAL KETAMINE FOR PAIN

- 34 patients enrolled
- Median age 29.5 years
- VAS 80mm
- 80% showed >20mm decrease in VAS
- No changes in VS/side effects mild and transient

World J Emerg Med 2015;7(1):19–24

INTRANASAL KETAMINE FOR PAIN

- A single-center, randomized, prospective, parallel clinical trial
- IN ketamine compared to IV and IM morphine in ED
- 90 patients aged 18–70
- Moderate-severe acute traumatic pain (≥80 mm on 100 mm [VAS])
- Randomized to receive either 1.0 mg/kg IN ketamine, 0.1 mg/kg IV MO or 0.15 mg/kg IM MO
- Pain relief and adverse effects recorded for 1 h post-administration

Shimonovich et al. BMC Emergency Medicine (2016) 16:43

INTRANASAL KETAMINE FOR PAIN

- 3 study groups showed a highly significant results
- Similar maximal pain reduction of 56 ± 26 mm for IN Ketamine, and 59 ± 22 and 48 ± 30 for IV MO and IM MO
- IN Ketamine provided clinically-comparable results to those of IV MO with regards to time to onset (14.3 ± 11.2 v. 8.9

CLINICAL PEARLS

- Ketamine 10mg/50mg/100mg/ml each 0.1mL will deliver 1mg/5mg/10mg per spray
- Order with Mucolox 15%-Mucoadhesive, more effective and need lower doses
- Recommend 0.1mL (1mg) into Each Nostril BID to start
- Always Start LOW and GO SLOW
- Some will add a 40% dose increase due to less bioavailability

KETAMINE

- Bioavailability Comparison
- Take a look at the differences in bioavailability of ketamine through these different routes:
- **Intravenous 100%**
- Intramuscular approximately 93%
- Intranasal approximately 45%
- Sublingual approximately 19-50%

Table 1. Route of administration and the starting dose of ketamine.

Route of administration	Starting dose
Intravenous	0.25–1 mg/kg (adults)*
	0.25–2 mg/kg (children)*
	1–2 mg/kg (adults)#
	2–6 $mg \cdot kg^{-1} \cdot min^{-1}$ (children)#
Intraosseous	0.5–1 mg/kg*
	1–2 mg/kg#
Intramuscular	4–5 mg/kg*[17]
	8–10 mg/kg#[17]
By mouth	3–15 mg/kg (children)*[9, 18]
	500 mg maximum (adults)*[9]
Intranasal	0.25–4 mg/kg*[16, 19, 20]
	3–9 mg/kg#[16, 19, 20]

*Analgesa and sedation dose; #Anesthesia dose.

SUMMARY/CONCLUSION

Ketamine is still undergoing experimental study in regards to its antidepressant effects, not ready for consistent clinical use

Ketamine has analgesic properties but has limited use in treating various types of pain

Well-designed, randomized clinical trials required to corroborate case reports of efficacy

Further investigation into ketamine's mechanisms of action may elucidate how to better utilize ketamine

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THANK YOU
QUESTIONS?